The Korean Journal of Physiology & Pharmacology (Korean J Physiol Pharmacol)

An Official Publication Founded in 1997
The Korean Physiological Society and The Korean Society of Pharmacology

Scope and Policy
The Korean Journal of Physiology and Pharmacology (Korean J Physiol Pharmacol, KJPP) is the official journal of both the Korean Physiological Society and the Korean Society of Pharmacology. The journal is published bi-monthly in English. Submission of any original paper in the physiological and pharmacological sciences and on the interactions of chemicals with biological systems is invited. KJPP does not publish work on the actions of crude biological extracts of unknown chemical composition (e.g. unpurified and unvalidated) or unknown concentration. All papers accepted for publication in KJPP will appear simultaneously in the print Journal and online.

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2015 대한생리학회 임원명단

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감사

| 우선희 | 임인자 |
Acknowledgement

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대한생리학회 회원 여러분, 안녕하십니까?

유난히도 무더웠던 여름이었습니다. 건강하게 잘 지내셨는지요?

그간 지난 5월 21일 경주에서 열린 제23회 기초의학학술대회를 비롯하여 본과학회 등에 참석하여 주신 회원 여러분들께 진심을 통하여 감사의 말씀을 드립니다.

오는 10월 21일(수)~23일(금)에는 부산대학교에서 제 67회 생리학회 학술대회가 개최됩니다. 기 조강연, 다양한 주제의 심포지엄 그리고 포스터 세션 등 풍성한 연구 정보들이 여러분을 기다리고 있습니다.

부산과 양산에서 열리는 이번 학술대회에 적극적으로 참여함으로써, 자신들의 연구결과의 발표는 물론 동료들의 연구발표도 경청함으로써 지식정보의 공유와 함께 개인 간의 긴밀한 교제를 통하여 우정을 돕히하는 기회가 될 것으로 생각합니다. 부디 많이 참석하시어 풍성한 학회가 되도록 하여 주시기 바랍니다.

그리고 학술대회를 준비하기 위해 애쓰신 이사님들 그리고 부산의대 관계자 여러분을 비롯하여 도움을 주신 많은 분들께 감사 드립니다.

끝으로 회원 여러분의 건강과 가정의 행복이 함께하기를 기원합니다.

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대한생리학회 이사장 나홍식
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| 12:00-12:30 | Mitochondrial DNA causes spreading necrosis in the heart James Downey (USA) |
| 12:30-13:00 | Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial reactive oxygen species Thomas Krieg (UK) |
| 13:00-13:15 | Coffee Break                                                             |
| **Session 2** | Chairs: Jae Ho Kim, Byeong Hwa Jeon  
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| 13:15-13:45 | Enlargement of myocardial infarct size by chronic kidney disease: a novel mechanism of disruption of Akt-GSK3beta/p70S6K signaling Tetsuji Miura (Japan) |
| 13:45-14:15 | Dual roles of reactive oxygen species in myocardial ischemia/reperfusion injury and protection Huang-Tian Yang (China) |
| 14:15-14:30 | Coffee Break                                                             |
| **Session 3** | Chairs: Dae Kyu Song, Sun-Hee Woo  
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| 14:30-15:00 | Physiological roles of unconventional eNOS expressed in the smooth muscle of skeletal and pulmonary arteries Sung Joon Kim (Korea) |
| 15:00-15:30 | Zinc, zinc transporters and cardioprotection Zhelong Xu (China)          |
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| **Session 4** | Chairs: Chae Hun Leem, Eun Hui Lee  
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| 15:45-16:15 | The role of TRPM4 in cardiac function and excitability Rudi Vennekens (Belgium) |
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| **Session 5** | Chairs: Moo Yoel Lee, Suhn Hee Kim  
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| 16:45-17:15 | Orai1 in ER/PM junctions Shmuel Mualem (USA)                             |
| 17:15-17:45 | Endosomal and lysosomal chloride/proton exchange by CLC proteins: surprising roles in physiology and pathology Thomas Jentsch (Germany) |
| 17:45-18:00 | Coffee Break                                                             |
| **Session 6** | Chairs: Hyoweon Bang, Suk Hyo Suh  
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| 18:30-18:40 | Closing Remarks                                                          |
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### 67th Annual Meeting of the Korean Physiological Society

#### Thursday, October 22

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- Hall A (모암 홀), Hall B (컨퍼런스 홀)
- 프리뷰룸, 포스터전시, 후원전시

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Pflügers Archiv Symposium - Cardiovascular physiology: Application and Translation

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<td>Dual roles of reactive oxygen species in myocardial ischemia/reperfusion</td>
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<td>Closing Remarks</td>
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Pflügers Archiv Symposium - Cardiovascular physiology: Application and Translation
## Symposium

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\(^1\)Cardiovascular and Metabolic Disease Center (CMDC), Department of Physiology, College of Medicine, Inje University, Busan, South Korea, \(^2\)Department of Physiology and Cell Biology, University of Nevada, School of Medicine, Reno, Nevada, USA

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**Geehoon Chung, Chae Young Kim, Hyun Geun Shim, Sang Jeong Kim**
1Department of Physiology, Seoul National University College of Medicine, 2Department of Biomedical Sciences, Seoul National University College of Medicine, 3Department of Brain & Cognitive Sciences, Seoul National University College of Natural Sciences

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Center for Neuro-Medicine, Brain Science Institute, Korea Institute of Science and Technology, Hwarangno 14-gil 5, Seongbuk-gu, Seoul 136-791, South Korea

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<td>College of Oriental Medicine and Professional Graduate School of Oriental Medicine, 1Hanbang Body-fluid Research Center, 2Brain Korea (BK)21 plus team, Professional Graduate School of Oriental Medicine, Wonkwang University, Iksan, Jeonbuk 540-749, Republic of Korea</td>
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<td>Department of Physiology and Institute of Dermatological Science, Seoul National University College of Medicine, Seoul, Republic of Korea</td>
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Fluid flow facilitates inward rectifier K+ current by convective restoring of [K+] at cell membrane surface

Jae Gon Kim1, Song Woong Park2, Hyang-Ae Lee2, Dongyun Byun1, Wan Soo Choi2, Kyung Chul Shin1, Ki Suk Kim2

Department of Physiology, KU Open Innovation Center, Research Institute of Medical Science, Konkuk University School of Medicine, Chungju, Chungbuk 380-701, South Korea

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Ion channel gene expression predicts survival in glioma patients

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Inhibitory modulation of H ERG K+ channels by endogenous polyunsaturated fatty acid-derived electrophiles, 4-HNE and 4-ONE

TLR3/-4-Priming Differentially Promote Ca2+ Signaling and Cytokine Expression and Ca2+-Dependently

†Department of Pharmacology, University of Vermont, Burlington, VT 05405 (USA)
‡Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104 (USA)
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S 59 P04-15 Electrophysiological Characterization of Novel KCNQ4 Mutant Channels
Hyun Been Choi, Mi-na Park, Min-Young Kim, Ah-Reum Kim, Byung Yoon Choi, Tong Mook Kang
Department of Physiology, SBRI, Sungkyunkwan University School of Medicine, Suwon, Korea, Department of Otorhinolaryngology-Head and Neck Surgery and Healthcare Research Institute, Seoul National University Hospital, Healthcare System Gangnam Center, Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Bundang Hospital, Seongnam, Korea

S 59 P04-16 Influence of Bisphenol-A on ion channel activities on Gonadotropin Releasing Hormone Neurons
Janardhan P. Bhattarai, Seong Kyu Han
Department of Oral Physiology, School of Dentistry & Institute of Oral Bioscience, Chonbuk National University, Jeonju

S 59 P04-17 The Conserved Gating Elements in CIRB domain of TRPC4 Channel
Chansik Hong, Jongyun Myeong, Joo Hyun Nam, Young-Cheol Shin, Misun Kwak, Insuk So
Department of Physiology, College of Medicine, Seoul National University, Seoul, 110-799, Korea, Department of Physiology, College of Medicine, Dongguk University, Gyeongju, 780-714, Korea

S 60 P04-18 KCNQ2/3 channel inhibition by ethanol is regulated by plasma membrane PI(4,5)P2 level
Kwon-Woo Kim, Dongil Keum, Hae-Jin Kweon, Byung-Chang Suh
Department of Brain and Cognitive Science, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu 711-873, South Korea

S 60 P04-19 Verapamil inhibits TRESK current in trigeminal ganglion neurons independently of the blockade of Ca2+ influx
Dawon Kang, Eun-Jin Kim, Ji Hyeon Ryu, Jaeehe Han
Department of Physiology, College of Medicine and Institute of Health Sciences, Gyeongsang National University, Jinju 660-751, South Korea

S 60 P04-20 Stable interaction of Ca2+ channel β subunit with high voltage-activated Ca2+ channels α1 subunit revealed by translocatable CaV β subunit systems
Jun-Hee Yoon, Byung-Chang Suh
Department of Brain and Cognitive Sciences, Daegu Gyeongbuk Institute of Science and Technology, Daegu, 711-873, South Korea

S 61 P04-21 Functional role of GABA as a gliotransmitter in epileptic hippocampus
Sudip Pandit, Hyang-Joo Lee, Hyun-Sill Cho, Yoon-Hyung Pae, Jin Bong Park
Department of Physiology, Brain Research Institute, School of Medicine, Chungnam National University, 6 Munhwa-Ro, Jung-gu, Daejeon, 301-131, Republic of Korea

S 61 P04-22 Gai-mediated TRPC4 activation by Polycystin-1 contributes to cystic disease via STAT1 activation
Misun Kwak, Chansik Hong, Kotdaji Ha, Ju-Hong Jeon, Insuk So
Department of Physiology, Seoul National University College of Medicine

S 61 P04-23 Single channel recordings of the positive pressure-specific mechanosensitive piezo2 ion channels in human MCC-13 Merkel cell line
Kyung Chul Shin, Sang Woong Park, Hyunj Park, Young Min Bae
Department of Physiology, KU Open Innovation Center, Research Institute of Medical Science, Chungju, Chungbuk, 380-701, South Korea
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<td>Department of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 151-742, Korea</td>
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<td>College of Pharmacy, Chungnam National University, 99 Daehak-ro, Yuseong-gu, Daegu 305-764, South Korea, Department of Bioactive Products, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet Rd, Hanoi, Vietnam</td>
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<td>Department of physiology, College of Medicine, Dongguk University, Kyungju 780-714, Korea, Channelopathy Research Center (CRC), Dongguk University College of Medicine, 27 Dongguk-ro, Gyungu 410-773, Republic of Korea</td>
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<td>Department of Physiology and Institute of Dermatological Science, Seoul National University College of Medicine, Seoul, Republic of Korea</td>
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<td>Joo Hyun Nam, Dong-Ung Lee</td>
<td>Department of Physiology, Dongguk University College of Medicine, Gyeongju 780-714; and Channelopathy Research Center (CRC), Dongguk University College of Medicine, 27 Dongguk-ro, Gyungu 410-773, Republic of Korea</td>
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<td>Joo Hyun Nam, Dong-Ung Lee</td>
<td>Department of Physiology, Dongguk University College of Medicine, 123 Dongdae-ro, Kyungju 780-714, Republic of Korea, Division of Bioscience, Dongguk University, Gyeongju 780-714, Republic of Korea</td>
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<td>Ga Yul Kim, Ji Yeon Song, Jeong Hoon Lee, Young Bounm Lee</td>
<td>Department of Physiology, University of Ulsan College of Medicine, 88 Olympic Ro 43-gil Songpa-gu, Seoul, Republic of Korea</td>
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<td>Lab. of Membrane Biochemistry and Biophysics, Dept. of Structure &amp; Functional Neural Network, Korea Brain Research Institute (KBRRI), Daegu, Korea 701-300</td>
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<td>Department of Physiology, College of Medicine, Konyang University, Daejeon 35365, Korea</td>
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<td>Department of Physiology and Samsung Biomedical Research Institute, School of Medicine, Sungkyunkwan University, Suwon, Republic of Korea</td>
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Voltage gated sodium channel 1.7 as therapeutic target for treatment of neuropathic pain
Sung-Young Kim
New Drug Laboratory, Daewoo Jil, Dugwe-ro, Poegok-eup, Cheon-gu, Yongin-si, Gyeonggi-do, 449-814, Korea

Autocrine insulin stimulates plasma membrane trafficking of KATP channel via P3K-VAMP2 pathway in MIN-6 cells
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Effects of nitric oxide on voltage-dependent K currents in human cardiac fibroblasts
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WK1 promotes tumor progression via TRPC6 activation in clear cell renal cell carcinoma
Ji-Hee Kim, Kyu-Hee Hwang, Minseob Eom, Seong-Woo Jeong, In Deok Kong, Kyu-Sang Park, Seung-Kyu Cha
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Klotho inhibits tumor progression via targeting Orai1 channels in cancer cells
Ji-Hee Kim, Kyu-Hee Hwang, Seong-Woo Jeong, In Deok Kong, Kyu-Sang Park, Seung-Kyu Cha
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Inhibition of N-type Ca2+ currents in rat peripheral sympathetic neurons by Imidazoline I1 receptors activation
Soo-Yeon Lee, Eun Jeong Kim, Ji-Hyun Jeong, Young-Hwan Kim, Duck-sun Ahn, Seungsoo Chung
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TRPC6 induces hepatic stellate cell activation causing liver fibrosis
Kyu-Hee Hwang, Ji-Hee Kim, Soo-Jin Kim, In Deok Kong, Kyu-Sang Park, Seung-Kyu Cha
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The organellar Ca2+ channel TRPML3 regulates early autophagosome biogenesis by interaction with phosphoinositides
Mi Kyung Kim, So Woon Kim, Hyun Jin Kim
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Trafficking-dependent N-glycan structure regulates cell surface expression of potassium channel Kv2.1b
Paul Christian Vicente, Jin Young Kim, Ji Seon Shim, Jeong-Ju Ha, Dong-Hyoon Kim, Min-Young Song, Jin-Sung Choi, Kang-Sik Park
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Tyrosine phosphorylation of Kv2.1 channel contributes to neuronal cell death in brain ischemia
Min-Young Song, Eun Ji Bae, Hye-Min Kang, Chan Park, Kang-Sik Park
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The phosphorylation sites of potassium channel Kv2.1 determine cell background specific differences in function between cerebellum and cerebrum
Ji Yeon Hwang, Eun Ji Bae, Ji Seon Shim, Kang-Sik Park
Department of Physiology, School of Medicine, Kyung Hee University, Seoul 02447, Korea

MicroRNA-200a/210 controls proliferation and Osteogenic differentiation of human adipose tissue stromal cells
Young Suk Kim, Hee Jeong Park, Keun Koo Shin, Seon Young Lee, Yong Chan Bae, Jin Sup Jung
Department of Physiology, School of Medicine, Pusan National University, Yangsan (626-870), Korea, Department of Plastic Surgery, School of Medicine, Pusan National University, Pusan (602-739), Korea
P05-02 MicroRNA-4284 controls proliferation and Adipogenic and Osteogenic differentiation of human adipose tissue stromal cells
Hee Jeong Park1, Young Suk Kim1, Keun Koo Shin1, Sun Young Lee1, Yong Chan Bae2, Jin Sup Jung1
1Department of Physiology, School of Medicine, Pusan National University, Yangsan (626-870), Korea, 2Department of Plastic Surgery, School of Medicine, Pusan National University, Pusan (602-739), Korea

P05-03(O-12) mTOR signaling in the insular cortex modulates neuropathic pain
Minjee Kwon1,2,*, Jeongsoo Han1,2,*, Myeounghoon Cha3, Un Jeng Kim4, Bae Hwan Lee4
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P05-04 Nerve injury-induced neuroplasticity in the insular cortex contribute to pain hypersensitivity
Jeongsoo Han, Minjee Kwon, Motomasa Tanioka, Bae Hwan Lee
Department of Physiology, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul 03722, Korea

P05-05 Alteration of cardiac hypertrophic marker gene expression by PCB 126 and PCB 77
Mi-Hyeong Park, Su-Hyun Jo
Department of Physiology, Institute of Bioscience and Biotechnology, BK21 plus Graduate Program, Kangwon National University College of Medicine, Chuncheon 200-701, Korea

P05-06 Impaired cholesterol homeostasis increases the secretion of beta-amyloid peptide in Familial Alzheimer’s disease-associated presenilin mutant
Yoon Young Cho, Oh-Hoon Kwon, Sungkwn Chung
Department of Physiology, Sungkyunkwan University School of Medicine, Suwon, Korea

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Yu Ran Lee, Gun Kang, Hee Kyoung Jo, Myoung Soo Park, Cuk-Seong Kim, Sunga Choi, Byeong Hwa Jeon
Infectious Signaling Network Research Center and Research Institute for Medical Sciences, Department of Physiology, School of Medicine, Chungnam National University, 3Preclinical Research Center, Chungnam National University Hospital, Daejeon, 301-747, Republic of KOREA

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Hyun Geun Oh, Oh Hoon Kwon, Sungkwn Chung
Dept. of Physiol., Sungkwn University Sch. of Med., Suwon, Republic of Korea

P05-09 The 18-kDa translocator protein inhibits vascular cell adhesion molecule-1 expression via inhibition of mitochondrial reactive oxygen species
Hee Kyoung Jo, Yu Ran Lee, Myoung Soo Park, Su Hyeon Kim, Sunga Choi, Byeong Hwa Jeon
Infectious Signaling Network Research Center and Research Institute for Medical Sciences, Department of Physiology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea, 3Preclinical Research Center, Chungnam National University Hospital, Daejeon, Republic of Korea

P05-10 O-GlcNAcylation-induced GPAT Expression is Critical for Anti-apoptosis under Hypoxia
Hyun Jik Lee, Eun Ju Song, Ki Hoon Lee, Dah Ihm Kim, Se Hee Ko, Gee Euhn Choi, Ji Young Oh, Ho Jae Han
Department of Veterinary Physiology, BK21 PLUS Creative Research Center and Research Institute for Veterinary Science, College of Veterinary Medicine, Seoul National University, 08826, Seoul, Korea

P05-11 Amyloid β-Induced abnormal Autophagolysosome formation leading defective mitochondrial accumulation causes neuronal cell death
Dah Ihm Kim, Jung Min Ryu, Ki Hoon Lee, Jeong Yeon Kim, Gee Euhn Choi, Ing In Chai, Ho Jae Han
Department of Veterinary Physiology, College of Veterinary Medicine, Research Institute for Veterinary Science, and BK21 PLUS Creative Veterinary Research Center, Seoul National University, Seoul 08826, Korea

P05-12 Aβ-Induced mTOR Activation is Important for Tau hyperphosphorylation through Regulation of Expression and Autophagy of CDK2 and CDK4
Ki Hoon Lee, Jung Min Ryu, Dah Ihm Kim, Jeong Yeon Kim, Gee Euhn Choi, Ho Jae Han
Department of Veterinary Physiology, College of Veterinary Medicine, Research Institute for Veterinary Science, and BK21 PLUS Creative Veterinary Research Center, Seoul National University, Seoul 08826, Korea
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Sei-Jung Lee, Hyeon Su Lim, Eun Ju Song, Jun Sung Kim, Kyung Ku Jang, Sang Ho Choi, Ho Jae Han*
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Young Hyun Jung, Sei-Jung Lee, Eun Ju Song, Hyeon Su Lim, Jun Sung Kim, Ho Jae Han*
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P05-15 Cdo regulates surface expression of the Kir2.1 K+ channel in myoblast differentiation
Jewoo Koh, Young-Eun Leem, Hyeon-Ju Jeong, Hyun-Ji Kim, Kyungjin Kang, Jongsun Kang, Hana Cho*
Department of Physiology, Department of Molecular Cell Biology, Department of Anatomy and Cell Biology, Sungkyunkwan University School of Medicine, Samsung Biomedical Research Institute, Suwon, 440-746, Republic of Korea

P05-16 Anti-adhesive activity of the ethanol extracts of Ulmus davidiana var japonica in cultured endothelial cells
Ki Mo Lee, Hee Kyung Joo, Yu Ran Lee, Myoung Soo Park, Gun Kang, Sunga Choi, Kwon Ho Lee, Byeong Hwa Jeon
Infectious Signaling Network Research Center and Research Institute for Medical Sciences, Department of Physiology, School of Medicine, Chungnam National University, Preclinical Research Center, Chungnam National University Hospital, Daejeon, Republic of KOREA, Department of Physical Therapy, Joongbu University, 201 Daehak-ro, Chubu-Myeon, Geumsan-Gun, Chungnam 312-702, Korea

P05-17 FBXO11 represses cellular response to hypoxia by destabilizing hypoxia-inducible factor-1α mRNA
Uk-Il Ju, Jong-Wan Park, Hyyoung Sook Park, Sang Jeong Kim, Hyoung-Sook Park*
Department of Biomedical Sciences, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-799, Republic of Korea, BK21 Plus KNU Biomedical Convergence Program, School of medicine Kyungpook National University, Daegu 702-422, Republic of Korea, BK21 Plus KNU Biomedical Convergence Program, School of medicine Kyungpook National University, Daegu 700-842, Korea Center for Theragnosis, Biomedical Research Institute, Korea Institute of Science and Technology, Seoul, Republic of Korea

P05-18 Fatty acid modulates nitric oxide synthase activity in hypertensive rat atrium
Yu Na Wu, Ji Hyun Jang, Sung Joen Kim, Yin Hua Zhang
Department of Physiology & Biomedical Sciences, Seoul National University, College of Medicine, Seoul, Republic of Korea

P05-19 TGFBIp targeting peptide evaluation
Haeuk Jung, Hye-Nam Son, Soyoun Kim, In-San Kim, Ha-Jeong Kim*
Department of Physiology, School of Medicine, Kyungpook National University, Daegu 702-422, Republic of Korea, BK21 Plus KNU Biomedical Convergence Program, School of medicine Kyungpook National University, Daegu 700-842, Korea Center for Theragnosis, Biomedical Research Institute, Korea Institute of Science and Technology, Seoul, Republic of Korea

P05-20 The regulatory role of phosphodiesterase 4 inhibitor rolipram in lipopolysaccharides-induced signaling in submandibular glands
Dong Un Lee, Wanhee Suk, Jeong Hee Hong
Department of Physiology, College of Medicine, Gachon University, 191 Hambakmeoro, Yeonsu-gu, Incheon, 406-799, Republic of Korea

P05-21 TRPC6 as a critical regulator in osteoclastogenesis
Jung Yun Kang, Yu-Mi Yang, Dong Min Shin
Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul 03722, Korea

P05-22 Homer2/3 modulate RANKL-induced NFATc1, osteoclastogenesis and bone metabolism
Yu-Mi Yang, Aran Son, Jung Yun Kang, Dong Min Shin
Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul 03722, Korea
S 75  P05-23  Osmo-mechanosensitive TRP channels regulate Ca\textsuperscript{2+}-mediated RANKL expression in mouse osteoblastic cells
Yu-Mi Yang, Jung Yun Kang, Aran Son, Hyo Jin Yang, Dong Min Shin
\textsuperscript{1}Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul 03722, \textsuperscript{2}Division of AIDS, Center for Immunopathology, Korea National Institute of Health, Chungju 28160, Korea

S 76  P05-24  Endothelin stimulates inflammatory bone loss in periodontitis
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\textsuperscript{1}Department of Oral Biology, \textsuperscript{2}BK21 PLUS Project, Yonsei University College of Dentistry, Seoul 03722, South Korea

S 76  P05-25(O-15)  Disarrangement of regulated exocytosis in TRPML1 knock-out mice
Soonhong Park\textsuperscript{1}, Min Seuk Kim\textsuperscript{2}, Shmuel Muallem\textsuperscript{2}, Dong Min Shin\textsuperscript{1}
\textsuperscript{1}Department of Oral Biology, BK21 PLUS Project, Yonsei University College of Dentistry, Seoul 03722, Korea, \textsuperscript{2}Molecular Physiology and Therapeutics Branch, NIDCR, NIH, Bethesda, MD 20892, USA, \textsuperscript{3}Department of Physiology, Lab of Oral Biology, College of Dentistry, Wonkwang University, Iksan, Jeonbuk 54538, Korea

S 76  P05-26  Calcium ion regulates WNK/OSR1/NKCC1 pathway in HSG cell-line
Soonhong Park\textsuperscript{1}, Sang Kyun Ku\textsuperscript{2}, Hye Won Ji\textsuperscript{1}, Jong-Hoon Choi\textsuperscript{2}, Dong Min Shin\textsuperscript{1,2}
\textsuperscript{1}Department of Oral Biology, BK21 PLUS Project and \textsuperscript{2}Department of Oral Medicine, Yonsei University College of Dentistry, Seoul 03722, Korea

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Department of Oral Biology, Yonsei University College of Dentistry, Seoul 03722, Korea

S 77  P05-28  Induction of IL-6 and IL-8 by activation of thermosensitive TRP channels in human PDL cells
Ga-Yeon Son, Dong Min Shin
Department of Oral Biology, Yonsei University College of Dentistry, Seoul 03722, Korea

S 77  P05-29  Bacterial PAMPs and allergens trigger increase in [Ca\textsuperscript{2+}]\textsuperscript{-}-induced cytokine expression in human PDL fibroblasts
Ga-Yeon Son, Dong Min Shin
Department of Oral Biology, Yonsei University College of Dentistry, Seoul 03722, Korea

S 77  P05-30  Corn Silk Extract Prevents Carrageenan-Induced Inflammatory Edema by Suppressing Expression of P-Selectin Glycoprotein Ligand-1
Han Na Choi\textsuperscript{1}, Yong Hwan Kim\textsuperscript{1}, Soo Jin Kim\textsuperscript{1}, Yun A Kim\textsuperscript{1}, Byeong Hwa Jeon\textsuperscript{1}, Hye Won Kim\textsuperscript{1}, Dong Woon Kim\textsuperscript{2}, Sang Do Lee\textsuperscript{1}
\textsuperscript{1}Department of Physiology, Departmeent of \textsuperscript{2}Anatomy, Chungnam National University School of Medicine, Daejeon, 301-747, Korea

S 78  P05-31  Airborne allergens induce protease activated receptor-2-mediated production of inflammatory cytokines in human gingival epithelium
Ga-Yeon Son, Dong Min Shin
Department of Oral Biology, Yonsei University College of Dentistry, Seoul 03722, Korea

S 78  P05-32  Macrophages programmed by apoptotic cells inhibit epithelial-mesenchymal transition in lung alveolar epithelial cells via PGE2, PGD2, and HGF
Young-So Yoon, Ye-Ji Lee, Jhee Lee
Department of Physiology, Tissue Injury Defense Research Center, School of Medicine, Ewha Womans University, Seoul, 158-710, Korea

S 78  P05-33  Suberoylanilide hydroxamic acid enhances apoptotic effect of TNF-α in human lung cancer cells via TNFR1 upregulation
Bo Ra You, Bo Ram Han, Soo Mi Kim, Sung Zoo Kim, Suhn Hee Kim and Woo Hyun Park
Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, 561-180, Republic of Korea

S 79  P05-34  Hydroquinone intensifies the death of valproic acid-treated SK-LU-1 cells
Bo Ram Han, Bo Ram Han, Soo Mi Kim, Sung Zoo Kim, Suhn Hee Kim, Woo Hyun Park
Department of Physiology, Medical School, Research Institute for Endocrine Sciences, Chonbuk National University, Jeonju, 561-180, Republic of Korea
**S 79** P05-36 Differential Expression of Taste Receptors in Tongue Papillae
Ha-Jung Choi, Soo-Young Ki, Young-Kyung Cho, Ki-Myung Chung, Kyung-Nyun Kim
Department of Physiology and Neuroscience, College of Dentistry and Research Institute of Oral Sciences, Gangneung-Wonju National University, Gangneung, 210-702, Korea

**S 79** P05-37 Expression of Bitter Taste Receptor Tas2r108 mRNA in Murine submandibular gland
Su-Young Ki, Ha-Jung Choi, Ki-Myung Chung, Young-Kyung Cho, Kyung-Nyun Kim
Department of Physiology and Neuroscience, College of Dentistry and Research Institute of Oral Sciences, Gangneung-Wonju National University, Gangneung, 210-702, Korea

**S 80** P05-38 A monoclonal antibody against transmembrane proteins of human umbilical vein endothelial cells is a potential inhibitor of endothelium-dependent relaxation in rat aorta
Bong-Woo Park1, Seung Hyo Jung2, Donghyen Lee3, Kang Pa Lee3, Gyoungho Boom Lee3, Hwan Myung Lee3, Junghwan Kim3, Kyung-Jong Won3, Bokyung Kim3
1Department of Physiology, Konkuk University School of Medicine, Danwol-dong 322, Chungju 380-701, Korea, 2Department of Cosmetic Science, College of Natural Sciences, Hoseo University, Asan 336-795, 3Department of Physical Therapy, College of Public Health & Welfare, Yongin University, Yongin 449-714, South Korea

**S 80** P05-39(O-3) TGF-β1-induced apoptosis via Nox4 is mediated by ERK1/2-mTORC1 activation in podocytes
Ranjan Das1, Shanhua Xu1,2, Xianglan Quan1, Tuyet Thi Nguyen1, Seung-Kyu Cha1, Seong-Woo Jeong1, In Deok Kim1
1Department of Physiology, 2Department of Global Medical Science, Yonsei University Wonju College of Medicine, Wonju, Korea

**S 81** P05-41 Nafamostat mesilate induces protective effects against TNF-α-induced vascular endothelial cell dysfunction by inhibiting reactive oxygen species production
Su Jeong Choi1, Jung-Bum Park1, Harsha Nagar1, Shin Kwang Kang3, Saet-byel Jung3, Sungju Lee4, Byeong Hwa Jeon1, Cuk-Seong Kim1
1Department of Physiology, School of Medicine, Chungnam National University, Daejeon 301-131, Republic of Korea, 2Department of Thoracic and Cardiovascular Surgery, 3Department of Endocrinology, 4Department of Rehabilitation Medicine

**S 81** P05-42 HN1 Promotes Tumorigenicity through Activation of the SREBP-1 and -2 Lipogenic Signaling Pathway in Hepatocellular Carcinoma
Hua Jin, Woo Hyun Park, Sung Zoo Kim, Suhn Hee Kim, Soo Mi Kim
Department of Physiology, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Republic of Korea

**S 82** P05-44 CTHRC1 Stimulates Growth and Metastasis in Esophageal Adenocarcinoma Cells by Activation of the β-catenin/c-Myc Signaling Pathway
Jie Gao1,2, Kwang Bok Lee1, Soo Mi Kim1
1Department of Physiology, 2Department of Orthopedic Surgery, Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Republic of Korea
Effect of Macrophage on Induction of Gefitinib Resistance in EGFR Mutated Non Small Cell Lung Cancer Cells
Subodh Sharma¹, Soo Jin Kim¹, Taeehe Kim¹, Young Hwan Kim², Ji Yeong Muni¹, Han Na Choi¹, Min Woong Kang³, Sang Do Lee³
¹Department of Physiology, ²Department of thoracic surgery, Chungnam National University School of Medicine, Daejeon, 301-747, Korea

Gas6/Mer signaling induces transactivation of LXRx-target gene arginase 2 and vascular endothelial growth factor via STAT1 transcription factor in macrophages
Eunjin Lim, Si Yoon Kim, Youn-Hee Choi, Jihee Lee
Injury Defense Research Center, School of Medicine, Ewha Womans University, Seoul 158-056, Korea

Nafamostat mesilate attenuates transient focal ischemia/reperfusion-induced brain injury via the inhibition of endoplasmic reticulum stress
Sun Kwan Kwon, Moonsang Ahn, Hee-Jung Song, Shin Kwang Kang, Saet-byel Sun Kwan Kwon, Moonsang Ahn, Hee-Jung Song, Shin Kwang Kang, Saet-byel Jung, Nagar Harsha, Sungju Lee, Jae Young Moon, Kwang-sun Suh, Sang Do Lee, Byeong Hwa Jeon, Dong Woon Kim, Cuk seong Kim
Department of Physiology, School of Medicine, Chungnam National University, Daejeon 301-131, Republic of Korea

Statin pretreatment inhibits LPS-induced EMT via the downregulation of TLR4 and NF-κB in hBECs
Seon Mee Park¹, Yangmi Kim
Department of Gastroenterology, Department of Physiology, College of Medicine, Chungbuk National University, Korea

Regulation of Autophagy by Rapamycin has inhibition cardio-toxicity role in Doxorubicin-Induced Cardiac Progenitor/Stem cells Dysfunction
Ji Hye Park¹,²,³, Sang Mo Kwon¹,²
¹Laboratory of Vascular Medicine and Stem Cell Biology, Department of Physiology, Pusan National University School of Medicine, South Korea, ²Convergence Stem Cell Research Center, Department of Physiology, Pusan National University School of Medicine, South Korea, ³Pusan National University Medical Science, Education Center (BK21 Program), Pusan National University School of Medicine, Yangsan 626-870, Korea

Serum protein Fetuin-B is involved in immune cells and vascular smooth muscle cells-linked atherosclerotic plaque stability
Donghyun Lee¹, Seung Hyo Jung¹, Kang Pa Lee¹, Gyoung Beom Lee¹, Suji Baek¹, Bong-Woo Park¹, Junghwan Kim¹, Hwan-Myung Lee¹, Kyung-Jong Won¹, Bokyung Kim¹
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DJ-1 contributes to sphingophosphorylcholine-induced differentiation of human mesenchymal stem cells into smooth muscle cells
Suji Baek¹, Kang Pa Lee¹, Seung Hyo Jung¹, Gyoung Beom Lee¹, Donghyun Lee¹, Bong-Woo Park¹, Dong Hyeon Lee¹, Hwan-Myung Lee¹, Kyung-Jong Won¹, Bokyung Kim¹
¹Department of Physiology, School of Medicine, Konkuk University, Chungju 380-701, Korea, ²Department of Cosmetic Science, College of Natural Sciences, Hoseo University, Asan 336-795, Korea

S32 nm laser irradiation suppresses restenotic lesion-related responses in PDGF-BB-stimulated vascular smooth muscle cells
Seung Hyo Jung¹, Suji Baek¹, Kang Pa Lee¹, Gyoung Beom Lee¹, Bong-Woo Park¹, Dong Hyeon Lee¹, Hwan-Myung Lee², Young Min Bae¹, Kyung-Jong Won¹, Bokyung Kim¹
¹Department of Physiology, School of Medicine, Konkuk University, 322 Danwool-dong, Chungju 380-701, Korea, ²Department of Cosmetic Science, College of Natural Sciences, Hoseo University, Asan 336-795, Korea

Angiotensin II induces migration via APE/Ref-1-mediated transactivation of sphingosine-1-phosphate receptor in vascular smooth muscle cells
Kang Pa Lee¹, Dong-Youb Lee¹, Dong Hyen Lee¹, SeungHyo Jung¹, Suji Baek¹, Yuri Park¹, Hwan Myung Lee², Kyung-Jong Won¹, Bokyung Kim¹
¹Department of Physiology, School of Medicine, Konkuk University, Seoul 143-701, Korea, ²Department of Cosmetic Science, College of Natural Sciences, Hoseo University, Asan 336-795, Korea

Inhibition of Pi transport across plasma and mitochondrial membrane prevents high phosphate-induced vascular calcification
Tuyet Thi Nguyen¹, Shanhua Xu²,³, Ranjan Das¹, Xianglan Quan¹, Ji-Hee Kim¹, Kyu-Hee Hwang²,³, Seung-Kyu Cha¹, Seong-Woo Jeong¹, In Deok Kong¹, Kyu-Sang Park¹
¹Department of Physiology and ²Global Medical Science, Yonsei University Wonju College of Medicine, Wonju, Korea
P06: Muscle, Cardiovascular, and G-I System

S 86  P06-01  Absence of of hypoxic augmentation of vasoconstriction in the femoral artery from eNOS deficient mice
Hyun-Ji Kim1,3,#
and Hepatology, Stanford University School of Medicine, Stanford, California, USA
Institute, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA, and
Department of Physiology, College of Medicine, The Catholic University of Korea, Banpo-daero 222, Seocho-gu, Seoul
137-790, Republic of Korea

S 86  P06-02  Augmented vascular reactivity and hypoxic pulmonary vasoconstriction in monocrotaline-induced pulmonary arterial hypertension rats
Hyun-Ji Kim1,3,#, Yin Hua Zhang1, Sung Joon Kim1,2, Hae Young Yoo1
Department of Physiology, Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul
110-799, KOREA

S 86  P06-03  Smooth Muscle Cell Genome Browser: Enabling the Identification of Novel Serum Response Factor Target Genes
Moon Young Lee1,3,#, Chanjae Park1, Robyn M. Berent1, Paul J. Park1, Robert Fuchs1, Hannah Syn1, Albert Chin1, Jared Townsend1, Craig C. Benson*, Hyun-Ji Kim1,3,#, Hae Young Yoo1
Department of Physiology, Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul
110-799, Korea, 3Chung-Ang University College of Nursing, Seoul 156-756, Korea

S 86  P06-04  Serum Response Factor Is Essential for Prenatal Gastrointestinal Smooth Muscle Development and Maintenance of Differentiated Phenotype
Chanjae Park1, Moon Young Lee1,3,#, Paul J Park1, Se Eun Ha1, Robyn Berent1, Robert Fuchs1, Joseph M Miano1, Laren S Becker1, Kenton M Sanders1, Seungil Ro1
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S 88  P06-05  Loss of Cdo leads to alteration in N-cadherin and connexin with intercellular coupling defects and cardiomyopathy
Hyun-Ji Kim1,3,#, Myong-Ho Jeong1,2, Kyu-Sil Choi1, Young-Hwan Song1, Gordon F. Tomaselli1, Jong-Sung Kang1,2, Hana Choi1,2
1Department of Physiology, Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, 440-746, 2Samsung Biomedical Research Institute, Samsung medical center, Seoul 135-710, 3Division of Cardiology, Seoul National University Bundang Hospital, 463-707, Republic of Korea, 4Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

S 88  P06-06  Sildenafil is effective to enhance the proliferation of skeletal myoblasts
Mei Huang, Keon Jin Lee, Mi Kyung Ahn, Eun Hui Lee
Department of Physiology, College of Medicine, The Catholic University of Korea, Banpo-daero 222, Seocho-gu, Seoul
137-701, Republic of Korea
S 88  P06-07 Interaction between mitsugumin 29 and TRPC3 participates in regulating calcium transients in skeletal 
Jin Seok Woo, Ji-Hye Hwang, Mei Huang, Mi Kyoung Ahn, Mi Ri Oh, Chung-Hyun Cho, Jianjea Ma, Eun Hui Lee
Department of Physiology, College of Medicine, The Catholic University of Korea, Banpo-daero 222, Seocho-gu, 
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Seoul 110-799, Republic of Korea ; Department of Surgery, Davis Heart and Lung Research Institute, The Ohio State 
University, Columbus, OH 43210, USA.

S 89  P06-08 Inhibition of nNOS facilitates myofilament disarray and cardiac hypertrophy in Ang II-induced hypertensive rat 
Ji Hyun Jang, Zai Hao Zhao, Sung Joon Kim, Yin Hua Zhang
Department of Physiology, Seoul National University, College of Medicine, Seoul, Republic of Korea

S 89  P06-09 Signaling pathway and physiological role of WNK1 in mouse skeletal muscle 
Hanul Kim, Ji-Hee Kim, Kyu-Hee Hwang, Seong-Woo Jeong, Seung-Kyu Cha, In Deok Kong
Departments of Physiology and Global Medical Science, and Institute of Lifestyle Medicine, Yonsei University

S 89  P06-10 Inhibition of Endoplasmic Reticulum Stress Normalizes Augmented Myogenic Responses in Coronary Arteries of the 
Spontaneously Hypertensive Rats 
Soo-Kyoung Choi, Mihwa Lim, Duck-Sun Ahn, Young-Ho Lee
Department of Physiology, College of Medicine, BK 21 Plus Project for Medical Sciences, Yonsei University, C.P.O Box 8044, Seoul 120-752, Korea

S 90  P06-11(O-6) Does eNOS-palmitoylation involve in palmitic acid-enhanced cardiac inotropy in rat cardiac myocyte? 
Chun Li Jin, Ji Hyun Jang, Yu Na Wu, Zai Hao Zhao, Sung Joon Kim, Yin Hua Zhang*
Department of Physiology, Seoul National University College of Medicine, Seoul 110-799, Korea

S 90  P06-12 Betal-adrenergic receptor antagonist and nitric oxide stimulator, nebivolol, prevents spontaneous contraction 
induced by metabolic substrates in rat cardiomyocytes 
Zai Hao Zhao, Ji Hyun Jang, Jae Hwi Sung, Yin Hua Zhang*
Department of Physiology & Biomedical Sciences, Seoul National University, College of Medicine, Seoul, 110-799 Korea

S 90  P06-13 Angiotensin IV protects cardiac reperfusion against via AT4R by inhibiting apoptosis and inflammation 
Byung Mun Park, Sun Hwa Lee, Byung Hyun Park, Yuan Kuichang, Suhn Hee Kim
Department of Physiology, Internal Medicine, and Biochemistry, Chonbuk National University Medical School, Jeonju, Korea

S 91  P06-14 Cerelbin gene dysfunction improves cardiac performance and mitochondrial energy metabolism in mice 
Sujin Noh, Hyoung Kyu Kim, Tae Hee Ko, Seung Hun Jeong, In-Sung Song, Sung Ryal Lee, Hye Jin Heo, Nari Kim, 
Kyung Soo Ko, Byoung Doo Rhee, Jin Han
National Research Laboratory for Mitochondrial Signaling, Department of Physiology, College of Medicine, 
Department of Health Sciences and Technology, Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

S 91  P06-15 DQAsome, a Mitochondria targeting carrier, shows cardiac toxicity via supressing cardiac Ca2+ signaling 
Hyoung Kyu Kim, Seung Hun Jeong, Tae Hee Ko, Sujin Noh, In-Sung Song, Sung Ryal Lee, Hye Jin Heo, Nari Kim, 
Kyung Soo Ko, Byoung Doo Rhee, Joon Sig Choi, Jin Han
Cardiovascular and Metabolic Disease Center, College of Medicine, Inje University, Busan, Korea

S 91  P06-16 The difference between vascular smooth muscle contraction and relaxation in four different aortic regions and their 
aortic parameters in rats 
Bolor-Erdene Sarankhuu, Nari Kim*
National Research Laboratory for Mitochondrial Signaling Laboratory, Department of Physiology, College of Medicine, 
Cardiovascular and Metabolic Disease Center, Inje University, Busan 613-735, Korea

S 92  P06-17 Role of Formyl Peptide Receptors on Mobilization of Peripheral Blood Stem Cells in Myocardial Ischemia Injury 
Soon Chul Heo, Yang Woo Kwon, Geun Ok Jeong, Jung Won Yoon, Tae Wook Lee, Il Ho Jang, Jae Kyung Park, Jae Ho Kim*
Department of Physiology, School of Medicine, Pusan National University, Yangsan 626-870, Gyeongsangnam-do, 
Republic of Korea; Research Institute of Convergence Biomedical Science and Technology, Pusan National University 
Yangsan Hospital, Yangsan 626-770, Gyeongsangnam-do, Republic of Korea
S 92  P06-18  Antihypertensive effects of fermented garlic extract through NO-cGMP-PKG pathway in SHR
Byung Mun Park', Seung Ah Cha', Yuan Kuichang', De Gil Kang', Suhn Hee Kim'
'Department of Physiology, Chonbuk National University Medical School, Jeonju, Korea, 'Department of Physiology,
Wonkwang University Oriental Medicine, Iksan, Korea

S 92  P06-19  Echinocochrome A inhibits vascular smooth muscle cell phenotype changing
Kyowon Seo, Seunghun Jeong, Jin Han, Nari Kim
Cardiovascular and Metabolic Disease Center (CMDC), National Research Laboratory for Mitochondrial Signaling, Inje
University, Busan 614-735, Korea

S 93  P06-20  The effect of microRNA-34c on angiogenesis capacity of high glucose-insulted mesenchymal stem cells
Yong Sook Kim', Youngkeun Ahn
'Biomedical Research Institute, Chonnam National University Hospital, Gwangju, South Korea 'Department of
Cardiology, Chonnam National University Hospital, Gwangju, South Korea

P07: Neurophysiology
S 93  P07-01  Epigallocatechin-3-Gallate Rescues LPS-impaired Adult Hippocampal Neurogenesis through Suppressing the TLR4-
NF-κB Signaling Pathway in Mice
'Dental Science Research Institute, Medical Research Center for Biomineralization Disorders, 'Department of Oral
Physiology, 'Department of Oral and Maxillofacial Surgery, School of Dentistry, Chonnam National University,
Gwangju 500-757, Republic of Korea, 'Department of Microbiology, college of Medicine, Seonam University,
Namwon 55724, Republic of Korea

S 93  P07-02  The effect of BD1047 in CCL2 mediated microglia activation in zymosan induced hyperalgesia in rats
Young Bae Kwon
Department of pharmacology, Medical School, Chonbuk National University, Jeonju, Korea

S 94  P07-03  Repetitive motor cortex stimulation for the chronic neuropathic pain
Myoung Hoon Cha, Bae Hwan Lee
Department of Physiology, Yonsei University College of Medicine, Seoul 03722, Korea

S 94  P07-04  Maresin 1 inhibits TRPV1 in temporomandibular joint (TMJ)-related trigeminal nociceptive neurons and TMJ
inflammation-induced synaptic plasticity in the trigeminal nucleus
Sang Taek Im, Lee Eun Lee, Chul-Kyo Park
Department of Physiology, College of Medicine, Gachon University, Incheon 406-799, Republic of Korea

S 94  P07-05  Neuroprotective Effects of Okadaic Acid Following Oxidative Injury in Organotypic Hippocampal Slice Culture
Un Jeng Kim', Kyung Hee Lee', Bae Hwan Lee'
'Department of Physiology, Yonsei University College of Medicine, Seoul 03722, Korea, 'Department of Dental
Hygiene, Division of Health Science, Dongseo University, Busan 47011, Korea, 'Brain Korea 21 PLUS Project for Medical
Science, Yonsei University College of Medicine, Seoul 03722, Korea

S 94  P07-06  NDL-PCBs inhibit store-operated Ca2+ entry
Se-Young Choi', Keimin Lee', Seung-Hyun Lee', Mi-Hyeong Park', Sungkwon Chung', Kyong-Tai Kim'
'Department of Physiology, Dental Research Institute, Seoul National University School of Dentistry, Seoul 110-
749, Korea, 'Department of Life Sciences, Division of Integrative Bioscience and Biotechnology, Pohang University
of Science and Technology, Pohang 790-784, Korea, 'Department of Physiology, Samsung Biomedical Research
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of Bioscience and Biotechnology, BK21 plus Graduate Program, Kangwon National University College of Medicine,
Chunchon 200-701, Korea

S 95  P07-07  The effect of ultrasound stimulation on neurogenesis
Dough Kim', Ha-Jeong Kim', Hak Jong Lee', Hyung Soo Han'
'Department of Physiology, School of Medicine, Kyungpook National University, Daegu 702-422, Republic of
Korea, 'BK21 Plus KNU Biomedical Convergence Program, Department of Biomedical Science, Kyungpook National
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Seoul National University College of Medicine, B2 Gumi-ro 173 beon-gil, Bundang-gu, Seongnam 463-707, Korea
**P07-08(O-7)** Necrotic cells Influence Migration and Proliferation of Glioblastoma cells through NF-kB/IL-8 Signaling
So-Hee Ahn, Hyunju Park, Jiwoo Lim, Yieun Jung, Jihee Lee Kang, Youn-Hee Choi
Department of *Physiology*, Ewha Womans University School of Medicine, Seoul 911-1, Korea, *Tissue Injury Defense Research Center*, Ewha Womans University School of Medicine, Seoul 911-1, Korea

**P07-09** Utilizing Ultrasound to Transiently Increase Blood-Brain Barrier Permeability, Modulate of the Tight Junction Proteins, and Alter Cytoskeletal Structure
Mi Jung Bae1,2, Young Mi Lee1, Seu Yeon Ryu1,2,3, Yeon Hee Kim5, Hyung Soo Han1, Hak Jong Lee1
Department of *Physiology*, BK21 Plus KNU Biomedical Convergence Program, Kyungpook National University School of Medicine, 101 Dongin 2 Ga, Jung Gu, Daegu 700-422, Korea Department of *Radiology*, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 463-707, Korea, *Tumor Heterogeneity and Network (THEN) Research Center*, School of medicine Kyungpook National University, Daegu 700-842, Korea

**P07-10** PAMAM dendrimer-conjugated TA attenuates mechanical allodynia by inhibiting spinal cord microglia activation
Hwisung Kim1, Hyungsuk Lim1, Hyunjung Min1, Sunghyoun Choi1, Jong-sang Park1, Sung Joong Lee1*
Department of Neuroscience and Physiology, Dental Research Institute, BK21-Plus, School of Dentistry, Seoul National University, Seoul 03080, Republic of Korea, *School of Chemistry and Molecular Engineering*, Seoul National University, 599 Gwanak-ro, Gwanak-gu, Seoul, 08826, Republic of Korea

**P07-11** Activation of satellite glia after peripheral nerve injury induces spinal cord microglia activation and neuropathic pain via ganglioside-TLR2 signaling
Hyoun Sub Lim1,2, Hyun Kyoung Lee1, Kyung Chul No1, Byung Hyun You1, Jae Hoon Oh1, Hyuck Jun Mok1, Byung Gon Kim1, Jong-Sang Park1, Kwang Pyo Kim1, Sung Joong Lee1*
Department of Neuroscience and Physiology, Dental Research Institute, BK21-Plus, School of Dentistry, Seoul National University, Seoul 110-799, Republic of Korea, *Interdisciplinary Program in Neuroscience, College of Natural Science*, Seoul National University, Seoul 151-747, Republic of Korea, *Department of Chemistry*, Seoul National University, Seoul 151-747, Republic of Korea, *Department of Applied Chemistry*, College of Applied Sciences, Kyung Hee University, Yongin 446-701, Republic of Korea, *Department of Brain Science and Neurology*, Ajou University School of Medicine, Suwon 443-721, Republic of Korea

**P07-12** Spinal leptin enhances NMDA receptor-mediated tactile hypersensitivity via the reactive oxygen species-phosphatidylinositol 3-kinase (ROS-PI3K) pathway in neuropathic rats
Se Jung Jung1, Euichan Lee2,2, Jae Beom Jun1, Min Kyung Ko1, Joong Woo Leem2
Department of *Physiology*, Brain Research Institute, Yonsei University College of Medicine, Seoul 120-752, Korea

**P07-13** Spinal D-serine induces increase in GluN1 phosphorylation and nociception via nNOS activation in mice: involvement of sigma-1 receptors
Sheu-Ran Choi1, Ji-Young Moon2, Soon-Gu Kwon3, Hoon-Seong Choi1, Mi-Ji Lee1, Ho-Jae Han1, Jang-Hern Lee1*
Department of *Veterinary Physiology*, BK21 PLUS Program for Creative Veterinary Science Research, Research Institute for Veterinary Science and College of Veterinary Medicine, Seoul National University, Seoul 151-742, Republic of Korea, *KM Fundamental Research Division*, Korea Institute of Oriental Medicine, Daejeon 305-811, Republic of Korea

**P07-14** Astrocyte gap junction contribution to development of mirror-image mechanical allodynia in peripheral inflammatory rats: Suppressive effect of spinal interleukin-1β on connexin 43 expression
Hoon-Seong Choi1, Sheu-Ran Choi, Soon-Gu Kwon, Mi-Ji Lee, Ho-Jae Han, Jang-Hern Lee1*
Department of *Veterinary Physiology*, BK21 PLUS Program for Creative Veterinary Science Research, Research Institute for Veterinary Science and College of Veterinary Medicine, Seoul National University, Seoul 151-742, Republic of Korea, *Department of Chemistry*, Seoul National University, Seoul 03080, Republic of Korea

**P07-15** Effects of TCDD exposure on the gonadotropin releasing hormone neurons in mice
Pravin Bhattarai1, Janardhan Prasad Bhattarai1, Dong Hyu Cho2, Seong Kyu Han1
Department of *Oral Physiology*, School of Dentistry & Institute of Oral Bioscience, Chonbuk National University, *Department of Obstetrics and Gynecology*, Chonbuk National University School of Medicine, School of Medicine, Chonbuk National University

**P07-16** Action of calcitriol on NMDA and kainate receptor-mediated actions in juvenile GnRH neurons
Pravin Bhattarai1, Janardhan P. Bhattarai1, Min Sun Kim1, Dong Hyu Cho1, Seong Kyu Han1
Department of *Oral Physiology*, School of Dentistry & Institute of Oral Bioscience, *Department of Pediatrics & Research Institute of Clinical Medicine*, School of Medicine, *Department of Obstetrics and Gynecology*, Chonbuk National University Hospital and School of Medicine, Chonbuk National University

**P07-17** Effect of BPA over pre- and post-natal development of Gonadotropin Releasing Hormone Neurons
Janardhan P. Bhattarai, Seong Kyu Han
Department of *Oral Physiology*, School of Dentistry & Institute of Oral Bioscience, Chonbuk National University, Jeonju
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<td>S98</td>
<td>Loss of Tumor Suppressor PML Promotes Cell Cycle Progression and Proliferation By Enhancing STAT-3 Activity</td>
<td>Jiwoo Lim, Hyunjoo Park, So-Hee Ahn, Yoon-Hee Choi</td>
<td>Department of Physiology, Ewha Womans University School of Medicine, Seoul 911-1, Korea</td>
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<td>S99</td>
<td>Necrotic cells Influence Glioblastoma progression through regulating MCP-1 and MIP-3α expression</td>
<td>Yieun Jung, So-Hee Ahn, Hyunjoo Park, Jihee Lee Kang, Yoon-Hee Choi</td>
<td>Department of Physiology, Ewha Womans University School of Medicine, Seoul 911-1, Korea</td>
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<td>S99</td>
<td>Generation and regulation of pacemaker activity by TRPC3 channels in nigral dopamine neurons</td>
<td>Ki Bum Um, Myoung Kyu Park</td>
<td>Department of Physiology, Sungkyunkwan University School of Medicine, Seoul 911-1, Korea</td>
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<td>S100</td>
<td>Noradrenergic Regulation of Cerebellar Output during Arousal</td>
<td>Seung-Eon Roh, Seung-Ha Kim, Chang-Hop Kim, Yong-Gyu Kim, Sun Kwang Kim, Sang Jeong Kim</td>
<td>Department of Physiology and Department of Biomedical Science, College of Medicine, Seoul National University, Seoul, South Korea</td>
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<td>S100</td>
<td>Treatment With Diluted Bee Venom Reduces Both Spinal Inflammatory Responses And Central Neuropathic Pain Behaviors After Spinal Cord Injury In Rats</td>
<td>Ji-Young Moon, Suk-Yun Kang, Seong Jin Cho, O Sang Kwon, Sun Hee Yeon, Kwang-Ho Choi, Kang-Hem Lee, Yeonhee Ryu</td>
<td>KM Fundamental Research Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea, Department of Veterinary Physiology, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea</td>
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<td>S100</td>
<td>Immunosuppressive effect of estrogen ameliorates pruritic atopic dermatitis in the pubertal female rats</td>
<td>Jeahye Lee, Hye Young Kim, Taeho Har, Seung Keun Back, Heung Sik Na</td>
<td>Neuroscience Research Institute and Department of Physiology, Korea University College of Medicine, 126-1 Anamdong 5 Ga, Seongbuk-Gu, Seoul, 136-705, Korea, Department of Pharmaceutics &amp; Biotechnology, College of Medical Engineering, Konyang University, Chungnam 320-711, Korea</td>
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<td>S100</td>
<td>Spontaneous firing system of substantia nigra dopamine neurons: proximal dendrites as an accelerator and the soma as a counteract balancer</td>
<td>Jinyoung Jang, Myoung Kyu Park</td>
<td>Department of Physiology, Sungkyunkwan University School of Medicine, Seoul 911-1, Korea</td>
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<td>S100</td>
<td>Hypotaurine action mediated by α-homomeric &amp; αβ-hetromeric glycine receptors in medullary dorsal horn neurons</td>
<td>Sun Mi Oh, Seong Kyu Han, Soo Joung Park</td>
<td>Department of Oral Physiology &amp; Institute of Oral Bioscience, School of Dentistry, Chonbuk National University, Jeonju, Korea</td>
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<td>S101</td>
<td>Role of Neuregulin-2 in synaptogenesis in newborn granule cells</td>
<td>Kyu-Hee Lee, Hyun-Su Lee, Che Ho Yang, Won-Ikyung Ho, Suk-Ho Lee</td>
<td>Department of Physiology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul, Korea</td>
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<td>S101</td>
<td>Portal hypertension is associated with the impairment of arterial baroreflex and hypoexcitability of aortic baroreceptor neurons in cirrhotic rats</td>
<td>Choong-Ku Lee, Jae-Won Lee, Seong-Woo Jeong</td>
<td>Department of Physiology, Yonsei University Wonju College of Medicine, Wonju 220-701, Korea</td>
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<td>S102</td>
<td>Intraplantar injection of DHEAS or PREGS enhance P2X mediated mechanical allodynia via sigma-1 receptors in rats</td>
<td>Soon-Gu Kwon, Sheu-Ran Choi, Hoon-Seong Choi, MIJ Lee, Jang-Hem Lee</td>
<td>Department of Veterinary Physiology, BK21 PLUS Program for Creative Veterinary Science Research, Research Institute for Veterinary Science and College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea</td>
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<td>S102</td>
<td>Investigation of leak channels important for pacemaking in the nigral dopamine neurons</td>
<td>Su Yun Hahn, Myoung Kyu Park</td>
<td>Department of Physiology, Sungkyunkwan University School of Medicine, Seoul 911-1, Korea</td>
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P07-31 LTP of dendritic spines in nigral dopamine neurons: possible link of reward and burst
Min Jung Kim, Miae Jang, Myyoung Kyu Park
Department of Physiology, Sungkyunkwan University School of Medicine, 2066, Seobu-ro, Janganggu, Suwon, KOREA

P07-32 Electroacupuncture alleviates mechanical allodynia via spinal opioidergic and alpha2-adrenergic mechanisms in oxaliplatin- or vincristine-induced neuropathy mice model
Jung-Wan Choi1, Suk-Yun Kang1, Kwon O Sang1, Yeon Sun Hee1, Yeon-Hee Ryu1, Hyun-Woo Kim2
1Korea Institute of Oriental Medicine, Daejeon, 305-811, South Korea 2Department of Physiology and Institute of Brain Research, Chungnam National University School of Medicine, Daejeon, 301-747, South Korea

P07-33(O-13) Agonist-independent activity of mGluR1 underlies homeostatic control of intrinsic excitability via IH in cerebellar Purkinje cells
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P07-34 Distinct responses of vagal and splanchnic nerves innervating liver to 5-HT receptor agonists in Guinea pigs
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P07-35 Primary afferents temporally encode the noxious stimulus for pain signaling
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P07-36 Three distinct cerebellum-dependent eye movement learning in pcp2-cre mice
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P07-37 Dysregulation of metabotropic glutamate receptor 5 in periaqueductal gray perpetuate chronic neuropathic pain
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P07-38 Upregulation of prelimbic metabotropic glutamate receptor 5 in chronic neuropathic pain state
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P07-39 Changes in Field Potentials Following Transcranial Direct Current Stimulation on the Motor Cortex of Rats in Vivo
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P07-40 Characterizing the function of Negr1, a newly-identified obesity-related gene, in the nervous system
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P07-41 The role of GABA on the motivational driving force for the pain attenuation following spinal cord injury in rats
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P07-42 Carvacrol inhibits mGluR1-evoked slow currents in cerebellum
Da Eun Jeon, Sang Jeong Kim
Department of Physiology, College of Medicine, Seoul National University
P07-43  Anti-inflammatory role of cytoplasmic Ref-1 in cultured astrocytes  
Hyang-Joo Lee, Hyun-Sil Chae, Sudip Pandit, Yoon-Hyung Pai, Byeong Hwa Jeon, Jin Bong Park  
Department of Physiology, Brain Research Institute, School of Medicine, Chungnam National University, 6 Munhwa-Ro, Jung-gu, Daejeon, 301-131, Republic of Korea

P07-44  Clonidine, an alpha-2 adrenoceptor agonist relieves mechanical allodynia in oxaliplatin-induced neuropathic mice; potentiation by spinal p38 MAPK inhibition without motor dysfunction and hypotension  
Ji-Hee Yeo, Seo-Yeon Yoon, Sol-Ji Kim, Jang-Hern Lee, Alvin J. Beitz, Dae-Hyun Roh  
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P07-45  Role of capsaicin-sensitive primary afferents in the development of hypersensitivity in a new mouse model for nitroglycerin-induced chronic migraine  
Sol-Ji Kim, Seo-Yeon Yoon, Ji-Hee Yeo, Dae-Hyun Roh  
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P08: Physiome and Systems Biology

P08-01  Altered rhythmic behaviors in Alzheimer’s disease model flies by dim light exposure at night  
Manivannan Subramanian, Mari Kim, Eunil Lee, Joong-Jean Park  
Department of Physiology, "Department of Preventive Medicine, Korea University College of Medicine, 73 Incheon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea

P09: Renal, Respiratory and Reproductive Physiology

P09-01  Signals governing the trafficking of PKD1L1 and PKD2L1 to primary cilia  
Kotdaji Ha, Insuk So  
Department of Physiology, Seoul National University, College of Medicine, Seoul, Republic of Korea

P09-02  Klotho ameliorates proteinuria through protecting podocyte injury  
Ji-Hee Kim, Kyu-Hee Hwang, Seong-Woo Jeong, In Deok Kong, Kyu-Sang Park, Seung-Kyu Cha  
Departments of Physiology and Global Medical Science, "Institute of Lifestyle Medicine and Nuclear Receptor Research Consortium, Yonsei University Wonju College of Medicine, Wonju, Gangwon-do, Republic of Korea

P09-03  Klotho inhibits tumor progression by IGF-1 receptor activation in human clear cell renal cell carcinoma  
Ji-Hee Kim, Kyu-Hee Hwang, Minseob Eom, Seong-Woo Jeong, In Deok Kong, Kyu-Sang Park, Seung-Kyu Cha  
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P09-04  Orai1 expression is closely related with favorable prognostic factors in clear cell renal cell carcinoma  
Kyu-Hee Hwang, Ji-Hee Kim, Sayamaa Khagavadorj, Minseob Eom, Kyu-Sang Park, Seong-Woo Jeong, In Deok Kong, Seung-Kyu Cha  
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P10: Other Area

P10-01  Improved application of the electrophoretic tissue clearing technology, CLARITY, to intact solid organs  
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Department of Physiology, Keimyung University School of Medicine, 1095 Dalgubeoldaero, Dalseo-Gu, Daegu, 704-701, Korea

P10-02  The Effect of Bio-active Materials Coated Fabric on Rat Skeletal Muscular Mitochondria  
Donghee Lee, Young-Won Kim, Misuk Yang, Hyemi Bae, Inja Lim, Hyowoon Bang, Jae-Hong Ko  
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Identification of Primo-Vascular System in Abdominal Subcutaneous Tissue Layer of Rats
Chae Jeong Lim, So Yeong Lee, Pan Dong Ryu
Laboratory of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul 151-742, Republic of Korea, Seoul 151-742, Republic of Korea

Toll-like Receptor 2 is Dispensable for an Immediate-early Microglial Reaction to Two-photon Laser-induced Cortical Injury In vivo
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MLN4924 can promote U373MG cell migration via src dependent phosphorylation of caveolin-1
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Study investigated the effects of Oligonol supplementation on sudomotor activity during heat load in human subjects
Jeong Beom Lee, Sun Jong Kang, Sang Eun Im, Jae Young Heo, Hyoung Soo Kim, Sung Mook Kim, Hyun Kyu Kang, Jung Ho Kim, Sung Woon Kim
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The role of TRPM7 in the progression of human renal cell carcinoma (RCC)
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A novel function of JHDM in Hepatic steatosis
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KSP inhibitor SB743921 induces death of multiple myeloma cells via inhibition of the NF-kB signaling pathway
Bayalamaa Nyamaa, In Sung Song, Yu Jeong Jeong, Hyoung Kyu Kim, Naru Kim, Jin Han
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The Effect of Low-Intensity Ultrasound in Resolution of Synovitis
Jee-In Chung, A Young Kim, Sumit Barua, Soo Yeon Lee, Eun Joo Baik
Department of Physiology, Department of Biomedical Science, Chronic Inflammatory Disease Research Center, Ajou University School of Medicine, Suwon, Korea

Role of CXCR2 in Acetylated Pro-Gly-Pro(Ac-PGP)-induced Vascular Regeneration in Murine Hind limb Ischemia Model
Yang Woo Kwon, Soon Chul Heo, Jung Won Yoon, Tae Wook Lee, Ba Reun Kim, Geun Ok Jeong, Jae Ho Kim
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S 112 P10-13 Wnt signaling pathway augments Endothelial Progenitor Cells commitment and its angiogenic potential through SDF1-CXCR4 axis
Yeon Ju Kim, Sang Mo Kwon
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S 112 P10-14(O-9) The Sulfated Polysaccharide Fucoidan Rescues Senescence of Endothelial Colony Forming Cells for Ischemic Repair
Jun Hee Lee¹, Takayuki Asahara², Sang-Mo Kwon¹
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S 113 P10-15 Novel angiogenic peptide stimulates mouse hindlimb ischemia repair
TaeWook Lee, YangWoo Kwon, SoonChul Heo, Ilho Jang, JaeHo Kim
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S 113 P10-16 Caffeine links dopamine, serotonin and prolactin release during thermal stress in human
Tae Wook Kim¹, Jeong Bum Kang¹, Jeong Beom Lee¹, Sun Jong Kang¹, Sang Eun Im¹, Jae Young Heo¹, Hyun Soo Kim¹, Sang Mook Kim¹, Hyun Kyo Kang¹, Jung Ho Kim¹, Sung Woon Kim¹
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S 113 P10-17 Improved sweat gland function during active heating in physically trained human
Jeong Beom Lee¹ *, Tae Wook Kim¹, Jeong Bum Kang¹, Sun Jong Kang¹, Sang Eun Im¹, Jae Young Heo¹, Hyun Soo Kim¹, Sang Mook Kim¹, Hyun Kyo Kang¹, Jung Ho Kim¹, Sung Woon Kim¹, Sang Woo Jang¹
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S 114 P10-18 Assessment of eye irritation potential of hair dye chemicals using human conjunctival keratinocytes
Ju Hyun Lim¹, Jeong Bum Bae¹, Hae-Rahn Bae¹
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S 114 P10-19 Effect of Samultang on HO-1 Mediated Vascular protection in HUVECs
Eun Sik Choi¹, Yun Jung Lee¹, Jung Joo Yun¹, Min Chol Kho¹, Ji Hun Park¹,², Xian Jun Jin¹,²,³,*, Daegi Kang¹,²,³,*, Ho Sub Lee¹,²,³,*,
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S 114 P10-20 Inhibitory Mechanism of Samchuleum on Renal Fibrosis
Jung Joo Yoon¹, Yoon Jung Lee¹, Byung Hyuk Han¹,²,³,*, Seung Namgung¹,²,³,*, Min Chol Kho¹,²,³,*, Ji Hun Park¹,²,³,*, Daegi Kang¹,²,³,*, Ho Sub Lee¹,²,³,*,
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S 115 P10-21 Inhibitory Effect of Hwagryunhaedoktang on TNF-α-induced vascular inflammation in human umbilical vein endothelial cells
Byung Hyuk Han¹,²,³,*, Yoon Jung Lee¹,²,³, Eun Sik Choi¹,²,³, Seung Namgung¹,²,³,*, Xian Jun Jin¹,²,³,*, Ho Sub Lee¹,²,³,*, Daegi Kang¹,²,³,*,
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S 115 P10-22 Study on the mechanism of vascular relaxation by mantidis ootheca
Hye Yoom Kim¹,²,³,*, Yoon Jung Lee¹,²,³,*, You Mee Ahn¹,²,³,*, Rui Tan¹,²,³,*, So Heun Lee¹,²,³,*, Han Sol Lee¹,²,³,*, Daegi Kang¹,²,³,*, Ho Sub Lee¹,²,³,*,
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Mitochondrial DNA causes spreading necrosis in the heart

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The past decade has seen a marked improvement in outcomes in patients with acute myocardial infarction (AMI) treated by reperfusion with percutaneous intervention (PCI). Much of that improvement appears to derive from loading with platelet P2Y12 ADP receptor inhibitors prior to PCI to block platelet aggregation. In animals clodipogrel, cangrelor, and ticagrelor have powerful anti-infarct effects themselves. Importantly, no additional protection occurs when any of the above platelet inhibitors is combined with ischemic pre- or postconditioning, presumably because the platelet inhibitor has already "conditioned" the heart. That is reflected in the disappointing results of all clinical trials of ischemic postconditioning that have been conducted since loading with platelet inhibitors gained widespread use. Unfortunately, although post-infarction morbidity and mortality has been cut in half by anti-platelet drugs, it is far from eliminated. While further protection is needed, conditioning based therapies will not provide it. Any effective treatment must target a process of cell killing against which conditioning is unable to protect. We recently found evidence that much of the cell death that occurs in myocardial infarction is due to inflammatory pyroptosis triggered by mitochondrial (mt) DNA released from dying myocardial cells. We propose that infarction is due to inflammatory pyroptosis triggered by mitochondrial DNA released from dying myocardial cells. DNase treatment also has an additive effect when combined with cangrelor. Another approach is DNase-1 given iv at reperfusion to destroy any extracellular mtDNA. DNase limits infarction in both in situ and neutrophil-free, isolated hearts. DNase treatment also has an additive effect when combined with cangrelor. Giving purified rat liver mtDNA to the isolated heart increases infarct size showing that it is very toxic; incubating mtDNA with DNase prior to injection detoxifies it. Fragments of mtDNA are known activators of TLR9. Accordingly, TLR9-activating oligodeoxynucleotides also increase infarct size in this model suggesting that TLR9 is probably involved in the toxicity. We conclude that strategies that prevent mtDNA-induced inflammation are very likely to effectively reduce infarct size in today's AMI patients.

Enlargement of myocardial infarct size by chronic kidney disease: a novel mechanism of disruption of Akt-GSK3beta/p70S6K signaling

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Chronic kidney disease (CKD), defined as chronic reduction of glomerular filtration rate and/or proteinuria, is a major risk factor of cardiovascular events and mortality after myocardial infarction. Enlargement of infarct size by CKD has been demonstrated in animal models, but its mechanism remains unclear. Our previous studies showed that different co-morbidities, including hypertension and diabetes, disrupt intracellular signaling pathways at distinct steps upstream of GSK3beta/p70S6K phosphorylation (Miki et al. Circulation 2000, Miki et al. Diabetes 2009, Yano et al. Hypertension 2011, Hotta et al. Circ Res 2010). Here we systematically analyzed the effect of CKD on cytoprotective signaling by use of a rat model of CKD, two-stage 5/6 nephrectomy. Infarct size after 20-min ischemia/2-h reperfusion was larger by 30% in CKD than in the control. CKD increased the level of Thr308 phosphorylation in Akt at baseline by 37%, though its levels upon reperfusion were similar in CKD and the control. In contrast, phosphorylation of Akt at Ser473 upon reperfusion was significantly suppressed by CKD, though its baseline phosphorylation level was unaffected. Inhibition of Akt-Ser473 phosphorylation upon reperfusion by Ku-0063794, an mTOR inhibitor, significantly enlarged infarct size in control rats. Protein levels of PDK1 and mTORC2, which phosphorylate Thr308 and Ser473 in Akt, respectively, were not changed by CKD. However, of PP2A regulatory subunits, B55alpha, a subunit targeting Thr308 in Akt, was selectively reduced by 24% in CKD. By overexpressing HA-tagged wild-type Akt and phospho-Thr308-mimetic mutant Akt (T308D) in HEK293 cells, we found that constitutive phosphorylation of Akt-Thr308 negatively regulates the response of Akt-Ser473 phosphorylation to its upstream signaling. These results indicate that a novel mechanism of Akt-GSK3beta/p70S6K signaling disruption, i.e., intramolecular inhibition of Ser473 phosphorylation, is responsible for the decrease in Akt phosphorylation by reduction of B55alpha-mediated Thr308 dephosphorylation, contributes to infarct size enlargement by CKD.
Cardioprotection against I/R injury via alleviating intracellular Ca2+ injurious but insufficient to reach the threshold to efficiently trigger reperfusion following ischemia in I/R injury and protection. Our results post-conditioning, we studied the level and roles of ROS during early muscle cells (PASMCs) express eNOS. In deep femoral arteries (DFAs) of arterial smooth muscle cells (DFASMCs) and pulmonary arterial smooth expresses eNOS. Since the activation of eNOS is triggered by increased from endothelium, and vascular smooth muscle is conventionally The role of eNOS is well known as the source of vasorelaxing NO released pulmonary arteries. Key Words: nitric oxide, eNOS, smooth muscle, hypoxia, skeletal artery, pulmonary artery, stretch
in murine ventricular cardiomyocytes and that deletion of the Trpm4 gene leads to shorter ventricular action potentials. To characterize if deletion of Trpm4 has an effect on the conduction properties of the heart, an in depth electrophysiological study was performed in living mice. An octopolar catheter was inserted into the right atrium and ventricle of the heart to measure intracardial electrograms. The atrial-His (AH) and His-ventricular (HV) intervals were calculated and no differences were found between WT and Trpm4-/- mice. Additionally, more detailed conduction parameters of the heart were determined by use of programmed electrical stimulation (PES) protocols. Sinus node recovery time (SNRT) was not different between WT and Trpm4-/- mice. Effective refractory period of atrium (AERP), AV node (AVERP) and ventricle (VERP) were in the same range in WT and Trpm4-/- mice. Wenckebach periodicity, the parameter for AV nodal conduction, was also not different between WT and Trpm4-/- mice. These results suggest that deletion of Trpm4 has no effects on the conduction properties of the murine heart.

PAS-8

Bicarbonate permeation through anion channels
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Anion channels are an essential component of the cells for keeping them alive and mediating their diverse functions. Although many anions can permeate anion channels, chloride and bicarbonate are the two most abundant anions that can be the charge carrier of anion channels in animal cells. Increasing evidence indicates that bicarbonate permeation though anion channel is involved in many basic biologic processes ranging from epithelial fluid secretion to neuronal excitation. However, the principle of ion selection and permeation by the anion channels, in particular that of bicarbonate, is largely unknown. By employing an integrated study of combined molecular, physiological, structural, and mathematical approaches, we provide evidence that electric permittivity and channel pore diameter are cardinal features, which determine the ion selectivity of anion channels. Importantly, many cellular stimuli dynamically modulate anion channel ion selectivity by changing pore size. Pore size change affects the bicarbonate permeability of anion channels by altering energy barriers of size-exclusion and ion dehydration of bicarbonate permeation. These findings provide key insights into the mechanism of how the ion permeation and selectivity of anion channels are determined.

PAS-9

Orai1 in ER/PM junctions
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When activated Orai1 and STIM1 cluster at ER/PM junctions both in model systems and in vivo. Until recently, the proteins that tether the ER and plasma membrane were not known and how targeting the STIM1-Orai1 complex to the ER/PM junctions affects channel activity. In this presentation the role of tether proteins in recruitment of the Orai1-STIM1 complex to specific ER/PM junctions and its regulation by SARAF that mediated the Ca2+-dependent inactivation of Orai1 will be discussed. In polarize secretory cells, like acinar cells Orai1 and STIM1 are assembled at apical pole ER/PM junctions. The significance of Orai1 function in pancreatic acinar cells junctions, as a model for other secretory cells, will be discussed.

PAS-10

Endosomal and lysosomal chloride/proton exchange by CLC proteins: surprising roles in physiology and pathology
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The CLC family of anion transporters comprises both plasma membrane Cl- channels and vesicular 2Cl-/H+-exchangers that are differentially expressed along the endosomal-lysosomal pathway. Their physiological and medical importance became apparent from human genetic disease and mouse models. CIC-5 is expressed on endosomes, mainly in epithelia. Its mutation in human Dent’s disease leads to proteinuria and kidney stones. Our KO mouse model revealed that CIC-5 is important for proximal tubular endocytosis. It disruption leads to hypercalciuria and kidney stones because of defective endocytosis and processing of calcitropic hormones. CIC-7, together with its beta-subunit Ostm1, resides on lysosomes. Disruption of either subunit leads to lysosomal storage, neurodegeneration and osteopetrosis in mice and men. CIC-4 mutations lead to human mental retardation, while disruption of CIC-3 and CIC-6 in mice entail neurodegeneration. The role of these transporters in endosomal/lysosomal function was previously attributed exclusively to impaired vesicular acidification, as these transporters may provide a shunt for the vesicular proton ATPase. While a role of CIC-5 in endosomal acidification has been ascertained, the lysosomal pH of CIC-7 KO mouse is, however, unchanged owing to a parallel cation conductance. We were puzzled by the fact that the vesicular CLCs are 2Cl-/H+-exchangers rather than Cl- channels. Both are suited, in principle, as shunts for proton pumping. We asked whether chloride/proton exchange is essential for their function and converted CIC-3, CIC-5 and CIC-7 into pure chloride conductances in KO mice. This is possible by single point mutations. Surprisingly, these mice revealed that these mice have almost identical phenotypes as the respective KO mice, suggesting an important role for H+-exchange dependent vesicular Cl- accumulation or changes in vesicular voltage. Another CIC-7 mouse model, in which we disrupted its ion transport totally without affecting the expression of the protein, furthermore indicated that the loss of protein-protein interactions explains some aspects of the CIC-7 KO mouse.
A short tribute to Pflügers Archiv (The European Journal of Physiology) and a sojourn to an endothelial anion channel  

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This lecture will comprise two parts: **First**, a short description of the oldest Physiology journal in the world will be given highlighting the main achievements which were published since 1868. This will be a short historical, philosophical sojourn. **Second**, I will shortly refer to one of the last orphan ion channels, the “Volume Regulated Anion channel (VRAC)”.* This channel is a main player in cellular volume regulation and plays an important functional role in the vascular endothelium, especially related to “Regulatory Volume Decrease” (RVD) and “Apoptotic volume decrease” (AVD). VRAC is activated by hypotonic cell challenges, by GTPγS, and as a more principle mechanisms by decreased intracellularionic strength. Several activation cascades will be discussed. Endothelial VRAC is slowly activated, shows variable inactivation at positive potentials, has a single channel of ~50 pS in outward direction versus ~10 pS inward direction, thus, rectification reflects no change in open probability but in conductance. Its permeation profile: I- > Cl-. Important physiological effects of VRAC for endothelial function will be described, e.g. the involvement in the driving force for Ca2+ entry into endothelial cells and its role in regulation of endothelial cell proliferation and also angiogenesis.  

The discovery of VRAC, stimulated many laboratories worldwide to analyze this sensor in many other cell types and to unravel the activation mechanisms of this channel. Unfortunately, it turned out to be extremely difficult to identify the molecular identity of this channel. Until the end of 2014, more than 10 possible candidates for VRAC have been put forward (for a comprehensive review see 1,2). Thus, during the last 15 years, shrinking and expanding list of candidates comprised P64 intracellular Cl channels ClC1, the Band 3 exchanger of chloride for drug resistance transporter MDR1 (a member of the superfamily of ATP-binding cassette transporters), the small cytosolic protein ICln (possibly a protein involved in spliceosomal snRNP, small nuclear ribonucleic particles, biogenesis), VDAC (Voltage-dependent anion channels, a class of porin ion channel located on the outer mitochondrial membrane) and recently TMEM16F (ANo6, probably Ca2+ activated Cl channels, scramblases of even cation channels). Now finally, the true nature of VRAC has been identified independently by two laboratories via screening of large whole-genome human siRNA libraries. The Leucine-Rich Repeats Containing 8A (LRRC8A) protein, belonging to family of proteins (LRRC8A-E) distantly related to pannexins, is likely the pore-forming subunit of VRAC (see 3,4). I will finally describe some properties of the LRRC8 proteins, highlight some features of the LRRC8A knockout mouse, and discuss the impact of the discovery of LRRC8 as VRAC on future research. The Lrcc8 gene has been first discovered in a girl with a gamma-globulinemia and has been identified as a component of the pre-B-cell receptor (pre-BCR) (see also 5). Surprisingly, in the LRRC8A ko, no B cell defect but severe problems with T-cell development, thymocyte depletion, survival and function have been described. There are also some striking puzzles left: over expression does not increase the current, pore identification is still weak, the knock outs have in addition to a T cell phenotype, an increased early in utero mortality, increased postnatal lethality, growth retardation, curly hair, hind limb weakness, hydropnephrosis, sterility, epidermal hyperkeratosis, thin skeletal muscle bundles, vacuolar renal tubular cells (cysts), and no ovarian corpora lutea (see 5). The link to the vascular function has still to be evaluated. More striking and exciting new properties are to expect and we are obviously in the beginning of an in depth understanding of the important ubiquitous anion channel VRAC.  

**References**  
Clinical application of human iPS cells for cardiovascular Medicine

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Although heart transplantation can drastically improve the survival, shortage of the donor heart is a serious problem. The regenerative medicine of the failing heart had been long awaited. To address this question, we had developed novel methods to induce human iPS cells from circulating human T lymphocytes using Sendai virus containing Yamanaka 4 factors. We had screened the factor that were expressed in future heart forming area of the early mouse embryo, found several growth factors and cytokines that can induce cardiomyocytes differentiation and proliferation, and applied them to human iPS cells. We performed transcriptome of the metabolic enzymes and fluxome analysis using 13glucose and 13lactic acid on ES/iPS cells and cardiomyocytes, and found that their metabolic pathways were completely different. Based on these findings, we purified cardiomyocytes using glucose-free lactate-supplemented medium. Purity of the cardiomyocytes was >99%, and they did not make teratoma formation. The transplanted cardiomyocytes using our technique can survive in the heart with more than 90%, and can show physiological growth after transplantation. Transplantation of ES/iPS-derived cardiomyocytes into the infarcted myocardium could improve cardiac function in rat and porcine model. We expect the combination of these techniques can achieve future heart regeneration.

CURRICULUM VITAE

Name: Keiichi Fukuda, M.D., Ph.D, FACC

Academic Career
1983 Graduated Keio University School of Medicine, Tokyo, Japan
1983 - 1987 Post Graduate School, Keio University, Tokyo, Japan
1987 PhD in Clinical Cardiology
1983 – 1985 Resident in Internal Medicine, Keio University School of Medicine
1985 – 1991 Resident in Cardiology, Keio University School of Medicine
1991 – 1992 Growth Factor Division, National Cancer Center Research Institute
1992 – 1994 Dept of Molecular Medicine, Beth Israel Hospital, Harvard Medical School
1994 – 1995 Cardiovascular Research Center, University of Michigan
1995 – 1999 Lecturer, Department of Cardiology, Keio University School
1999 – 2004 Assistant Professor, Institute for Advanced Cardiac Therapeutics, Keio University
2005 – 2010 Professor, Dept of Regenerative Medicine, Keio University
2010-Present Professor, Department of Cardiology, Keio University
2007 – Present Vice Dean, Keio University School of Medicine

Honors and Awards
1. Keio University School of Medicine Sanshikai Kitajima Prize (2000)
2. Tokyo Metropolitan Medical Association Medical Prize (2001)
7. Mochida Memorial Medical Science Prize (2011)
8. Imura Memorial Clinical Research Award (2012)
9. President lecture Award of International Society for Heart Research (2014)
Ca\textsuperscript{2+}-activated K\textsuperscript{+} channel expression on cell membrane in physiological and pathophysiological conditions

Shinkyu Choi, Ji Aee Kim, Suk Hyo Suh

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Ion channels play key roles in the control of cellular functions, and thus cellular functions are greatly affected by altered expression of ion channels on cell membrane. Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels (K\textsubscript{Ca}1.1, K\textsubscript{Ca}2.3, and K\textsubscript{Ca}3.1), which are expressed in smooth muscle cells (SMCs) and endothelial cells (ECs), regulate cellular functions by modulating Ca\textsuperscript{2+} influx through Ca\textsuperscript{2+} entry channels or endothelium-dependent responses, such as NO release and endothelium-dependent hyperpolarization. Altered expression of these Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels on cell membrane was found in physiological (normal pregnancy, and aging) and pathophysiological (aging, and vascular diseases such as pregnancy-induced hypertension and Fabry diseases) conditions.

K\textsubscript{Ca}1.1, or K\textsubscript{Ca}2.3 and K\textsubscript{Ca}3.1 was upregulated in gastric SMCs or ECs from aged mice, respectively, compared to young mice. Ca\textsuperscript{2+}-activated K\textsuperscript{+} currents were markedly increased without affecting the channel activity. K\textsubscript{Ca}1.1 upregulation in gastric SMCs impaired intracellular Ca\textsuperscript{2+} mobilization and decreased p-MLC levels, causing contractile dysfunction of aged gastric smooth muscle. On the other hand, endothelial K\textsubscript{Ca}2.3, and K\textsubscript{Ca}3.1 upregulation markedly increased K\textsubscript{Ca}3.1 activation-induced, NO- and prostacyclin-resistant endothelium-dependent relaxation, and thereby compensating diminished endothelium-dependent relaxation to NO in aged mice. In addition, K\textsubscript{Ca}2.3, and K\textsubscript{Ca}3.1 were upregulated in ECs from normal pregnancy, which might cause pregnancy-associated vasodilation and angiogenesis. On the other hand, K\textsubscript{Ca}2.3, and K\textsubscript{Ca}3.1 were downregulated in ECs from vascular diseases, such as pregnancy-induced hypertension and Fabry disease, and the downregulation of these K\textsuperscript{+} channels contributes to endothelial dysfunction in vascular diseases. Finally, we'll discuss about the mechanisms to control the expression of these K\textsuperscript{+} channels on cellular membranes.

**Key Words:** Ca\textsuperscript{2+}-activated K\textsuperscript{+} channel, Smooth muscle cells, Endothelial cells, Cellular dysfunction, K\textsuperscript{+} channel expression on cell membrane

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**CURRICULUM VITAE**

**Name:** Suh, Suk Hyo

**Academic History**

1985 Seoul National University, College of Medicine, B.S., M.D.
1993 Seoul National University, Ph.D. (Physiology)

**Professional Experience**

1995-2006 Assistant Professor, Department of Physiology, College of Medicine, Ewha Women’s University
1998-2000 Guest Professor, Catholic University in Leuven (Belgium)
2006-Present Professor, Department of Physiology, College of Medicine, Ewha Women’s University

**Publication List (Representatives)**

Epidemic increases of the obesity in the industrialized countries not only deterioration personal health but also become heavy burden for national health care system by increasing health care costs. To address this problem, great effort has been made to investigate body weight regulation mechanism and found that hormones originate from adipose tissue, intestine, pancreas, and hypothalamus regulate energy balance via activating neurons in hypothalamus, vagus nerve and nucleus tractus solitarii (NTS). Among them, two distinct type neurons each of them co-express agouti-related peptide and neuropeptide Y (AgRP/NPY neuron) or proopiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART neuron) was become primary research subject. Many hormones that activate POMC/CART neuron reduce appetite and increased energy expenditure. Contrary, activation of AgRP/NPY neuron has opposite effect. POMC/CART expressing neuron is present both of the arcuate nucleus (ARC) neurons of the hypothalamus and NTS but until recently most of the obesity research focused on neuron in ARC. In addition that nutrients and sensory signals including mechanical stimuli from other brain regions are integrated with ARC-mediated hormonal signal for regulate energy balance. Despite latest advances, still there is no effective medicine which can break or slow down epidemic increase of obesity. In this presentation, I will make short summary of the recent progress in obesity research and will discuss about why such progress couldn’t lead to new drug development. In addition, I will introduce some alternative attempts to reduce appetite by stimulating satiety transmitting cranial vagus nerves.

Key Words: Obesity, metabolism, appetite, vagus nerve, nucleus tractus solitarii
Recent advances in studying tactile sensation
Kyung Chul Shin, Hyunji Park, Sang Woong Park, In-Hwa Lee, Jae Gon Kim, Young Min Bae
Department of Physiology Konkuk University School of Medicine

Compared with other types of senses, understanding of tactile sensing is relatively undeveloped because molecular identities of the ion channels that mainly contribute to the generation of receptor potentials at mechanosensing cells are not fully uncovered yet. Transient receptor potential, degenerin/epithelial Na channels, and piezo have been known as good candidates for the ion channels of mechanoreceptors. Activation of these channels generates inward currents and receptor potential in a physiological setting. Especially, critical roles of piezo2 ion channel in Merkel cells and their Aβ afferent fibers have been suggested in a couple of recent studies. In this talk, I’ll briefly review on this promising piezo2 touch-sensing channel. In addition, I would like to suggest a possibility of non-contact tactile sensation based on the following observations: To validate the feasibility of utilizing laser for non-contact tactile stimulation, we provide evidence at cell and ion channel levels. We found that 532 nm laser-stimulation activated the piezo-like mechanosensitive ion channels in mechanosensing neuro2a and Merkel cells, which implies the plausibility of non-contact tactile sensation using laser. These results support the hypothesis that laser stimulation may induce tactile sensation by activating mechanosensitive ion channels of somatosensory cells in human skin.

Key Words: Tactile sensation, Piezo, Merkel cell, Laser, Non-contact

Physical responses to pulsed laser stimulation in human skin
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Recently, it has been demonstrated by physical, perceptual, and simulation studies that laser-induced thermoelastic effects in human skin can evoke tactile sensations. The temporal evolution of the thermoelastic effects induced by pulsed laser absorption in human skin can be divided into four regimes: heating, transient, quasi steady-state, and thermal diffusion regimes. When the inertial or stress confinement condition is met in the heating regime, very high thermoelastic stresses build up. In the transient regime, the skin reconfigures itself as it responds to the forces caused by the thermoelastic stresses. In the quasi steady-state regime, the skin reaches mechanical equilibrium state, where the net force becomes zero but the thermoelastic stresses still exist because of the nonuniform temperature distribution. In the last, or thermal diffusion, regime, the thermoelastic stresses decay to zero as the temperature distribution becomes uniform by the thermal diffusion process. In this presentation, physical responses to pulsed laser stimulation in human skin are investigated in terms of the laser-induced thermoelastic effects. Optical, thermal, and mechanical responses to pulsed laser absorption in human skin are examined in detail.

Key Words: Laser–tissue interactions, thermoelastic effects, photomechanical effects

Cortical Responses to tactile sense induced by laser in humans
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The present study investigates the human cortical responses to tactile stimuli generated by laser. Laser has been primarily used in neurophysiological studies to evoke nociceptive feelings in humans. However, our recent study has shown that laser could evoke non-nociceptive tactile sensations in humans. We examine human cortical activity related to such non-painful feelings by laser and compare different cortical activities when participants experienced painful feelings or non-painful feelings. The human EEG is particularly measured and analyzed to study cortical responses. The sensorimotor rhythms in the alpha and beta frequency bands are main features examined here. We also utilize the decoding analysis to compare cortical patterns in response to different tactile stimuli. Taken together, we demonstrate that cortical responses to non-nociceptive laser stimuli are more similar to those to mechanical stimuli than to those to painful stimuli or thermal stimuli.

Key Words: laser, EEG, tactile, sensorimotor

When nanoscience meets optogenetics
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Nanoparticle-mediated delivery of functional macromolecules is a promising method for treating a variety of human diseases. Among nanoparticles, cell-derived exosomes have recently been highlighted as new therapeutic strategies for the in vivo delivery of nucleotides and chemical drugs. Here, we describe a new tool for intracellular delivery of target proteins, named ‘exosomes for protein loading via optically reversible protein–protein interaction’ (EXPLOR). By integrating a reversible protein–protein interaction module controlled by blue light with the endogenous process of exosome biogenesis, we were able to successfully load cargo proteins into newly generated exosomes. Treatment with protein-loaded EXPLORs was shown to significantly increase intracellular levels of cargo proteins in recipient cells in both a time- and dose-dependent manner. These results clearly indicate the potential of EXPLORs as a mechanism for the efficient intracellular transfer of protein-based drugs into recipient cells and tissues both in vitro and in vivo.

Key Words: optogenetics, drug delivery, protein transduction
Mitochondria are pivotal organelles as ATP producing factories as well as Ca\(^{2+}\) stores. However, the mechanisms and physiological significance of mitochondrial Ca\(^{2+}\) dynamics are not well understood. To get more insight into the mechanisms and significances, we performed physiome studies by combining wet physiological experiments and in silico mathematical analyses, especially focusing on mitochondrial Ca\(^{2+}\) extruding Na\(^+/Ca\(^{2+}\) exchanger (NCLX). In B lymphocytes, analyses of a mathematical model predicted that NCLX activity affects endoplasmic reticulum (ER) Ca\(^{2+}\) content and antigen receptor-mediated cytoplasmic Ca\(^{2+}\) rise. The model predictions were validated by NCLX knockdown and knockdown in DT40 and A20 B lymphocytes and by pharmacological inhibition of NCLX. In HL-1 cardiomyocytes, NCLX knockdown resulted in reduction of sarcoplasmic reticulum (SR) Ca\(^{2+}\) content and in prolongation of cycle length of spontaneous Ca\(^{2+}\) oscillation and action potential generation. Our mathematical model well reproduced and explained the experimental results. We propose that NCLX functions as a Ca\(^{2+}\) provider to ER/SR and is important for antigen receptor-induced Ca\(^{2+}\) response of B lymphocytes and automaticity of cardiomyocytes.

**Related publications**


**Key Words:** physiome, mitochondria, calcium, B lymphocyte, cardiomyocyte

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**S-III-3**

A physiomic approach for the electrophysiological variation of the heart induced by the ischemia of coronary artery

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Heart ischemia due to coronary artery stenosis can induce electrophysiological change in heart muscle, showing abnormal EKG signals. The sequential physiological events from stenosis of a coronary artery to variation in the heart's electric field have not been delineated. To investigate this phenomenon mathematically, we implemented an integrative model of the heart covering a wide range of levels (from cells to organs, the torso, and coronary hemodynamics). An electrophysiological model of an ischemic cell was incorporated into tissue and organ models of the human ventricle. This was coupled with a stenosed coronary model to simulate the effect of reduced blood flow through a stenosed coronary artery on cardiac electrophysiology and virtual EKG signals according to the location and duration of coronary stenosis. Coronary blood flow was solved by computational fluid dynamics coupled with a lumped parameter model. Using this model, we first predicted the regional blood perfusion pressure and determined whether the myocardial cells in the region were in a state of ischemia. If so, KATP channels were activated to reduce the action potential duration (APD), which eventually affected the heart's electric activity. Then the electrical pattern across the surface of the torso was converted into EKG signals.

**Key Words:** coronary artery stenosis, ischemic cell, ATP-sensitive potassium channel, numerical simulation, patient-specific model

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**S-III-4**

Electromechanical delay in human ventricle under various load conditions: simulation study

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Pacemaker depolarization in interstitial cells of Cajal (ICC) is believed to be induced by oscillatory increases in cytosolic Ca\(^{2+}\) and subsequent activation of Ano1 channel. However, there are findings that the block of SOCE (store-operated calcium entry) or Na-K-Cl cotransporter (NKCC) can terminate pacemaker activity of ICCs indicating that they might be involved in the initiation or maintenance of pacemaker depolarization. We hypothesized that the SOCE contributes to pacemaker depolarization by mediating Ca\(^{2+}\) depletion in endoplasmic reticulum (ER) with activation of Ano1. As for the NKCC, we hypothesized that NKCC contributes to plateau phase by mediating Cl\(^{-}\)-loss by Ano1 activation during pacemaker depolarization with the reverse-mode operation of Na/Ca exchanger. We updated our recent mathematical model of ICCs in mouse small intestine by incorporation of SOCE and NKCC. The updated model faithfully reproduces the experimentally obtained recordings of SOCE and Ano1 current. Block of either NKCC or SOCE in our mathematical model of ICCs terminates pacemaker activity. However, the contribution of NKCC to pacemaker activity in a beat-to-beat manner was not envisioned in our mathematical model. Instead, NKCC seems to play a significant role in maintaining Cl\(^{-}\)-equilibrium which is critical for Ano1 activation. Incorporation of SOCE allows the model to drive pacemaker activity without diastolic depolarization. Animal experiments are essential to validate the role of NKCC in pacemaker mechanism of ICCs.

**Key Words:** ICCs, NKCC, Ano1, SOCE, pacemaker activity
One of the subset of the heart failure (HF) is dyssynchrony of the heart depolarization and the myofiber shortening phase which leads to severe HF condition. Time interval between the heart depolarization (electrical activation) and onset myo-fiber shortening (mechanical activation) in one cycle of heart rhythm is known as electromechanical delay (EMD). Experimental study of Russell et al. in dog and human heart also showed that mechanical load prolonged the EMD. These studies leads to a presumable solution that if the mechanical load of the ventricle is decreased, the EMD will also be decreased. However, no one ever proved that. To measure the mechanical load effect on three-dimensional (3D) EMD distribution cannot be obtained experimentally so far due to the limitation of measurement devices. The purpose of the study is to quantify the effect of mechanical afterload on EMD by using 3D cardiac physiome model. To construct an integrated model of a cardiovascular system, we combined the 3D image-based electromechanical model of failing canine ventricles with a lumped model of the circulatory system. In order to apply various mechanical afterload condition, we changed the aortic flow resistance with scale factors of 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0. The local electrical activation times, which is obtained from Durrer et al., were mapped to the ventricular computational mesh. The local mechanical activation time was defined as the 10% of the strain lowest value of the ventricle models following Constantino et al. Therefore, EMD can be derived by subtracting EAT from MAT in space. Finally, EAT, MAT and EMD increased in the degradation of Ca2+ concentration level, which means that the MAT and EMD are emphasized under more severe HF condition induced by Ca2+ remodeling. And we found that the MAT and EMD increased depending on mechanical afterload. Ventricles with five times higher aortic flow resistance induced almost 20% more prolonged EMD than normal case. Although this study have proved that mechanical afterload increases EMD with computational method, it can be used for treatment of patients who suffer from prolonged EMD in novel way. Key Words: Cardiac physiome model, Electromechanical delay, Mechanical activation time, Mechanical afterload

Model based interpretation of oral glucose tolerance test
Young Boum Lee, Jeong Hoon Lee, Ga Yul Kim, Ji Yeon Song, Pham Duc Doung, Chae Hun Leem
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Oral glucose tolerance tests (OGTTs) are used commonly to diagnose diabetes mellitus (DM). The changes on blood glucose and insulin by OGTTs contain information of the intestinal absorption, hepatic control of glucose and insulin, pancreatic insulin secretion and peripheral tissue glucose and insulin control. Therefore, an appropriate dynamic model could reveal those information from OGTT data. We developed an OGTT model containing five compartments for insulin dynamics and two compartments for glucose dynamics based on previous reports. Anthropometric data of individuals were used to assume the cardiac output. Simplex and Levenberg-Marquardt algorithms were then used to fit the data obtained from 42 normal subjects (24 males and 20 females) and eight subjects with DM. We found clear gender differences in the intestinal glucose absorption kinetics, glucose sensitivity in the pancreas, maximal insulin production capacity and endogenous glucose production. There were also differences between normal and DM subjects. For example, pancreatic and liver dysfunctions were evident in DM cases. The differences between normal and DM subjects in glucose and insulin dynamics in the pancreas, liver and peripheral tissues, such as insulin resistance, insulin secretion and the relative roles of glucose disposal in each organ, were demonstrated clearly and quantitatively in a time-dependent manner. This study revealed the quantitative dynamic interaction between glucose and insulin using OGTT data and revealed organ function during the OGTT. Using this approach, we identified the dysfunctional organs for glucose and insulin regulation. Data produced using this model will allow a personalized and targeted approach for health issues related to glucose and insulin. (Supported by the grant No. NRF-2015M3A9B6028310, NRF-2014M3A9D7034366 & 2015K000247 from MSIP/COMPA) Key Words: Oral glucose tolerance test, glucose, insulin, diabetes mellitus, model
S-IV-1

Oxygen availability and skeletal muscle mitochondrial function in health and disease
Russell S. Richardson
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Oxygen, as the final electron acceptor in the electron transport system, is vital for life. However, until recently, our understanding of the influence of oxygen availability has been hindered by the inability to assess intramuscular oxygenation and estimate intramuscular oxygen partial pressure (PiO₂). Therefore, the evaluation of basal intracellular oxygenation of human skeletal muscle utilizing proton nuclear magnetic resonance spectroscopy (¹H NMRS) of myoglobin (Mb) is an important development that can facilitate the assessment of the oxygen cascade from air to myocyte and provide valuable insight into the impact of oxygen transport and availability on mitochondrial function in health and disease. In combination with other techniques such as direct Fick measurements (arterial and venous blood), mitochondrial function in health and disease. In combination with other techniques such as direct Fick measurements (arterial and venous blood), mitochondrial function assessments that provide a unique perspective on the role of oxygen availability, mitochondria, and physical function.

S-IV-2

Effects of exercise training on myokines expression and insulin sensitivity in diet-induced obese rats
Kijin Kim, Nayoung Ahn, Suryun Jung, Jayoung Byun, Kwangbae Park, Sungwook Kim, Yeunho Jung, Solee Park
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The purpose of this study was to investigate effects of resistance training on myokines expression and insulin sensitivity in young and middle-aged rats. 50wks and 10wks of male Wistar rats were randomly assigned for exercise and sedentary groups after 1-week of adaptation period. The resistance exercise training was carried out using ladder climbing with weight attached to the tail (3day/week, 8weeks). The high-fat induced rats were randomly assigned for 4 groups (FD, FP, FEx, FPEx). The 8-week of resistance exercise and high-protein diet significantly reduced body weight and abdominal fat weight. Also an insulin resistance of skeletal muscle significantly improved. In the basal level, TNF-α, IL-1β and NFkB protein were expressed 2-3 fold higher in middle-aged group than in young group. After 8 weeks of training, there was no change in the level of NFkB and IL-1β in both middle-aged and young groups. The level of TNF-α was highly decreased in ME group, but this decreased level was still higher than any of young group. Therefore resistance exercise training with use ladder climbing were effective tool to decrease inflammation in skeletal muscle, but training responses were gradually decreased with aging. And an 8-week resistance training and high-protein diet improve insulin resistance as the improvement of body composition and mitochondrial biogenesis in sarcopenic obese rats.

Key Words: sarcopenia, myokine, resistance exercise, insulin sensitivity, aging

S-IV-3

Moderate exercise training inhibits lipid metabolism and macrophage infiltration in high fat diet-induced obese mice
Wang Lok Lee, Young Ran Lee, Hee Geun Park, Jun Hyun Jeong
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PURPOSE: This study was investigated to determine the effect of moderate exercise training on adipose tissue remodeling and macrophage infiltration in high fat diet induced obese mice. METHODS: To accomplish the purpose of this study, C57BL/6 male mice were fed high fat diet (45% fat diet) during experimental period. The animals were divided into 2 groups; HD (high fat diet control, n=10), and HE (high fat diet with moderate exercise training, n=10). Exercise training was performed for 12 weeks on a treadmill running for 40-50 min/day at 10-22 m/min, 0% grade, 5 days/week. RESULTS: As a result, body weight and epididymal fat pad weight were significantly decreased in HE compared with HD (p <.05). Also, the size of adipose was significantly reduced in HE compared with HD (p <.05). Macrophage infiltration markers (CD11c, F480, CD86) mRNA expression were significantly decreased in HE compared to HD (p <.05). Moreover, adipogenesis marker (aP2) mRNA expression was significantly decreased in HE compared to HD (p <.05). CONCLUSION: These findings suggest that moderate exercise training has beneficial effects to inhibit adipose tissue remodeling and macrophage infiltration in high fat diet-induced obese mice.

Key Words: high-fat diet, moderate exercise, adipocyte, macrophage infiltration, lipid metabolism

S-IV-4

Gene expression profiling in skeletal muscle with aerobic exercise
Jung-Jun Park
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It is well known that regularly performed aerobic exercise induces major adaptations in skeletal muscle. These include increases in the mitochondrial content and respiratory capacity of the muscle fibers. The major metabolic consequences of these adaptations are a slower utilization of muscle glycogen and blood glucose, a greater reliance on fat oxidation, and less lactate production during exercise of a given intensity. These results in the large increase in the ability to perform prolonged strenuous exercise that occurs in response to aerobic exercise training. However, molecular mechanism underlying these adaptations still remains unclear. One of the potential reasons for this difficulty may include limited time to investigate each candidate gene related these adaptations. Therefore, we studied gene expression profile of skeletal muscle on middle-aged overweight men (n=5) and women (n=5) with fasting hyperinsulinemia (> 10 IU/ml) following aerobic exercise training. Aerobic exercise training program was composed of high intensity (65-80% of VO₂ max) and high dose (4-5 days/week) for 9 months. Affymetrix U133A chips were used for gene expression profiling. Analysis was done by using d-Chip, RMA, GeneSpring software with a fold change cutoff of 1.5 and statistical difference at p <.05. Two-round amplification was performed to produce enough target cRNA for expression profiling. Not surprisingly, we found that there was a trend towards the increased expression of those genes most strongly
Changes of muscle insulin-like growth factor-I and concentrations of inflammatory cytokines in rat skeletal muscle following denervation and diabetes-induced atrophy

Byeong-hwan Jeon
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Muscle atrophy is the result of several diseases and conditions. In systemic disease, many factors contribute to muscle atrophy. Insulin-like growth factor-I (IGF-I) is a local and systemic hormone that contributes to muscle growth. The aim of this study was to investigate the role of local IGF-I in muscle atrophy during systemic disease. Local muscle tissue damage was observed and compared in both streptozotocin (STZ)-induced diabetic and denervated rats. In these animal models, we measured the expression of IGF-1 in muscle by real-time PCR and serum concentrations of inflammatory cytokines by ELISA. In addition, muscle weight and blood glucose levels were observed for six weeks. The results showed that muscle mass decreased during the first week in denervated rats. In diabetic rats, muscle mass showed no significant reductions but was significantly lower than that in the control group. Inflammatory factors including TNF-α and IL-6 were significantly higher in diabetic rats than in the control group. The results showed that muscle mass decreased during the first week in denervated rats. In diabetic rats, muscle mass showed no significant reductions but was significantly lower than that in the control group. Inflammatory factors including TNF-α and IL-6 were significantly higher in diabetic rats than in the control group.

Key Words: Denervation, Diabetic, Growth Hormone, Inflammatory Markers, Muscle Atrophy

Therapeutic development of optimized mesenchymal stem cells and delivery technology for myocardial infarction

Youngkeun Ahn
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Despite substantial advances in therapeutic modalities, cardiovascular disease remains the leading cause of death worldwide. Cell-based therapy represents a new generation in the evolution of biomedical therapeutics. The mesenchymal stem cells (MSC) have been emerged as representative adult stem cells due to their safety and efficacy and have rapidly been applied in a broad field of disorders. MSC have the capability to transdifferentiate, modulate immune system, and stimulate endogenous regenerative potential in injured heart. In Korea, FCB Pharmicell developed the first MSC product (Hearticellgram-AMI) to be approved for clinical use in acute myocardial infarction. It was approved for sale in July 2011, although concerns have been raised over the unsatisfactory efficacy. Accumulating data from preclinical and clinical studies demonstrate the safety of MSC in a range of cardiovascular diseases, but also raise an issue about a wide gap between the results and expected outcomes. Our research findings suggest that the regenerative activity of MSC is evidently associated with donor’s pathophysiological factors such as diabetic stress. The potential disadvantage of autologous cell therapy is that patients with risk factors may fail to get functional recovery. We identified the mediators in MSC insulted with diabetic stress such as Krüppel-like factor 2 (KLF2), angiopoietin-like 4 (Angptl4), microRNA-132 (miR-132), and miR-34c. Additionally, we are searching for safe priming agent to reprogram the stem cell fate. In this lecture, I will discuss the current status of MSC therapy for cardiovascular disease, and demonstrate the underlying mechanism of MSC exposed by diseased niche to optimize their effectiveness in the clinical setting.

Key Words: mesenchymal stem cell, myocardial infarction, therapy, optimization

Transforming stem cell therapy with nanobiomaterials

Byung-Soo Kim
School of Chemical and Biological Engineering, Seoul National University, Seoul, Korea

Nanobiomaterials can direct stem-cell fate both in vitro and in vivo by displaying stem-cell-regulatory signals in a precise fashion. This presentation will show how new technologies of biomaterials can be used to regulate stem cell differentiation. Graphene and its derivatives can promote adsorption of cell-adhesion signals and soluble signals, which can be applied to enhancement of stem cell differentiation into cardiac [1-3] and chondrogenic lineages [4]. Although these materials can promote the differentiation of stem cells, the difficulties associated with engineering graphene into 3D macrostructured scaffolds have hampered the application of graphene in tissue engineering and regenerative medicine. From a practical perspective, carbonized polycrylonitrile (cPAN), a highly ordered carbon isomorph that resembles the graphitic structure of graphene, could be a promising alternative, as cPAN can be easily processed into 3D scaffolds. We demonstrate the fabrication of microporous 3D scaffolds of cPAN

Key Words: Aerobic exercise, Skeletal muscle, Gene expression profile

S-IV-5

Associated with the more oxidative/type I fiber/heart-like phenotype, and the down-regulation of genes associated with the glycolytic, type II fiber phenotype. Most interesting founding was that many of these genes have functionally related promoter elements. These data suggest the possibility that an “aerobic transcriptional phenotype” may be present in exercise trained skeletal muscle prior to its detection by classic immuno/histochemical fiber-typing techniques, which means these physical adaptations are responsible for the improved glucose uptake, insulin sensitivity and lipid profiles.

Key Words: Aerobic exercise, Skeletal muscle, Gene expression profile

S-V-1

Therapeutic development of optimized mesenchymal stem cells and delivery technology for myocardial infarction

Youngkeun Ahn
Department of Cardiology, Chonnam National University Hospital, Gwangju, South Korea, 501-757

Despite substantial advances in therapeutic modalities, cardiovascular disease remains the leading cause of death worldwide. Cell-based therapy represents a new generation in the evolution of biomedical therapeutics. The mesenchymal stem cells (MSC) have been emerged as representative adult stem cells due to their safety and efficacy and have rapidly been applied in a broad field of disorders. MSC have the capability to transdifferentiate, modulate immune system, and stimulate endogenous regenerative potential in injured heart. In Korea, FCB Pharmicell developed the first MSC product (Hearticellgram-AMI) to be approved for clinical use in acute myocardial infarction. It was approved for sale in July 2011, although concerns have been raised over the unsatisfactory efficacy. Accumulating data from preclinical and clinical studies demonstrate the safety of MSC in a range of cardiovascular diseases, but also raise an issue about a wide gap between the results and expected outcomes. Our research findings suggest that the regenerative activity of MSC is evidently associated with donor’s pathophysiological factors such as diabetic stress. The potential disadvantage of autologous cell therapy is that patients with risk factors may fail to get functional recovery. We identified the mediators in MSC insulted with diabetic stress such as Krüppel-like factor 2 (KLF2), angiopoietin-like 4 (Angptl4), microRNA-132 (miR-132), and miR-34c. Additionally, we are searching for safe priming agent to reprogram the stem cell fate. In this lecture, I will discuss the current status of MSC therapy for cardiovascular disease, and demonstrate the underlying mechanism of MSC exposed by diseased niche to optimize their effectiveness in the clinical setting.

Key Words: mesenchymal stem cell, myocardial infarction, therapy, optimization

S-V-2

Transforming stem cell therapy with nanobiomaterials

Byung-Soo Kim
School of Chemical and Biological Engineering, Seoul National University, Seoul, Korea

Nanobiomaterials can direct stem-cell fate both in vitro and in vivo by displaying stem-cell-regulatory signals in a precise fashion. This presentation will show how new technologies of biomaterials can be used to regulate stem cell differentiation. Graphene and its derivatives can promote adsorption of cell-adhesion signals and soluble signals, which can be applied to enhancement of stem cell differentiation into cardiac [1-3] and chondrogenic lineages [4]. Although these materials can promote the differentiation of stem cells, the difficulties associated with engineering graphene into 3D macrostructured scaffolds have hampered the application of graphene in tissue engineering and regenerative medicine. From a practical perspective, carbonized polycrylonitrile (cPAN), a highly ordered carbon isomorph that resembles the graphitic structure of graphene, could be a promising alternative, as cPAN can be easily processed into 3D scaffolds. We demonstrate the fabrication of microporous 3D scaffolds of cPAN

Key Words: stem cell therapy, nanobiomaterials, differentiation

S-V-3

Mitochondrial function in stem cell differentiation

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Cardiomyocytes that differentiate from pluripotent stem cells (PSCs) provide a crucial cellular resource for cardiac regeneration. The mechanisms of mitochondrial metabolic and redox regulation for efficient cardiomyocyte differentiation are, however, still poorly understood. Here, we show that inhibition of the mitochondrial permeability transition pore (mPTP) by Cyclosporin A (CsA) promotes cardiomyocyte differentiation from PSCs. We induced cardiomyocyte differentiation from mouse and human PSCs and examined the effect of CsA on the differentiation process. The cardiomyogenic effect of CsA mainly resulted from mPTP inhibition rather than from calcineurin inhibition. The mPTP inhibitor NIM811, which does not have an inhibitory effect on calcineurin, promoted cardiomyocyte differentiation as much as CsA did, but calcineurin inhibitor FK506 only slightly increased cardiomyocyte differentiation. CsA treated cells showed an increase in mitochondrial calcium, mitochondrial membrane potential, oxygen consumption rate, ATP level, and expression of genes related to mitochondrial function. Furthermore, inhibition of mitochondrial oxidative metabolism reduced the cardiomyogenic effect of CsA while antioxidant treatment augmented the cardiomyogenic effect of CsA. Our data show that mPTP inhibition by CsA alters mitochondrial oxidative metabolism and redox signaling, which leads to differentiation of functional cardiomyocytes from PSCs.

Key Words: pluripotent stem cells, mitochondria, cardiomyocytes, Cyclosporin A

S-V-4

Hair growth promotion by adipose-derived stem cells: Fact or Fiction?

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Adipose-derived stem cells (ASCs) have been used in tissue repair and regeneration. Recently, it was reported that ASC transplantation promotes hair growth in animal experiments, and a conditioned medium of ASCs (ASC-CM) induced the proliferation of hair-composing cells in vitro. However, ASCs and their conditioned medium show a limitation to their effectiveness in clinical uses. ASC preconditioning is one strategy that can be used to enhance the efficacy of ASCs and ASC-CM. Therefore, I will highlight the functional role of ASCs in hair cycle progression and also the advantages and disadvantages of their application in hair regeneration. In addition, I will introduce novel ASC preconditioning methods to enhance hair regeneration using ASC stimulators, such as vitamin C, platelet-derived growth factor, hypoxia, and ultraviolet B.

Key Words: Adipose-derived stem cells (ASCs), conditioned medium, hair regeneration, ASC preconditioning
Ambivalent role of phosphate in health and disease

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Inorganic phosphate (P_i) plays an essential role in cell signaling and energy metabolism. Particularly, P_i in mitochondria not only provides a substrate for ATP synthesis but also activates respiratory chain. Mitochondrial P_i uptake is driven by nutrient-generated pH gradient, which results in further development of mitochondrial electrical gradient. This hyperpolarization accelerates electrogenic ATP/ADP3- translocation, and exported ATP in cytosol acts as a main stimulus for insulin exocytosis. However, mitochondrial P_i overload elicits reactive oxygen species (ROS) generation and precipitates opening of PT pore. High P_i increases the abundance of plasmalemmal P_i transporters and induces cytosolic alkalinization, which further augments mitochondrial P_i uptake and superoxide production. Mitochondrial ROS caused by excessive P_i leads to mitochondrial dysfunction and ER stress and, as a consequence, deteriorates insulin content and secretion. In vascular smooth muscle cells, oxidative stress due to mitochondrial P_i uptake triggers osteogenic gene upregulation and calcific changes. Most of pathologic alterations by exposure of high P_i can be prevented by either mitochondrial antioxidants or suppressions of plasmalemmal and mitochondrial P_i transporters. There are conflicting roles of cellular P_i, which might be a novel therapeutic target to improve mitochondrial energy metabolism or to prevent pathogenic consequences such as metabolic and cardiovascular morbidities.

Key Words: Inorganic phosphate, Mitochondria, Oxidative stress, Phosphate transporters

Role of zinc on hypoglycemia-induced neuron death

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Oxidative stress and zinc release are both known to contribute to neuronal death after hypoglycemia; however, the cause-effect relationships between these events are not established. Here we found, using a rat or a mice model of profound hypoglycemia, that the neuronal zinc release and translocation that occur immediately after hypoglycemia are prevented by the nitric oxide synthase inhibitor 7-nitroindazole but not by overexpression of superoxide dismutase-1 (SOD-1). However, overexpression of SOD-1 prevented activation of poly(ADP-ribose) polymerase-1 (PARP-1) and neuronal death, suggesting that zinc release is upstream of superoxide production. Accordingly, zinc-induced superoxide production was blocked in neuronal cultures by the NADPH oxidase inhibitor apocynin and by genetic deficiency in the p47(phox) subunit of NADPH oxidase. A key role for the vesicular zinc pool in this process was suggested by reduced superoxide formation and neuronal death in mice deficient in zinc transporter 3. Together, these findings suggest a series of events in which nitric oxide production triggers vesicular zinc release, which in turn activates NADPH oxidase and PARP-1. This sequence may also occur in other central nervous system disorders in which zinc, nitric oxide, and oxidative stress have been linked.

Key Words: Zinc, Oxidative stress, Hypoglycemia, Neuronal Death, NADPH oxidase

Roles of ion channels in cell death processes

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Apoptosis, which is anti-inflammatory, and necrosis, which is pro-inflammatory, represent the extremes of the cell death spectrum. In the context of cellular volume regulation of two processes, apoptosis and necrosis can be characterized by apoptotic volume decrease (AVD) and necrotic volume increase (NVI), respectively. AVD concurrent with cell shrinkage is induced by activation of K+ and Cl− channels at early apoptosis before caspase activation, whereas NVI is caused by activation of Na+ channels. Here, we introduce a novel combined mode of cellular demise—caspase-dependent necrotic necrosis. Most importantly, it is mainly characterized with release of marked amount of oligo- or poly-nucleosomes and their attached damage-associated molecular patterns (DAMPs) and initiated by caspase activation. Caspase-activated DNase has dual roles in nucleosomal release as it can degrade extracellularly released chromatin into poly- or oligo-nucleosomes although it prohibits release of nucleosomes. Osmotically triggered water movement following Cl− influx and subsequent Na+ influx appears to be the major driving force for nucleosomal and DAMPs release although the specific Cl− channels are not yet certain.

Key Words: Cancer cell death, Nucleosome, DAMPS, Caspase, Calpain, Cl− Channel

Zinc homeostasis and osteoarthritis

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Osteoarthritis (OA), primarily characterized by cartilage degeneration, is caused by an imbalance between anabolic and catabolic factors. Here, we investigated the role of zinc (Zn2+) homeostasis, Zn2+ transporters, and Zn2+-dependent transcription factors in OA pathogenesis. Among Zn2+ transporters, the Zn2+ importer ZIP8 was specifically upregulated in OA cartilage of humans and mice, resulting in increased levels of intracellular Zn2+ in chondrocytes. ZIP8-mediated Zn2+ influx upregulated the expression of matrix-degrading enzymes (MMP3, MMP9, MMP12, MMP13, and ADAMTS5) in chondrocytes. Ectopic expression of ZIP8 in mouse cartilage tissue caused OA cartilage destruction, whereas Zip8 knockout suppressed surgically induced OA pathogenesis, with concomitant modulation of Zn2+ influx and matrix-degrading enzymes. Furthermore, MTF1 was identified as an essential transcription factor in mediating Zn2+/ZIP8-induced catabolic factor expression, and genetic modulation of Mtf1 in mice altered OA pathogenesis. We propose that the zinc-ZIP8-MTF1 axis is an essential catabolic regulator of OA pathogenesis.

Key Words: Zinc, ZIP8, MTF1, Cartilage, Osteoarthritis
S-VII-1

Gai-mediated TRPC4 activation by polycystin-1 contributes to the endothelial dysfunction in polycystic kidney diseases

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Polycystin-1 (PC1) is a candidate protein for polycystic kidney diseases (PKD) and regulates a number of cellular processes, for example, heterotrimERIC G protein and transcription factor. We have previously reported that TRPC4/CS channel can be activated by Gai-coupled receptors. We assumed that PC1 might act as a Gai-coupled receptor, so there might be interaction between PC1 and TRPC4/S via Gai proteins based on the phenotypes, that is, aneurysm in PKD and endothelial dysfunction in TRPC4-/- mice. Here, we identified that PC1 dominantly interacts with Gai3 using co-immunoprecipitation. Thus we recorded the activity of TRPC4/CS heterologously co-expressed with PC1 in HEK293 cells. PC1 activated TRC4/S channel (4 ± 1 → 41 ± 14 pA/pF) by modulating G-protein signaling without change in TRPC4 translocation. Intracellular 0.2 mM GTPγS-induced TRPC4 activation was not significantly different in the presence or absence of PC1. C-terminal fragment (CTF) of PC1 did not affect TRPC4/CS activity due to loss of N-terminus containing G-protein coupled receptor proteolytic site (GPS). Dominant negative Gai3 (G202T) mutant inhibited PC1-activated TRPC4 current. TRPC5 was also activated by full-length PC1 (54 ± 8 → 114 ± 16 pA/pF). Using Fura-2 indicator, we observed intracellular Ca2+ increase by PC1 through TRPC4/S channel. We, next, investigated whether TRPC4 induces activation of STAT (signal transduction and transcription) proteins, leading to cell proliferation or death. We observed that STAT1 and STAT3, but not STAT6 activation by PC1 is independent on Src kinase cascades. Interestingly, TRPC4 promoted STAT1 activation. When PC1 co-expressed with TRPC4, STAT1 activation was further increased compared to each sole expression, causing cystic cell death. To determine the role of PC1 with TRPC4 activation in endothelial cell migration, we performed a loss of function screening assay and a wound-healing assay in HUVECs (human umbilical vein endothelial cells). The downregulation of PC1 and TRPC4 activity by the PC1 knockdown or TRPC4 antagonist inhibition of the migration of HUVECs. Our findings indicate an important function between PC1 and TRPC4/CS in modulation of intracellular Ca2+ signaling and provides a new potential therapeutic approach targeting TRPC4/CS channel in polycystic kidney disease, especially intracranial aneurysms.

S-VII-2

Simulation-based study of PIP2-mediated regulation of TRP channels based on voltage-sensing phosphatase and FRET measurements

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Transient receptor potential (TRP) protein constitutes a large superfamily of cation channels, which activate in response to a variety of physicochemical stresses and have been implicated in an unprecedentedly huge repertoire of body functions and dysfunctions. However, despite much efforts, quantitative studies defining the exact functions of TRP channels are entirely missing. To make a break-through in this situation, we recently introduced the Förster Resonance Transfer (FRET) technique to chase a dynamic change in the endogenous phosphatidylinositol 4,5-bisphosphate (PIP2) level and investigated its impact on TRPC3/6/7 and TRPM4 channels. To control the endogenous PIP2, level in a graded manner, we employed the voltage-sensing phosphatase (VSP), the activation of which can readily be controlled by changing the intensity and duration of depolarization. With this optimal combination, we could quantify the temporal relationships between the endogenous PIP2 level and the activities of these channels whereby to be able to construct dynamic numerical models. The results of simulation based on these models indicate that seemingly small differences in PIP2 sensitivity among different homologues or among wild type and single amino acid mutants can nonlinearly be amplified to cause greatly different ultimate responses. In this talk, I would discuss the significance of these findings in their possible connections to hypertensive and arrhythmic disorders.

S-VII-3

Roles of TRPM4 in cardiac electrical activity and its perturbations

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TRPM4 forms a non-selective cation channel activated by internal Ca2+. It is widely expressed among tissues, with a high level in heart. Its functional expression was demonstrated in cardiomyocytes of several mammalian species including human. The identification of TRPM4 inhibitors (flufenamic acid, S-phenanthroline) allowed revealing TRPM4 current properties in cardiac cells and unmasking its role in action potential. This was also supported by the generation of Trpm4-null mice allowing studying the impact of gene disruption. At the electrical level, TRPM4 participates in diastolic depolarization and beating rate in the sino-atrial node. It prolongs the duration of the action potential in cardiomyocytes and Purkinje fibers cells. In rat, TRPM4 inhibition prevents cardiac ischemia-reperfusion injuries and decreases the occurrence of arrhythmias. In addition to these in-vitro studies, TRPM4 mutations have been identified in patients with inherited cardiac diseases including conduction blocks and Brugada syndrome. Even if a global understanding of its role is not yet available, these data indicate that TRPM4 is an actor in cardiac electrophysiology. Note that in addition to these direct implications on cardiac electrophysiology, TRPM4 was also reported to modulate ventricular contractility and cardiac development or hypertrophy.

S-VII-4

Activation of calcium-dependent monovalent cation current by shear stress in atrial myocytes: possible role of TRPM4

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Atrial myocytes are subjected to shear stress during the cardiac cycle under physiological or pathological conditions. The ion currents
regulated by shear stress remain poorly understood. We report the characteristics, molecular identity and activation mechanism of the shear stress-sensitive current (I_{shear}) in rat atrial myocytes. Shear stress of about 16 dyn/cm^2 was applied to single myocytes using a pressurized microflow system, and the current was measured by whole-cell patch clamp. In symmetrical CsCl solutions with minimal concentrations of internal EGTA, I_{shear} showed an outwardly rectifying current–voltage relationship (reversal at approximately -2 mV) and was well sustained. The current was conducted primarily (approximately 80%) by monovalent cations, but not Ca^{2+}. It was suppressed by intracellular dialysis with 15 mM EGTA, selective inhibitors of transient receptor potential melastatin subfamily 4 (TRPM4), in intracellular introduction of TRPM4 antibodies, or knock-down of TRPM4 expression, suggesting that TRPM4 carries most of this current. A notable reduction in I_{shear} occurred upon inhibition of Ca^{2+} release through the ryanodine receptors or inositol 1,4,5-trisphosphate receptors (IP_3Rs) and upon depletion of sarcoplasmic reticulum Ca^{2+}. In type 2 IP_3R (IP_3R2) knock-out atrial myocytes, I_{shear} was 10–20% of that in wild-type myocytes. Inhibition of protein kinase C, another protein activated by shear stress, atrial myocytes, TRPM4, type 2 IP3R and phospholipase C signaling, eliminated the sustained I_{shear} with no effect on initial I_{shear}. Immunocytochemistry revealed that TRPM4 and IP_3R2 were expressed at peripheral junctional sites with considerable co-localization. Our data suggest that shear stress activates TRPM4 current by triggering Ca^{2+} release from the IP_3R2 in peripheral domains of atrial myocytes.

Key Words: shear stress, atrial myocytes, TRPM4, type 2 IP3R

S-VIII-1

Both sides of mGluR5 in maladaptive pain brain

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Neuropathic pain patients often suffer from long-lasting severe pain symptoms still after the nerve injury-induced peripheral change is diminished. This chronic pain is considered as maladaptive byproduct of nociceptive circuits of the nervous system. In contrast to detailed understanding of alterations related to increased pain transmission of primary afferent and spinal cord, much less is known about the alteration of brain functions related to pain perception and modulation. Here we hypothesized that functional change of mGluR5 in the brain contributes to pathogenesis of chronic neuropathic pain. That is, with the peripheral dysregulation settled, altered brain itself should reproduce pain and maintain it even in the absence of peripheral sensitization. We focused on the role of metabotropic glutamate receptor 5 (mGluR5) in the brain in that mGluR5 is widely expressed in the nervous system and contributes to the plastic change of the neurons in the diverse variety of physiological and pathological states. Given the diverse role of mGluR5 in neuronal plasticity, it is assumable that mGluR5 also plays a role in maladaptive change of pain processing in the brain during chronic neuropathic pain state. We identified the functional role of mGluR5 in pain processing and the altered mGluR5 activity in pain brain using behavior analysis combined with microPET imaging and slice patch-clamp techniques. Our study revealed bidirectional actions of mGluR5 in pain processing, demonstrating its functional roles in pain modulation and pain perception, respectively.

Key Words: Neuropathic pain, Metabotropic glutamate receptor 5, Brain imaging, Electrophysiology

S-VIII-2

Targeting of acid-sensing ion channels (ASICs) to the plasma membrane

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Acid-sensing ion channels (ASICs) are proton-activated cation channels which play important roles as typical proton sensors during pathophysiological conditions and normal synaptic activities. Among the ASIC subunits, ASIC2a and ASIC2b are alternative splicing products from the same gene, ACCN1. It has been known that ASIC2b is insensitive to proton, unlike ASIC2a. Here we report their differential subcellular distribution in heterologous expression system, and elucidate underlying mechanisms for their trafficking to the cell surface. By constructing chimeras, we identified the first transmembrane (TM1) domain and the proximal post-TM1 domain (17 amino acids) of ASIC2a as critical forward trafficking signals of ASIC2 proteins. Additionally, we demonstrated that the proximal post-TM1 domain of ASIC2a is also involved in proton-sensitivity of ASIC2. Finally, we discovered that ASIC2b can be delivered to the plasma membrane from the ER by heteromeric assembly with ASIC2a. Our study has uncovered hidden trafficking mechanisms of ASIC2.

Key Words: Acid-sensing ion channels, proton sensor, membrane trafficking, regulation
**S-VIII-3**

**Discovery of novel mGluR1 antagonists for the potential treatment of neuropathic pain**

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Glutamate is the major excitatory neurotransmitter and known to activate the metabotropic and ionotropic glutamate receptors in the brain. Among these glutamate receptors, metabotropic glutamate receptor 1 (mGluR1) has been implicated in various brain disorders including anxiety, schizophrenia and chronic pain. Several studies demonstrated that the blockade of mGluR1 signaling reduced pain responses in animal models, suggesting that mGluR1 is a promising target for the treatment of neuropathic pain. In an effort to identify potent and selective mGluR1 negative allosteric inhibitors for treatment of neuropathic pain, structure and ligand-based molecular modeling studies were undertaken. Hierarchical combining ligand-based vHTS protocols of pharmacophore and naïve Bayesian classification models with the structure-based protocol showed high synergistic effects in enrichment factors. We have developed mGluR1 antagonists with an aryl isoxazole and tetrahydrothieno pyridine scaffold. Several compounds are orally active in vivo. We believe that these compounds can serve as a useful tool for the investigation of the role of mGluR1 and a promising lead for the potential treatment of neuropathic pain.

**Key Words:** metabotropic glutamate receptor 1

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**S-VIII-4**

**The roles of GABA on neuropathic pain and reward following spinal cord injury in rats**

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GABA is the major inhibitory neurotransmitter in the central nervous system includes sensory and psychiatric pathophysiology. To investigate the roles of GABA at both sensory and psychiatric abnormality, the present study tested GABA-mediated neuropathic pain and reward mechanism following spinal cord injury in rats. SCI was produced by T10 clip compression injury (35g, 1 min) in ages with 180-225 g male SD rats. To test the roles of GABA, paw withdrawal response, ultrasound vocalization, in vivo extracellular single cell recording, HPLC-microdialysis and immunohistochemistry were performed. Prior to injury, the baseline paw withdrawal threshold and ultrasound vocalization was recorded, respectively. Post injury days 40, SCI groups showed significantly decreased paw withdrawal threshold at both hindpaws and increased ultrasound vocalization compared to before injury, respectively (*p<0.05). In vivo extracellular electrophysiology at the ventral tegmental area (VTA), GABA neuron activity (characterized by less than 1 ms full action potential duration and > 5 Hz frequency) showed increased firing rates (13.6 ± 1.7 spikes/sec) compared to sham control groups (7.3 ± 1.1 spikes/sec). In addition the ultrasound vocalization also showed increased changes in SCI groups. In immunohistochemistry, glutamic acid decarboxylase (GAD) 67 showed increased expression compared to sham control groups (*p<0.05) at the VTA. In HPLC-microdialysis at the VTA, the concentration of glutamate (608.3±0 nM) and GABA (98.8±50.5 nM) in SCI groups showed increases compared to sham controls (353±0 nM and 4±1.3 nM), respectively.

Taken together, the present study suggests that chronic neuropathic pain reveals the increased activity of VTA GABA neurons that result in the suppression of dopaminergic neurons. In addition, the intrathecal administration of GABA receptor agonists at the spinal cord resulted in the attenuation of neuropathic pain and neuronal hyperexcitability that suggests the decreased tone of spinal GABAergic tone following SCI. In conclusion, the present data suggests that the specific modulations of the endogenous tone of GABA are important factor for the therapeutic treatment at both sensory and psychiatric abnormality. This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP)(NRF-2015R1A5A7037508) and NRF-2014R1A1A4A01004179.

**Key Words:** GABA, Neuropathic Pain, Reward, Spinal cord injury
Glycosaminoglycans increase the phagocytic ability of macrophages via the activation of AMP-activated protein kinase and cytoskeletal reorganization

Glycosaminoglycans (GAGs) control a variety of physiological processes. However, the roles of GAGs in inflammatory processes are unclear. This study was performed to identify the role of GAG isolated from the sea hare Aplysia kurodai (A. kurodai), which is an East-Asian species of marine gastropods. The role of GAG in macrophage phagocytosis was assessed. Treatment with GAG activated macrophage RAW264.7 cells, which exhibited increased cell size, cellular spreading, and vacuole formation. In addition, GAG increased the phagocytic ability of RAW264.7 cells. The GAG-induced activation and phagocytosis of macrophages were reduced with compound C, an inhibitor of AMPK, whereas AICAR, an activator of AMPK, induced the activation and phagocytosis of macrophages. However, the activation pattern was different between GAG and AICAR. GAG induced vacuolization and spreading, whereas AICAR induced primarily spreading. Disruption of cytoskeletal reorganization with nocodazole and cytochalasin D reduced the GAG-activated phagocytic ability, cellular spreading, and vacuole formation. Our results suggest that GAG isolated from the sea hare A. kurodai may have potential therapeutic role in involved in the cellular spreading. The AMPK activation is primarily increased the phagocytic ability of macrophages via AMPK activation and cytoskeletal reorganization. The AMPK activation is primarily involved in the cellular spreading. Our results suggest that GAG isolated from the sea hare A. kurodai may have potential therapeutic role in inflammatory disease.

Key Words: AMPK, Aplysia, Glycosaminoglycans, Inflammation, Phagocytosis

Electrophysiological profiling of cardiac myocytes underlying metabolic substrates-induced spontaneous contractions in normal and hypertensive rats

Cyanidin-3-glucoside (C3G), a component of anthocyanin, has been reported to protect against glutamate-induced neuronal cell death. The present study aims to investigate action potential (AP) profile, L-type Ca2+ channel (ILTCC) and Na+-Ca2+ exchanger (INCC) activities in LV myocytes from Sham and Angiotensin II-induced hypertensive rats (HTN). Result: 1) NF and NF+ISO did not affect the upstroke or the resting membrane potentials. 2) AP duration (APD, APD10, APD20) were prolonged by NF and further more by NF+ISO in sham. 3) In HTN, APD10, APD20 were reduced compared to those in sham. In addition, the effects of NF or NF+ISO on APD10 or APD 20 prolongation were less prominent. 4) APD50 and APD90, however, were prolonged with NF+ISO and significantly more than those in sham. 5) NF or NF+ISO significantly increased outward INCC without changing inward INCC in sham. In HTN, outward INCC was increased and similar tendency were observed for inward INCC. 6) In both Sham and HTN, INCC was reduced by NF and was increased by NF+ISO. Conclusion: The present results suggest that NF significantly prolongs APD which increases the susceptibility of arrhythmia in cardiac myocytes under metabolic stress following beta-adrenergic stimulation. Additional mechanisms (apart from LTCC or NCK) those underlie anomalous Ca2+ and Zn2+ signaling that may contribute to arrhythmogenicity in normal and hypertensions with metabolic syndrome need to be explored further.

Key Words: hypertension, NCK, arrhythmia, metabolic syndrome, APD

Inhibitory effects of cyanidin-3-glucoside on amyloid beta (25-35)-induced neuronal cell death in cultured rat hippocampal neurons

Increasing evidences implicate changes in [Ca2+]/i and oxidative stress as causative factors in amyloid beta (Aβ)-induced neuronal cell death. Cyanidin-3-glucoside (C3G), a component of anthocyanin, has been reported to protect against glutamate-induced neuronal cell death by inhibiting Ca2+ and Zn2+ signaling. The present study investigated to determine whether C3G has a protective effect against Aβ-induced neuronal cell death in cultured rat hippocampal cells and pure hippocampal neurons from embryonic day 17 fetal Sprague-Dawley rats using digital imaging methods for Ca2+, Zn2+, MMP and ROS, and MTT assay for cell survival. Pretreatment with C3G (10 µg/ml) for 30 min inhibited Aβ-induced [Ca2+]i increases in the cultured rat hippocampal neurons. C3G significantly inhibited Aβ-induced mitochondrial depolarization. C3G blocked Aβ-induced formation of ROS. C3G also significantly inhibited Aβ-induced (Zn2+)i increases. Treatment with C3G (10 µg/ml) for 48 h attenuated Aβ-induced neuronal cell death in cultured rat pure hippocampal neurons. Taken together, all these results suggest that cyanidin-3-glucoside inhibits Aβ-induced Ca2+ signaling, mitochondrial depolarization, formation of reactive oxygen species and Zn2+ signaling in cultured rat hippocampal neurons, which is involved in neuroprotection. This work was carried out with the support of “Cooperative Research Program for Agriculture Science & Technology Development (PJ009830022015)” Rural Development Administration, Republic of Korea.

Key Words: Ca2+, flavonoid, Zn2+
Endocytosis of KATP channels drives glucose-stimulated depolarization in pancreatic β-cell

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Glucose homeostasis of the body relies primarily on the ability of pancreatic β-cells to regulate insulin secretion in response to the changes in blood glucose concentrations. Membrane depolarization by high glucose stimulation, which leads to Ca2+ entry to initiate insulin vesicle exocytosis, is mediated by inhibition of KATP currents, and ATP-dependent channel closure has been known to be responsible. Here we investigate the role of KATP channel endocytosis to glucose-stimulated membrane depolarization in INS-1 cells. High glucose stimulation (17 mM) induced a decreased in surface level of KATP channel proteins, and this decrease was abolished by inhibiting endocytosis using dynasore (a dynamin inhibitor). Interestingly, dynasore significantly inhibited glucose-stimulated membrane depolarization, while it did not affect the glucose-induced increase in intracellular ATP concentrations. Membrane depolarization could be induced under glucose-deprived conditions by reducing surface levels of KATP channels using blebbistatin (a myosin II ATPase inhibitor). These results suggest that the decreased surface KATP channel density by endocytosis is a key mechanism that drives glucose-stimulated membrane depolarization, while ATP-dependent channel closure plays a minor role.

Key Words: KATP channel, pancreatic beta cell, insulin secretion, glucose

Effects of etomoxir on lipid metabolism and oxidative stress in peripheral tissues

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Fatty acids are the main energy substrates supplied to developing mammals and as fuels for energy production in tissues. Carnitine palmityl-transferase 1 (CPT1) is the rate-limiting enzyme in mitochondrial fatty acid oxidation. The CPT1 inhibitor, etomoxir improves sarcoplasmic reticulum function and in vivo heart performance, and delays the dilative ventricular remodelling, whereby metabolic signals appear to be involved. Recent reports indicate a shift from fatty acid oxidation to glucose oxidation leads to a reduced gluconeogenesis and improved economy of cardiac work. However etomoxir causes ATP depletion as well as oxidative stress, and oxidative stress is implicated in a variety of physiological and pathological processes. The purpose of this study was to compare the effects of etomoxir on lipid metabolism and oxidative stress in various tissues such as heart, liver, kidney, and skeletal muscle. Male C57BL/6 mice at 8 weeks of age were randomly divided into four groups: 1) saline, 2) etomoxir (1 mM), 3) lipid (20% Intralipid), 4) lipid plus etomoxir. At 3-4 days before the experiments, mice were anesthetized, and an silicone catheter was inserted in the jugular vein. Mice were infused with saline, etomoxir, lipid and lipid plus etomoxir for 6h (2.5 μl/min). We analyzed gene expression using real-time PCR. The plasma levels of triglyceride and free fatty acid were increased by etomoxir and lipid. However, the plasma levels of glucose were decreased by etomoxir, when compared with lipid group. In heart, etomoxir decreased mRNA levels of sterol regulatory element-binding protein 1c (SREBP1c), fatty acid synthase (FAS), and stearoyl-CoA desaturase 1 (SCD1) involved in fatty acid synthesis. In liver, the lipid increased SREBP1c and FAS mRNA levels, whereas etomoxir decreased SREBP1c and FAS mRNA levels. Etomoxir also increased peroxisome proliferator activated receptor-α (PPAR-α) and acyl CoA oxidase (ACO) mRNA levels involved in fatty acid β-oxidation. In kidney, the lipid increased FAS mRNA levels. Etomoxir decreased the mRNA levels of SREBP1a, SREBP1c, FAS and ACC. In both liver and kidney, etomoxir increased fatty acid binding protein 1 (FABP1) mRNA levels. Lipid or etomoxir increased oxidative stress marker, 4-HNE and nitrotyrosine, only in heart. There was no differences in gene expression-related with lipid metabolism in skeletal muscle. These results suggest that etomoxir decreases gene expression related with fatty acid synthesis except skeletal muscle and induces oxidative stress only in heart.

Key Words: Etomoxir, CPT1 inhibitor, Lipid metabolism, Oxidative stress, Fatty acid synthesis
Oleanolic acid is known to possess beneficial effects on the regulation of the cardiovascular homeostasis. However, the exact nature of the role of oleanolic acid on the regulation of body fluid balance and blood pressure homeostasis and its mechanisms involved are not well defined. We hypothesized that oleanolic acid inhibits the renin-angiotensin system and accentuates renal function. Experiments were performed to identify the effects of oleanolic acid on the renal function, blood pressure, and the renin-angiotensin system in normotensive and hypertensive rats. Oleanolic acid (0, 20, and 30 mg/kg/day) was administered orally for 1 or 3 weeks. Here, we found that oleanolic acid suppressed the renin-angiotensin system. Oleanolic acid increased urinary volume, and urinary excretion of Na+, K+, and Cl−, concomitantly with an increase in clearance for creatinine in normotensive rats. Also, oleanolic acid decreased urinary osmolarity. Oleanolic acid significantly suppressed arterial blood pressure in renal hypertensive rats. Furthermore, oleanolic acid suppressed plasma levels of renin activity, angiotensin II, aldosterone, and renal renin contents, and gene expressions by real-time PCR of renin, angiotensin converting enzyme and angiotensin II type 1 receptor in the kidney cortex from normotensive and hypertensive rats. Oleanolic acid elicited dual effects on the angiotensin II type 2 receptor: suppression with low and accentuation with high dose. These findings suggest that oleanolic acid modulates body fluid and salt balance and blood pressure homeostasis by suppressing the systemic and intrarenal renin-angiotensin system. Key Words: oleanolic acid, renin, angiotensin II, angiotensin I-converting enzyme, angiotensin II receptor subtype 1, natriuresis, blood pressure

**P03-02(O-11)**

The impact of exercise training on vascular mitochondria and arterial function

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Exercise training is recognized to improve skeletal muscle mitochondrial respiratory capacity, however the impact of chronic exercise on vascular mitochondrial respiratory function is unknown. We hypothesized that exercise training would concomitantly increase both vascular mitochondrial respiratory capacity and vascular function. Arteries from both sedentary (SED, n=8) and swim trained (EX, 5 weeks, n=8) male mice were compared in terms of mitochondrial respiratory function, mitochondrial content, markers of mitochondrial biogenesis, redox balance, nitric oxide (NO) signaling, and vessel function. Mitochondrial complex I and complex I+II state 3 respiration and the respiratory control ratio (RCR, complex I+II state 3 respiration / complex I state, 2 respiration) were greater in vessels from EX than SED mice, despite similar levels of arterial citrate synthase activity (CSA) and mitochondrial DNA content. Furthermore, compared to the SED mice, arteries from the EX mice displayed elevated transcript levels of PGC-1α (Ppargc1a) and the downstream targets Cox4i1, Idh2, Idh3a, increased MrpSOD protein expression, increased endothelial NO synthase (eNOS) phosphorylation (Ser1177), and suppressed reactive oxygen species generation (all P < 0.05). Although there were no differences in EX and SED mice in terms of classically assessed endothelium-dependent and endothelium-independent vasorelaxation, phenylephrine-induced vasoconstriction was blunted in vessels from EX compared to SED mice and this effect was normalized by NOS inhibition. These training-induced increases in vascular mitochondrial respiratory capacity and evidence of improved redox balance, which may, at least in part, be attributable to elevated NO bioavailability, have the potential to protect against age and disease-related challenges to arterial function. Key Words: exercise, vascular mitochondrial function, shear stress, mitochondrial biogenesis, ROS

**P03-03**

The adiponectin response research of combined exercise in overweight child

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Purpose: The purpose of this study is to assess the combined exercise...
P03-04
Food-dependent exercise-induced anaphylaxis (FDEIAn) response research in human

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Food-dependent exercise-induced anaphylaxis (FDEIAn) is induced by different types and various intensities of physical activity, and is distinct from food allergies. It has been shown that consumption of allergenic food followed by exercise causes FDEIAn symptoms. Intake of allergenic food or medication before exercise is a major predisposing factor for FDEIAn. Urticaria and severe allergic reactions are general symptoms of FDEIAn. Dermatological tests and serum IgE assays are the typical prescreening methods, and have been used for several decades. However, these screening tests are not sufficient for detecting or preventing FDEIAn. It has been found that exercise may stimulate the release of mediators from IgE-dependent mast cells that can result in FDEIAn when a certain threshold level has been exceeded. Mast cell degranulation might be a major factor to induce FDEIAn but this has not been determined. A number of foods have been reported to be involved in the onset of FDEIAn including wheat, eggs, chicken, shrimp, shellfish, nuts, fruits, and vegetables. It is also known that aspirin increases the occurrence of type I allergy symptoms when combined with specific foods. Moreover, high intensity and frequent exercise are more likely to provoke an attack than low intensity and less frequent exercise. In this paper, we present the current views of the pathophysiological mechanisms underlying FDEIAn within the context of exercise immunology. We also present a detailed FDEIAn definition along with etiologic factors and medical treatment for cholinergic urticaria (UC) and exercise-induced anaphylaxis (EIA).

Key Words: Food, Exercise, Anaphylaxis, FDEIAn

P03-05
Novel anthropometry-based calculation of the body heat capacity in the Korean population

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Heat capacity (HC) has an important role in the temperature regulation process, particularly in dealing with the heat load. The actual measurement of the body HC is complicated and is generally estimated by body-composition-specific data. This study compared the previously known HC estimating equations and sought how to define HC using simple anthropometric indices such as weight and body surface area (BSA) in the Korean population. Six hundred participants were randomly selected from a pool of 902 healthy volunteers aged 20 to 70 years for the training set. The remaining 302 participants were used for the test set. Body composition analysis using multi-frequency bioelectrical impedance analysis was used to access body components including body fat, water, protein, and mineral mass. Four different HCs were calculated and compared using a weight-based HC (HC_{Eq1}), two HCs estimated from fat and fat-free mass (HC_{Eq2} and HC_{Eq3}), and an HC calculated from fat, protein, water, and mineral mass (HC_{Eq4}). HC_{Eq1} generally produced a larger HC than the other HC equations and had a poorer correlation with the other HC equations. HC equations using body composition data were well-correlated to each other. If HC estimated with HC_{Eq4} was regarded as a standard, interestingly, the BSA and weight independently contributed to the variation of HC. The model composed of weight, BSA, and gender was able to predict more than a 99% variation of HC_{Eq4}. Validation analysis on the test set showed a very high satisfactory level of the predictive model. In conclusion, our results suggest that gender, BSA, and weight are the independent factors for calculating HC. For the first time, a predictive equation based on anthropometry data was developed and this equation could be useful for estimating HC in the general Korean population without body-composition measurement.

Key Words: Heat capacity, body surface area, weight-based HC, fat-free mass, mineral mass

P03-06
Effect of long-term exercise on circulating levels of Dickkopf-1 and frizzled-related protein-1 in breast cancer patients

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Background: Dickkopf-1 (DKK1) and secreted frizzled-related protein-1 (SFRP1) are inhibitors of Wnt/β-catenin signaling. Accumulating evidence suggests that higher serum level of DKK1 is positively correlated with pathologic conditions such as cancer and atherosclerosis. Furthermore, DKK1 disrupts osteoblast differentiation and precipitates osteoporosis. Several recent studies showed that exercise reduces DKK1 level in healthy volunteers or experimental animals. We investigated the changes of serum levels of DKK1 and SFRP1, as Wnt/β-catenin inhibitors, by long-term exercise in breast cancer patients.

Methods: Subjects were separated into two groups (exercise training group [EG: n=8] and control group [CG: n=7]). EG underwent an 12-week training (two times aerobic training per week and two times resistance training per week, more than 40 min). After 12 weeks exercise training and 6 weeks detraining, we evaluated metabolic syndrome markers and plasma adiponectin level in two groups. Moreover, high intensity and frequent exercise. In this paper, we present the current views of the pathophysiological mechanisms underlying FDEIAn within the context of exercise immunology. We also present a detailed FDEIAn definition along with etiologic factors and medical treatment for cholinergic urticaria (UC) and exercise-induced anaphylaxis (EIA).

Key Words: Exercise, Anaphylaxis, FDEIAn

Effect of long-term exercise on circulating levels of Dickkopf-1 and frizzled-related protein-1 in breast cancer patients

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Key Words: Exercise, Anaphylaxis, FDEIAn
cancer patients. **Methods:** 25 breast cancer patients (50.4±11.8 years of age) after chemo- or radiotherapy were participated. Intervention groups were randomized to 12 wks of breast cancer exercise program (n = 11) or control group (n = 13). Blood samples were collected to examine the serum level of DKK1 and SFRP1. **Results:** The serum levels of DKK1 (p < .05) and SFRP1 (p < .05) were significantly reduced during 12 wks exercise program. However, those in control group were not changed during 12 wks. Exercised group showed remarkable increases in circumference were significantly decreased in exercised group compared to control group (p < .05). Also, body fat percentage and abdominal flexibility (p < .05). Body fat percentage and abdominal circumference were significantly decreased in exercised group compared to control group (p < .05). **Conclusion:** Our results suggest that long-term exercise decreases serum levels of DKK1 and SFRP1 which may contribute to the beneficial effects of exercise in cancer patients. **Key Words:** DKK1, SFRP1, Breast cancer patients

**P03-07**

Effect of cardiorespiratory endurance training on power production in figure skaters

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The aim of this study was to compare different forms of plyometric and cardiorespiratory endurance training on the vertical jump ability and 30-m sprint speed to improve performance capability among female figure skaters. Twenty participants were randomly allocated to either the plyometric combined with long, slow distance training group (PL) or the plyometric combined with high-intensity interval training group (PI), with 10 participants in each group. The participants performed the exercises five times per week over 12 weeks. The experimental protocol consisted of the 1) familiarization period; 2) baseline test; 3) 12-week training intervention; and 4) vertical jump and 30-m sprint speed tests. 1. Analysis of the data revealed that the vertical jump ability improved to a greater extent after PI (4.49%) as compared to that observed after PL (2.6%; p<.05). 2. Analysis of the data revealed that the 30-m sprint speed improved to a greater extent after PI (5.75%) as compared to that observed after PL (2.98%; p < .05). Thus, cardiorespiratory endurance training alters power production. Accordingly, plyometric and interval complex training are effective exercise methods for power production. **Key Words:** Plyometric, HIIT training, LSD training, Power Production

**P03-08**

The effect of AQP3 deficiency in fuel selection during a single bout of exhausting exercise  
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The aquaporin-3 (AQP3) is an integral membrane protein facilitating the transport of water and glycerol across cell membranes. However, detailed localization and function of AQP3 in skeletal muscle is currently unknown. We investigated the capacity to perform a single bout of exhausting exercise in AQP3 knockout mice and analyzed the parameters related to skeletal muscle energy metabolism at exhaustion.

Both immunohistochemistry and double immunofluorescence staining revealed that AQP3 expressed at the cell surface with no evidence for colocalization with either AQP1 or AQP4 in skeletal muscle. When exposed to a single bout of treadmill running at the speed up to 12 m/ min with 10° incline until exhaustion, AQP3 knockout mice exhibited earlier fatigue with shorter average time to exhaustion than the wild-type C57Bl/6J control. After exhausting exercise, plasma and muscle glucose, muscle glycogen, and plasma and liver triglyceride levels decreased, whereas plasma and liver glycerol levels increased compared to those at rest in both AQP3 knockout and wild-type mice. However, muscle glycerol as well as liver glycogen concentrations decreased after exercise in wild-type mice, but rather increased in AQP3 knockout mice. These findings suggest that decreased glycerol efflux from skeletal muscle in AQP3 knockout mice might result in low exercise capacity due to the limitation in constant energy supply through hepatic gluconeogenesis from glycerol during the prolonged endurance exercise.  
**Key Words:** Aquaporin-3, Glycerol, Exhausting exercise, Intramuscular triglyceride

**P04-01**

Transient receptor potential canonical 4 (TRPC4) channel regulation by phosphotyesterase 5 inhibitor via the cyclic guanosine 3’5’-monophosphate  
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The transient receptor potential (TRP) protein superfamily consists of a diverse group of cation channels that bear structural similarities to the Drosophila TRP. TRP superfamily is distinct from other groups of ion channels in displaying a daunting diversity in ion selectivity, modes of activation, and physiological functions. Nevertheless, they all share the common feature of six transmembrane domains, varying degrees of sequence similarity, and permeability to cations. The fourth transmembrane domain lacks the complete set of positively charged residues necessary for the voltage sensor in many voltage-gated ion channels. It is generally speculated that TRPC channels are activated by stimulation of Gq-PLC-coupled receptors and oxidation. Second messenger molecule cyclic guanosine monophosphate (cGMP) of nitric oxide was activated soluble guanylyl cyclase (sGC). cGMP then phosphorylates specific down-stream targets, such as the protein kinase Gc(GK), cGMP-binding phosphodiesterases (PDEs) and ion channel. cGMP is degraded by the activity of PDE isoenzymes catalyzing the hydrolysis of cGMP to the inactive form 5’GMP. Here, we report the functional relationship between TRPC4 and cGMP. TRPC4 gene was overexpressed in HEK 293 cells that cGMP selectively activated TRPC4 channels and increased cytosolic calcium level by TRPC4 channel. We investigate to phosphorylation sites in TRPC4 channels. Thus, S688A phosphorylation site is important to associate PKG via cGMP. We have found that cGMP triggered TRPC4-like canonical current in prostate smooth muscle cell. cGMP and TRPC4 could suggest a new therapeutic agent for benign prostatic hyperplasia (BPH) syndromes. **Key Words:** Ion channel, PDE inhibitor, cGMP

**P04-02**

Fluid flow facilitates inward rectifier K+ current by convective restoring of [K+] at cell membrane

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Nicardipine inhibits hERG Channel

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Drug-induced long QT syndrome is known to be associated with the onset of torsades de pointes (TdP), resulting in a fatal ventricular arrhythmia. QT interval prolongation can result from blocking the human ether-a-go-go-related gene (hERG) channel, which is important for the repolarization of cardiac action potential. Nicardipine, a Ca-channel blocker and antihypertensive agent, has been reported to increase the risk of occasional serious ventricular arrhythmias. We studied the effects of nicardipine on hERG K+ channels expressed in HEK293 cells and Xenopus oocytes. The cardiac electrophysiological effect of nicardipine was also investigated in this study. Our results revealed that nicardipine dose-dependently decreased the tail current of the hERG channel expressed in HEK293 cells with an IC50 of 0.43 μM. On the other hand, nicardipine did not affect hERG channel trafficking. Taken together, nicardipine inhibits the hERG channel by the mechanism of short-term channel blocking. Two S6 domain mutations, Y652A and F656A, partially attenuated (Y652A) or abolished (F656A) the hERG current blockade, suggesting that nicardipine blocks the hERG channel at the pore of the channel.

Key Words: Nicardipine, hERG, LQTS, HEK293, Xenopus oocyte
Shear stress induces longitudinal Ca\(^{2+}\) wave via autocrine activation of P2Y1 purinergic signaling in atrial myocytes

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Atrial myocytes are exposed to shear stress during cardiac cycle and hemodynamic disturbance. It is known that shear stress elicits longitudinal global Ca\(^{2+}\) wave ("L wave") in atrial myocytes (1). Here, we investigated cellular mechanisms for shear-mediated Ca\(^{2+}\) response in atrial myocytes using two-dimensional confocal Ca\(^{2+}\) imaging. We applied shear stress to single myocytes using pressurized micro flow system. Atrial myocytes were enzymatically isolated from male Sprague-Dawley rats (230−300 g) and from wild-type (WT) and type 2 inositol 1,4,5-trisphosphate receptor (IP3R) knockout (KO) mice (C57/B6, 24-28 g). Shear stress of ~16 dyn/cm\(^2\) aperiodically induced L wave 1.2±0.26 times for 8 s-long exposure (n=39), with a delay of 0.2-3 s. Shear-induced L wave was restituted after 3-4-min resting period after the first occurrence. Pharmacological blockade of either ryanodine receptor (RyR) by using 1 mM tetracaine or IP3R (3 μM 2-APB) abolished the L wave occurrence under shear stress. In type 2 IP3R KO cells, shear stress failed to induce L wave. Consistent with these results, inhibition of phospholipase C (PLC) using U73122 (5 μM) removed shear-induced L wave, although its inactive analogue U73343 (5 μM) did not affect it. These observations indicate that PLC-IP3-IP3R signaling and Ca\(^{2+}\)-mediated Ca\(^{2+}\) release via RyRs play a role in the generation of L wave under shear. Pre-treating atrial cells with the blockers for stretch-activated channel, TRPM4 or NADPH oxidase did not alter the occurrence of L wave under shear. Suramin (10 μM), the inhibitor of purinergic receptor, suppressed the L wave occurrence under shear stress. Antagonist of P2Y1 receptor RS52179 (200 nM), but not P2X receptor antagonist (iso-PPADS 1~50 μM), eliminated the L wave generation under shear. Suppression of connexon that releases ATP using carboxenolone (50 μM), or extracellular application of apyrase (2 U/mL) that metabolizes ATP inhibited the occurrence of L wave under shear. Our data suggest that shear stress enhances the frequency of Ca\(^{2+}\) sparks by producing ROS via NOX, and that prolonged enhancement in spark frequency by shear stress may be partly mediated by increase in the SR Ca\(^{2+}\) loading. These mechanisms may partly explain the shear-mediated enhancement in Ca\(^{2+}\) transient in ventricular myocytes.

Key Words: shear stress, ventricular myocytes, Ca\(^{2+}\) spark, NOX, ROS

Changes of K\(^{+}\) channel currents in skeletal smooth muscle by exercise training in sciatic nerve-injured rats

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K\(^{+}\) channel currents determine the plasma membrane potential of vascular myocytes, influencing arterial tone. Voltage-gated K\(^{+}\) channel current (IK\(_{\text{V}}\)) counterbalances the depolarization and voltage-operated Ca\(^{2+}\) channel (VOCC) activation. Moderate increase in extracellular [K\(^{+}\)] ([K\(^{+}\)]\(_{\text{ex}}\)) induces relaxation of small arteries via augmenting inwardly rectifying K\(^{+}\) channel current (IK\(_{\text{ir}}\)) and membrane hyperpolarization. The K\(^{+}\)-vasodilation is one of the mechanisms for the regional control of skeletal blood flow in response to exercise. In the rats underwent endurance exercise training (ET, rodent treadmill running) for two weeks, both IK\(_{\text{ir}}\) and IK\(_{\text{V}}\) were increased by almost two fold in the skeletal arterial (SKASMC) and cerebral arterial smooth muscle cells (CASMCs) [Jin CZ et al 2011]. We also tested whether unilateral sciatic nerve injury and paralysis of the lower hindlimb affects IK\(_{\text{ir}}\) and IK\(_{\text{V}}\) in rat SKASMCs. Atrophy of gastrocnemius and tibialis posterior were confirmed in the injured leg, and the amplitude of IK\(_{\text{ir}}\) was decreased in the SKASMCs from the injured legs. However, the amplitude of IK\(_{\text{ir}}\) was increased in the SKASMCs from the counter lateral legs. When 2-4 weeks of ET were combined with the sciatic nerve injury model, IK\(_{\text{ir}}\) was increased in both injured and intact legs. Interestingly, the decreased IK\(_{\text{ir}}\) in the injured leg was increased to the level even higher than normal condition. The recovery of IK\(_{\text{ir}}\) and IK\(_{\text{V}}\) by ET might be one of the mechanisms for the beneficial effects of regular exercise on the rehabilitation of motor nerve release events in injured and examined myocytes. 

Key Words: sciatic nerve injured, exercise training, IK\(_{\text{ir}}\), IK\(_{\text{V}}\), skeletal arterial smooth muscle cell
Ion channel gene expression predicts survival in glioma patients
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Ion channels are important regulators in cell proliferation, migration, and apoptosis. The malfunction and/or aberrant expression of ion channels may disrupt these important biological processes and influence cancer progression. In this study, we investigate the expression pattern of ion channel genes in glioma. We designate 18 ion channel genes that are differentially expressed in high-grade glioma as a prognostic molecular signature. This ion channel gene expression based signature predicts glioma outcome in three independent validation cohorts. This signature is independent of traditional clinical, molecular, and histological factors. Resampling tests indicate that the prognostic power of the signature outperforms random gene sets selected from human genome in all the validation cohorts. More importantly, this signature performs better than the random gene signatures selected from glioma-associated genes in two out of three validation datasets. This study confirms the central role of ion channels in brain cancer. Individualized profiling of ion channel gene expression serves as a superior and independent prognostic tool for glioma patients. This study also suggests that due to their central role in the cancer disease process, ion channels may serve as potential drug targets in cancer therapy.

Key Words: ion channel, glioma, gene expression, molecular signature, microarray

P04-09
Tonic inhibition of TREK-2 K2P channels by intrinsic PI(4,5)P2 is the physiological mode of regulation
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TWIK-related two-pore domain K+ channels (TREK) are activated by various physicochemical conditions including anionic phospholipids such as PI(4,5)P2. However, there has been controversy over the direction of regulation by PI(4,5)P2 that are dynamically generated by PI kinases using ATP. Here we investigated heterologously and intrinsically expressed TREK-2 in HEK293T, COS-7, WEHI-231 B cells, and primary astrocytes. Also, TREK-1 in HEK293T were compared. TREK-1 and TREK-2 current (I_{TREK}) commonly increased spontaneously by dialysis with ATP-free solution or by membrane excision for inside-out (i-o) patch clamp. The I_{TREK,1} and I_{TREK,2} were inhibited by ATP in all types of cells. The ATP-dependent inhibition was prevented by wortmannin, a PI kinase inhibitor. Consistently, I_{TREK,2} and I_{TREK,2} were totally inhibited by 10μM PiP2. The ATP-dependent inhibition of I_{TREK,1} was more prominent in HEK293T and WEHI-231 than COS7 and astrocytes. Confusingly, poly-L-lysine (poly-L, polycationic agent) treatment also abolished I_{TREK,1} which was reversed by treatment with polyanionic heparin. In HEK293T cells coexpressing TREK-2 and voltage-sensitive lipid phosphatase (Dr-VSP), I_{TREK,2} was increased by depolarisation initially, then suppressed with sustained depolarization. The inhibition of I_{TREK,2} by the unspecific charge screening (poly-L) or by the excessive stimulation of Dr-VSP suggested dual modes of regulation by Pi(4,5)P2. Physiologically, we suggest that the ATP-dependent intrinsic Pi(4,5)P2 induces tonic inhibition of TREK-2, the level of which appears different between the cell types.

Key Words: ion channel, glioma, gene expression, molecular signature, microarray

P04-10
Inhibitory modulation of hERG K+ channels by endogenous polyunsaturated fatty acid-derived electrophiles, 4-HNE and 4-ONE
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Oxidative stress occurs in the pathophysiological conditions such as inflammation, reperfusion after ischemia and aging. Lipid peroxidation products 4-Hydroxynonenal (4-HNE) and 4-Oxononenal (4-ONE) are peroxidation products of ω6-polyunsaturated fatty acid peroxidation, and have been studied as endogenous electrophiles that are potential harmful signaling molecules by formation of 4-HNE(4-ONE)-protein adducts. Previously we have reported the modulation of several ion channels including Kv, SOCE and hERG channels by exogenous electrophile molecules (e.g. curcumin). Here we investigate the effects of 4-HNE and 4-ONE on hERG current overexpressed in HEK-293 cells and the action potentials of guinea-pig ventricular myocytes (GPVMs). Acute application of 4-HNE (30~100 μM) and 4-ONE (1~10 μM) gradually but significantly decreased the tail current of hERG (iERG,tail). The half-activation voltage (actV1/2) was shifted to the left by 4-HNE, while not by 4-ONE. The action potential duration (APD) of GPVMs was prolonged by 100 μM 4-HNE and 10 μM 4-ONE. Long-term incubation (> 1 h) with lower concentrations of 4-HNE (10 μM) induced time-dependent suppression of iERG,tail. Western blot analysis revealed that membrane expression of hERG protein was reduced by the long-term incubation with 10 μM 4-HNE while not by 4-ONE. Consistently, the incubation with 10 μM 4-HNE significantly prolonged the APD of GPVMs as well as QT prolongation of ECG. Taken together, the suppression of hERG by higher dose of 4-HNE and 4-ONE may participate in cytoxic and proarrhythmic effects. Sustained exposure to 4-HNE could impair hERG trafficking.

Key Words: hERG channel, lipid peroxidation product, 4-hydroxynonenal, 4-oxononenal

P04-11
TLR3-/4- Priming Differentially Promote Ca2+ Signaling and Cytokine Expression and Ca2+-Dependently
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Acute application of 4-HNE (30~100 μM) and 4-ONE (1~10 μM) gradually but significantly decreased the tail current of hERG (iERG,tail). The half-activation voltage (actV1/2) was shifted to the left by 4-HNE, while not by 4-ONE. The action potential duration (APD) of GPVMs was prolonged by 100 μM 4-HNE and 10 μM 4-ONE. Long-term incubation (> 1 h) with lower concentrations of 4-HNE (10 μM) induced time-dependent suppression of iERG,tail. Western blot analysis revealed that membrane expression of hERG protein was reduced by the long-term incubation with 10 μM 4-HNE while not by 4-ONE. Consistently, the incubation with 10 μM 4-HNE significantly prolonged the APD of GPVMs as well as QT prolongation of ECG. Taken together, the suppression of hERG by higher dose of 4-HNE and 4-ONE may participate in cytoxic and proarrhythmic effects. Sustained exposure to 4-HNE could impair hERG trafficking.

Key Words: hERG channel, lipid peroxidation product, 4-hydroxy brononal, 4-oxononenal
Ca²⁺-dependently potentiate cytokine release in hMSCs. Differentially enhance Ca²⁺ signaling and cytokine expression and intracellular Ca²⁺. The data demonstrate that TLR3- and TLR4-priming hMSCs. The enhanced cytokine release vanished upon chelation of Both poly (I:C) and LPS exposure enhanced cytokine release from Orai and STIM expression and store-operated Ca²⁺ entry in hMSCs. S 58

Key Words: MSCs, TLRI, TLRII, LPS, Poly(I:C)

P04-13

ATP sensitive potassium currents on Human Periodontal ligament cells

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Adenosine-5'-triphosphate (ATP) has been mentioned in dental research on multiple levels, such as inflammation, mechanical strain and pain, making the system particularly relevant for the specific challenges in the oral cavity. There are studies showing human periodontal ligament cell respond to mechanical stress by increasing ATP release, which participates in bone resorption or bone homeostasis. So, in this study, we used the RT-PCR and patch-clamp techniques to investigate the presence of KATP channel subunits and influence of ATP on the KATP channel opening on PDL cells. We observed transcripts for Kir6.1, Kir6.2 and Sur2B in mRNA isolated from the PDL cells. In inside-out patches, the single channel conductance of 163 pS at symmetrical K⁺ concentration of 140 mM, as well as an outward rectification at voltages positive to +60 mV was recorded at the ATP- free bath solution. Single channel currents were almost inhibited when adding 5 mM ATP in the bath solution. However, the currents did not respond with 100 μM glibenclamide a subunit specific ATP channel blocker. Further, reversal potential was found to be 0 mV at symmetrical concentration (140 mM) of K⁺ in bath solution. These results support that human PDL cells express KATP channels. This research was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2014R1A1A2054241) and (2015R1D1A1A01018700)

Key Words: human periodontal ligament cell, Inside-out patch, KATP channels

P04-12

Close Spatio-Association of Transient Receptor Potential Canonical (TRPC4) channel with Gαi in TRPC4 activation process

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TRPC channels are Ca²⁺-permeable nonselective cation channels that are activated by a wide variety of stimuli, including G-protein-coupled receptors (GPCRs). TRPC is commonly assumed to be activated by Gq/ phospholipase C-coupled receptors. However, the other molecular mechanisms by which Gαi proteins regulate TRPC4 remain unclear. Here, we found that Gαi2 regulates TRPC4 activation by direct binding. To investigate this mechanism, we used whole patch clamp and FRET. We tagged an isoform of mTRPC4 and G protein with CFP and YFP, respectively, and transiently transfected cells with the FRET pair. The FRET efficiency between TRPC4B and the constitutively active mutant form of Gαi2 was nearly 15% and was greater than that observed with wild-type Gαi2 (nearly 5%). Gβγ and the TRPC4 channel showed a fluorescence resonance energy transfer (FRET) efficiency lower than 6%. In HEK293 cells transfected with the M2 muscarinic receptor, the application of carbachol (CCh) increased the FRET efficiency between TRPC4B and Gαi2 from 4.7 ± 0.4% (n = 7) to 12.6 ± 1.4% (n = 7). We also found that the TRPC4 channel directly interacts with Gαi2 but not with Gq or Gqα10 when the channel is open. We analyzed the calcium levels in HEK293 cells expressing the channels and Gαi2 or Gqα10 using the calcium indicator YC6.1 (yellow cameleon-6.1). In response to the application of carbachol (CCh) concentration lower than 1 μM in bath solution. However, the currents did not respond with 100 μM glibenclamide a subunit specific ATP channel blocker. Further, reversal potential was found to be 0 mV at symmetrical concentration (140 mM) of K⁺ in bath solution. These results support that human PDL cells express KATP channels. This research was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2014R1A1A2054241) and (2015R1D1A1A01018700)

Key Words: human periodontal ligament cell, Inside-out patch, KATP channels

P04-14

Physiological temperature increase the calcium sensitivity and current activation of TMEM16F (ANO6)

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TMEM16F, also known as ANO6, belongs to a family of putative Ca²⁺-activated Cl⁻ channel (CaCC). Different to other classical CaCC such as TMEM16A (ANO1), activation of ANO6 requires very high cytosolic Ca²⁺ concentration ([Ca²⁺]c>3μM) and strong positive membrane potentials. Moreover, even with the high [Ca²⁺]c, ANO6 current appears very slowly; >10 min to reach a steady-state. These properties were confirmed in all the three functioning variant (V1, 2, and 5) of ANO6. The low Ca²⁺-sensitivity and slow kinetics of ANO6 pose some doubt about the physiological roles as an ion channel. In the present study, using whole-cell patch recordings, we identified that the three types of ANO6 isoforms (V1, V2 and S) transiently activated in HEK293T cells are activated by lower [Ca²⁺]c under physiological temperature (37°C). Among them, however, V2 and V5 showed significantly higher sensitivity; activated by 400nM [Ca²⁺]c whereas V1 by 1μM [Ca²⁺]c. Furthermore, V2 and V5 showed significantly more prolonged time of activation than V1; after making the whole-cell configuration, the currents reached maximal size after 543.3 ± 72.48 s, 56.67 ± 9.55
s and 62.5 ± 4.53 s for V1, V2 and V5, respectively. The temperature-dependent effect was reversible. In inside-out patch, all isoforms of ANO6 exhibit higher calcium sensitivity as well as channel activity at physiological temperature even though they showed different kinetics. This study may provide the possibility of ANO6 functional action as ion channel in variable tissues and cells depending on the variant forms of ANO6.

Key Words: ANO6, variant forms, temperature, TMEM16F

P04-15

Electrophysiological Characterization of Novel KCNQ4 Mutant Channels

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KCNQ4 encodes a voltage-gated K+ channel (Kv7.4), and is highly expressed in the hair cells of the cochlea and plays a pivotal role in maintaining cochlear K+ homeostasis. It has been known that many mutations in the KCNQ4 gene induce autosomal dominant non-syndromic hearing loss (ADNSHL) prominent in the high frequencies and associate with deafness mapping the DFNA2 locus. Here, we provide two novel KCNQ4 mutants that found in Korean families, p.R331Q and c.811_816 del mutation. To evaluate electrophysiological consequences and to confirm the pathogenicity of the mutations, we expressed each mutant in HEK cells and compared them with wild type KCNQ4 channel (WT-KCNQ4). To explore whether the mutants play a role of dominant negative, each mutant (MT) was co-expressed with WT-KCNQ4 at the ratio of 3:1. With a conventional whole-cell patch-clamp technique, the current densities of KCNQ4-mediated K+ current were compared. For pharmacological separation of KCNQ4 current, linoperdine (10 μM) and retigabine (30 μM) were treated to inhibit and activate KCNQ4-mediated current, respectively. No appreciable amounts of linoperdine-sensitive KCNQ4 current was measured from the cells expressed with either p.R331Q or c.811_816 del mutant, confirming their pathogenic potential. Half activation voltages of the linoperdine-sensitive current from p.R331Q and c.811_816 del mutant (-17 mV) were significantly different from that of WT-KCNQ4 (-26 mV), but similar to that of GFP-transfected HEK cells (-15 mV). Both mutants abolished KCNQ4-mediated current when they were co-expressed with WT-KCNQ4 (WT:MT=3:1), suggesting their dominant negative roles. Interestingly, KCNQ4 activator retigabine can activate KCNQ4-mediated K+ current in p.R331Q-expressed cells, but not in cells with c.811_816 del mutant. Retigabine-activated p.R331Q current showed the same voltage dependence with WT-KCNQ4 current. Taken together, both p.R331Q and c.811_816 del mutant are estimated as loss-of-function mutations with a dominant negative effect. However, R331Q still preserves response to KCNQ4 activator (retigabine), and therefore being activated on demand.

Key Words: KCNQ4, mutation, ADNSHL, DFNA2, hearing loss

P04-16

Influence of Bisphenol-A on ion channel activities on Gonadotropin Releasing Hormone Neurons

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Bisphenol-A (BPA), a monomer of polycarbonate plastics, and epoxy resins is an environment pollutant which has been considered as endocrine disruptor. So, in this study, we investigated the effects of the BPA on gonadotropin-releasing hormone (GnRH) neurons using single cell electrophysiology on GnRH-green fluorescent protein (GnRH-GFP) transgenic mice. Conventional whole cell patch-clamp recordings were performed. In this study, we showed that 100% of GnRH neurons responded to 300 μM of BPA with a markedly prolonged inward current. The effect of BPA not only persisted in the presence of tetrodotoxin, but also in the presence of amino acid receptor antagonists, indicating the direct site of action is on postsynaptic GnRH neurons. Further, BPA-induced inward currents were concentration dependent. In addition, these inward currents were not blocked by gabazine, a selective GABAA receptor antagonist but were completely blocked by bicuculline, a broad (synaptic and extrasynaptic) GABAA antagonist. Apart from direct action of BPA as a GABAA receptor agonist, it significantly blocked the voltage gated potassium, calcium and sodium ion channels on GnRH neurons suggesting the direct influence on ion channel physiology of GnRH neurons. These results demonstrate that BPA can act directly on GnRH neurons to induce excitation via extra synaptic GABAA receptors and may influence GnRH neuron signaling via inhibition of voltage gated potassium, calcium and sodium ion channels on GnRH neurons. This research was supported by Basic Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2013R1A1A2053566) and (2014R1A1A2054241).

Key Words: Endocrine disrupting chemicals, Bisphenol-A, GnRH neurons, patch-clamp, GABAergic

P04-17

The Conserved Gating Elements in CIRB domain of TRPC4 Channel

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The activity of transient receptor potential (TRP) channel complexes is regulated via interactions with various binding partners. The structures of TRPV1 (vanilloid subfamily) and TRPA1 (ankyrin repeats subfamily) have been recently defined using electron cryo-microscopy techniques underlying functional architecture in the activity of TRP proteins. However the activation mechanism of classical TRP (TRPC) channel in gating property still remains controversial. Based on a low level of homology in cytoplasmic region following the coiled-coil domain among TRP proteins, we focused on the highly conserved TRP motif and CIRB (CaM- and IP3R-binding) domain near pore helix. To investigate structural architecture of TRPC4 channel, we mutated positively charged amino acids physically adjacent to CIRB domain. The basal activity of the alanine mutants was analyzed by perfusion of external Cs+ solution with high permeability. We found that replacing a conserved K715 with high permeability. We found that replacing a conserved K715...
or R716 within CIRB domain was activated by 2- to 5-fold increases in open probability and steady-state. Double mutant of K715/R716 (KR/AA) showed increased activity induced by the infusion of GTPyS or the stimulation of muscarinic (Gaq, or Gai/o-coupled) receptor at most fivefold compared to wild-type (WT) of TRPC4β. In the KR/AA mutant using intracellular Ca2+-buffered solution with EGTA, nominally free [Ca2+]i of 0 or 200 nM induced inward currents of 135 ± 29 or 441 ± 75 pA/pF, respectively (WT; 0.9 ± 0.3 or 20 ± 15 pA/pF). Although the double mutant of TRPC4β channel was also increased in inside-out patches with wild-type channel, the mutant exhibited single-channel conductance and surface expression similar to wild-type channel. While the basal activity of histidine mutant (KR/HH) at a neutral pH of internal solution was increased to Cs+ current of 92 ± 29 pA/pF similar to that of KR/AA, internal solution at pH 5.4 significantly decreased Cs+ current due to the protonated (i.e. positively charged) histidine at an acidic pH. The negatively charged (KR/DD) mutant completely lost activity induced by constitutively active mutant of inhibitory Gα proteins (Gai/o) and significantly decreased the interaction with Gai2 by FRET. The function of KR region of TRPC4α channel is similar to that of TRPC4β channel. Collectively, the neutralization of KR charged amino acids activates TRPC4 channel by competing with binding proteins in CIRB domain of TRPC4. The structural and mechanistic roles of the CIRB domain are responsible for TRPC4 activation acting as an inner helix gate and G loop gate.

Key Words: TRPC, Gi, Charge, Gating, Neutralization

P04-18

KCNQ2/3 channel inhibition by ethanol is regulated by plasma membrane PI(4,5)P2 level

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KCNQ2/3 channel is known that M-type channel which is one of the voltage-gated potassium channel. It was known that KCNQ2/3 channel is regulated by plasma PI(4,5)P2 level. The membrane PI(4,5)P2 play as cofactor for activating KCNQ2/3 channel. KCNQ2/3 channel is generally expressed in central and peripheral neurons. Also, KCNQ2/3 channels are expressed in Ventral tegmental area (VTA) dopamine neuron, which is associated with brain reward system. It was known that excitability of VTA neuron could reinforce the brain reward system, which is critically induced by ethanol. Although it was known that M-channel in VTA neuron is inhibited by ethanol, molecular mechanism of M-channel inhibition has not been studied. In this study, we investigated that alcohol affects KCNQ2/3 channels and alcohol inhibition mechanisms is related with PI(4,5)P2 level. We tested the inhibition in living tsA201 cells using pharmacology, electrophysiology, FRET, confocal microscopy methods. We found that alcohol inhibition was occurs transiently and the inhibition was related by carbon chain length and conformation of alcohols. Also, the inhibition was related with plasma membrane PI(4,5)P2 level, the inhibition has the KCNQ channel subunit specificity. Therefore, even though alcohols have low specificity to KCNQ2/3, these results indicate that alcohols could play an important physiological role as an inhibitor. Also, understanding this mechanism will give some evidences to develop alcohol-selective therapy for overcoming or preventing alcohol addiction.

Key Words: KCNQ2/3 channel, PI(4,5)P2, electrophysiology, alcohol

P04-19

Verapamil inhibits TRESK current in trigeminal ganglion neurons independently of the blockade of Ca2+ influx

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The TWIK-related spinal cord K+ (TRESK, K2P18.1) channel is the only member of the two-pore domain K+ (K2P) family that is predominantly expressed in Ventrall tegmental area (VTA) dopamine neuron, which is associated with brain reward system. It was known that excitability of VTA neuron could reinforce the brain reward system, which is critically induced by ethanol. Although it was known that M-channel in VTA neuron is inhibited by ethanol, molecular mechanism of M-channel inhibition has not been studied. In this study, we investigated that alcohol affects KCNQ2/3 channels and alcohol inhibition mechanisms is related with PI(4,5)P2 level. We tested the inhibition in living tsA201 cells using pharmacology, electrophysiology, FRET, confocal microscopy methods. We found that alcohol inhibition was occurs transiently and the inhibition was related by carbon chain length and conformation of alcohols. Also, the inhibition was related with plasma membrane PI(4,5)P2 level, the inhibition has the KCNQ channel subunit specificity. Therefore, even though alcohols have low specificity to KCNQ2/3, these results indicate that alcohols could play an important physiological role as an inhibitor. Also, understanding this mechanism will give some evidences to develop alcohol-selective therapy for overcoming or preventing alcohol addiction.

Key Words: KCNQ2/3 channel, PI(4,5)P2, electrophysiology, alcohol

P04-20

Stable interaction of Ca2+ channel β subunit with high voltage-activated Ca2+ channels α1 subunit revealed by translocatable CaV β subunit systems

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The ancillary β subunit of voltage-gated Ca2+ (CaV) channel is known to play an important role in regulating cell surface expression and biophysical gating properties of high-voltage activated (HVA) Ca2+ channels via a type-specific interaction with CaV α1 subunit. However, the molecular mechanism of CaV channel regulation by β subunit is not clearly determined. Several recent studies showed that the interaction between CaV α1 and CaV β subunit is not dynamic but stable. Here we developed the rapamycin-induced translocatable systems with CaV α1 and β subunit to reveal the molecular interaction properties between CaV α1 and CaV β subunit. We found that cytosol-localized CaV β subunits were well translocated to the intracellular target membranes by rapamycin application, whereas plasma membrane-bound CaV β subunits were not moved. When the CaV β subunit was expressed together with CaV α1, it was not translocated to the target membranes by rapamycin, probably due to the irreversible CaV α1-CaV β interaction. Confocal imaging experiments showed that in the presence of CaV α1 subunits, translocation of CaV β subunits to endoplasmic reticulum (ER) triggered artificial ER-PM junctions and then formed puncta

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Functional role of GABA as a gliotransmitter in epileptic hippocampus

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Nowadays, it is claimed that GABA present in astrocyte is the major source of tone inhibition in cerebellum and other brain areas. Although, GABAergic tone current in hippocampal pyramidal neurons are targeted for anti-epileptic drug (AED’s) in seizures or epilepsy, source of GABA mediating them in epileptic condition remains unclear. Loss of GABAergic interneurons and less presynaptic GABA release in pyramidal neurons are the ones that lead to neuronal hyper excitability during seizure or epilepsy, saying that the GABAergic tone current is maintained in these conditions. Using whole cell patch clamp recording, here we show that bestrophin1 (Best1) mediated GABA release and its component of the GABAergic tone current in mouse model of seizure using 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB), which blocks recombinant Best1 channels. Intracellular basic (L.c.v) injection of kainic acid (KA) produced GABAergic tone current in mice. Time schedule of 1, 3, 7 and 15 days after kainate injection was made in order to see its long lasting effect on GABAergic tone current mediated by best1 released GABA. ICR and BALB/c mice exhibited the NPPB sensitive current after the kainate injection which was gradually decreased with the time, in contrast we did not see any portion of NPPB sensitive current in best1 knockout (KO) mice with the kainate injection. N6-711, a GABA transporter (GAT-1) blocker induced a larger inward current in 3 day kainate injected mice compared to wild type (WT) control but 3 day kainate injected KO mice had similar response to WT. Further, through the immunohistochemical staining we see the increased GABA and best1 in GFAP positive cells from kainate injected mice. To find out the functional significance of best1 expression in pyramidal layer astrocytes from kainate injected mice, best1 KO and WT mice were injected with kainate then compared the seizure response and latent period in the groups. We did not see the latent period difference between the groups, yet seizure activity was lasted long in KO mice on the injected day and remained hyper activate until 11th day after the kainate injection compared to WT. Maximal electroshock seizure (MES) test was conducted where KO mice displayed higher seizure sensitivity in compared to WT control after 3 day kainate injection. In conclusion, enhanced GABA and best1 in pyramidal layer astrocytes in kainate model mediate and contribute to maintain GABAergic tone current in compensation of decreased GABA level in epilepsy. Also it may also play a role in suppression of the seizure.

Key Words: tonic GABAA current, bestrophin1, hippocampus

Goi-mediated TRPC4 activation by Polycystin-1 contributes to cystic disease via STAT1 activation

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Polycystin-1 (PC1) regulates a number of cellular processes (ex. heterotrimeric G protein, transcription factor etc.) through the formation of complexes with the polycystin-2 (PC2) ion channel or with other signal transduction proteins. Although Ca2+ modulation by polycystins has been reported between transient receptor potential (TRP) channels, the function with TRPC subfamily regulated by G-protein signaling has remained elusive. We have previously reported that TRPC4/C5 channel can be activated by Go through direct interaction1. Here, we identified that PC1 dominantly interacts with Ga3 using co-immunoprecipitation. Thus we recorded the activity of TRPC4/C5 heterologously co-expressed with PC1 in HEK293 cells. PC1 activated TRPC4 channel (4 ± 1 ± 41 ± 14 pA/pF) by modulating G-protein signaling without change in TRPC4 translocation. Intracellular 0.2 mM GTPγS-induced TRPC4 activation was not significantly different in the presence or absence of PC1. C-terminal fragment (CTF) of PC1 did not affect TRPC4/C5 activity due to loss of N-terminus containing G-protein coupled receptor proteolytic site (GPS). Dominant negative Ga3 (G202T) mutant inhibited PC1-activated TRPC4 current. TRPC5 also was activated by full-length PC1 (54 ± 8 ± 114 ± 16 pA/pF). We, next, investigated whether TRPC4 induces activation of STAT (signal transduction and transcription) proteins, leading to cell proliferation or death. We observed that STAT1 and STAT3, but not STAT6 activation by PC1 is independent on Src kinase cascade. Interestingly, TRPC4 promoted STAT1 activation. When PC1 co-expressed with TRPC4, STAT1 activation was further increased compared to each sole expression. Our findings indicated an important function between PC1 and TRPC4/C5 in modulation of intracellular Ca2+ signaling and provided a new potential therapeutic approach targeting TRPC4/C5 channel in polycystic kidney disease.

Key Words: polycystin, TRPC, STAT
The role of PIP2 signaling in NALCN regulation

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NALCN (Sodium leak channel, non-selective) is predominantly expressed in neurons where it regulates the resting membrane potential and neuronal excitability. Both in mammals and invertebrates, animal models revealed an involvement of NALCN in many biological processes such as locomotor behaviors, sensitivity to volatile anesthetics, and respiratory rhythms. Although NALCN was reported to be activated either by M3 muscarinic receptor or by lowering [Ca2+]o, the underlying mechanisms of this NALCN activities remain poorly characterized. In this study, I examined the regulation of NALCN by phosphatidylinositol 4,5-bisphosphate (PIP2). As previously reported, I first confirmed that NALCN was activated by M3 muscarinic receptor and also by lowering [Ca2+]o, using the conventional whole-cell patch clamp technique. To examine whether phosphoinositide is implicated in the regulation of the NALCN, I tested the effects of the Phospholipase C (PLC) inhibitor, U73122 on NALCN activity, which blocked muscarinic receptor-induced activation of NALCN. This result was also confirmed by the confocal imaging technique. Acetylcholine (ACh) induces PIP2 hydrolysis. Thus, one possibility is that PIP2 depletion might lead to augmentation of NALCN activity. In line with this hypothesis, supplementing PIP2 to cells blocked the activation of NALCN by M3 muscarinic receptor. Consistently, the depletion of PIP2, by intracellular application of a PIP2 antibody strongly increased the NALCN activity whereas PIP2 reduced the NALCN activity in a dose dependent manner. In addition, the increased channel activity by the PIP2 antibody was inhibited by 10 μM Gd3+, a NALCN inhibitor. Taken together, these data suggest that membrane PIP2 negatively regulates NALCN at rest. This inhibition was released by PIP2, depletion resulting from the PIP2 antibody or a muscarinic agonist, leading to NALCN activation.

Key Words: NALCN, Phosphoinositide, PLC, PIP2, muscarinic receptor

Proton modulates common gate of CIC-1 chloride channel via helix O

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The CIC proteins play many important physiological roles by transporting anion across plasma membrane. The CIC family consists of two subfamilies, channels and antiporters, that share similarity in their structures and mechanism; a homodimer with two gating residues, Proton, similar to its role in antiporter, provides energy in CIC channels and affects common gate that regulates the closing of both pore simultaneously. Conserved glutamate (Gluin) at the intracellular part of the protein is known to provide proton pathway in CIC antiporters. Unlike the antiporter, Gluin is replaced by valine in C1C-1 channels, and the mechanism underlying how proton modulates the common gate is largely unknown. Previously, myotonic mutations in human CIC-1, G523D and G499R in helix O and N were respectively reported to exhibit reversed voltage dependency in the common gate, similar to that of wild type under a low extracellular pH condition. In our study, molecular modelling data suggest that those two mutants are related to fixation of helix O at the extracellular part, and we tentatively concluded that these mutants resemble the conformational change caused by low extracellular pH. We also identify that serine (S537) residue at the C-terminal of helix O locates near the central pore of the channel and hypothesized that it regulates the proton transport in CIC-1 channels. Mutating the serine residue to negatively charged amino acids largely diminished the effect of proton at low extracellular pH condition, displaying no significant difference compared to wild type. Double mutant G523D and S537E also showed retained voltage dependency in the common gate. Replacing the valine residue (V292) corresponding to Gluin in the CIC antiporters to glutamate reduced the common gate. Collectively, these data reveal that proton transport across the CIC-1 channel is largely linked to the common gate via S537 and V292 is a key evolutionary step in CIC proteins.

Key Words: CIC-1, pH, Common gate, Chloride, Proton
Glycosmis stenocarpa increases Ca\textsuperscript{2+} influx, Ca\textsuperscript{2+} receptor inhibitor propranolol, protein kinase A inhibitors KT5720 or Sun-Hee Woo ventricular myocytes in rat ventricular myocytes. These results indicate that Mu-A-mediated positive inotropic effect of β-adrenergic receptor, CaMKII, PKA, or PLC failed to suppress the enhancement of Ca\textsuperscript{2+} influx through the L-type Ca\textsuperscript{2+} channels (I\textsubscript{Ca,L}) in rat ventricular myocytes. In the present study, we further examined whether the enhancements of contractility and I\textsubscript{Ca,L} by Mu-A are mediated by its effect on PKC or not. Cell shortenings and I\textsubscript{Ca,L} were measured using the video edge detection method and perforated patch-clamp technique, respectively. The positive inotropic effect of Mu-A (25 μM) reached a maximum after about 2-min exposures, and then decayed after a about 1-min steady-state. Mu-A transiently enhanced the I\textsubscript{Ca,L} with a similar time course. The positive inotropic effect of Mu-A was not inhibited by pre-treatment of β-adrenergic receptor inhibitor propranolol, protein kinase A inhibitors KT5720 or H89, Ca\textsuperscript{2+}-calmodulin-dependent protein kinase II (CaMKII) blocker KN93, or phospholipase C (PLC) inhibitor U73122. Interestingly, the Mu-A-mediated positive inotropy was eliminated by preincubation of PKC inhibitors GF109203X or calphostin C. Consistently, the PKC blocker prevented the Mu-A-induced I\textsubscript{Ca,L} enhancement, although the inhibition of β-adrenergic receptor, CaMKII, PKA, or PLC failed to suppress the stimulatory effect of Mu-A on I\textsubscript{Ca,L}. These results indicate that Mu-A-mediated positive inotropy may be mediated by increase in I\textsubscript{Ca,L} via PKC in rat ventricular myocytes. 

**Key Words:** Murrayafoline-A, positive inotropy, PKC, L-type Ca\textsuperscript{2+} current, ventricular myocytes

**P04-27**

Enhancements of contraction and L-type Ca\textsuperscript{2+} current by murrayafoline-A via protein kinase C in rat ventricular myocytes

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It has been recently reported that murrayafoline-A (1-methoxy-3-methylcarbazole, Mu-A), which is isolated from the dried roots of Glycosmis stenocarpa increases Ca\textsuperscript{2+} transients by directly activating protein kinase C (PKC), and that its positive inotropic effect is dependent on enhancement of Ca\textsuperscript{2+} influx through the L-type Ca\textsuperscript{2+} channels (I\textsubscript{Ca,L}) in rat ventricular myocytes. In the present study, we further examined whether the enhancements of contractility and I\textsubscript{Ca,L} by Mu-A are mediated by its effect on PKC or not. Cell shortenings and I\textsubscript{Ca,L} were measured using the video edge detection method and perforated patch-clamp technique, respectively. The positive inotropic effect of Mu-A (25 μM) reached a maximum after about 2-min exposures, and then decayed after a about 1-min steady-state. Mu-A transiently enhanced the I\textsubscript{Ca,L} with a similar time course. The positive inotropic effect of Mu-A was not inhibited by pre-treatment of β-adrenergic receptor inhibitor propranolol, protein kinase A inhibitors KT5720 or H89, Ca\textsuperscript{2+}-calmodulin-dependent protein kinase II (CaMKII) blocker KN93, or phospholipase C (PLC) inhibitor U73122. Interestingly, the Mu-A-mediated positive inotropy was eliminated by preincubation of PKC inhibitors GF109203X or calphostin C. Consistently, the PKC blocker prevented the Mu-A-induced I\textsubscript{Ca,L} enhancement, although the inhibition of β-adrenergic receptor, CaMKII, PKA, or PLC failed to suppress the stimulatory effect of Mu-A on I\textsubscript{Ca,L}. These results indicate that Mu-A-mediated positive inotropy may be mediated by increase in I\textsubscript{Ca,L} via PKC in rat ventricular myocytes. 

**Key Words:** Murrayafoline-A, positive inotropy, PKC, L-type Ca\textsuperscript{2+} current, ventricular myocytes

**P04-28**

Enhancing skin barrier homeostasis via modulation of calcium ion channels by topical botanical products

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Intracellular Ca\textsuperscript{2+} signaling via various calcium channels, such as Orai1, Transient receptor potential (TRP)A1 and TRPV3, has been shown to directly modulate epidermal proliferation, differentiation, barrier homeostasis, and inflammation. Ca\textsuperscript{2+} influx through these channels eventually generates intracellular Ca\textsuperscript{2+} signaling that results in different outcomes dependent on the individual Ca\textsuperscript{2+} channel type. For example, keratinocyte proliferation and migration through Orai1, epidermal barrier formation and keratinocyte differentiation through TRPA1, and keratinocyte cornification through TRPV3. Therefore, a specific agonist/antagonist for each calcium channel is required for maintaining skin barrier homeostasis and for the treatment of dermatological diseases. To identify botanically derived chemicals for topical use in functional cosmetics or agents for dermatological diseases, novel modulators of Orai1, TRPA1 and TRPV3 were identified by screening the extracts (plus their fractions) of 30 medicinal herbs and their constituents. The potencies of the activating or inhibiting compounds on the channels were determined by an automated patch clamp system. Biophysical properties of the channel modulation by the hit products were reanalyzed using conventional whole-cell patch clamp recordings. The protocol for the test compounds was 30 μg/ml. We also found three fractions with TRPA1 agonist activity. Chemical constituents of the agonists or antagonists will be discussed.

**Key Words:** skin barrier, TRPV3, TRPA1

**P04-29**

Epidermal growth factors activate TRPC4 and TRPC5, reducing desensitization of TRPC5 channel

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Receptor-operated Ca\textsuperscript{2+} (ROC) channels are activated via ligand-mediated activation of receptor tyrosine kinase (RTK) and G protein-coupled receptors (GPCR). The evidence for activation of classical transient receptor potential (TRPC) channels in ROC entry is linked to G\textsubscript{q}, PLC, G and EGF (epidermal growth factor). A recent study suggested the involvement of TRPC4 in the activation of a store-operated current in corneal epithelial cells by EGF. However, the primary activation mechanism of TRPC4 remains controversial. Although we previously reported that TRPC4 and TRPC5 channels are activated by G\textsubscript{q} proteins, we further investigated the effect of EGF on TRPC4 and TRPC5 activity in our hands. We recorded the currents by whole-cell patch clamp on HEK293 cells transiently transfected with TRPC4 or TRPC5. The external application of EGF activated TRPC4β channel, but not TRPC4α. Under the serum deprived conditions, EGF significantly enhanced TRPC4β activation (43.4 ± 13.9 pA/pF). Similarly, TRPC5 channel was activated by EGF. EGF induced an increase in La\textsuperscript{3+}-sensitive TRPC5 current. Interestingly, the treatment of EGF blocked desensitization of the activated current. Taken together, these results confirmed that EGF activates TRPC4β and TRPC5 channels. It needs to be further studied to unveil the mechanism how EGF activates TRPC4β and attenuates the desensitization of TRPC5 channel, respectively.

**Key Words:** TRPC4, EGF, leptin
Inhibition of the extrinsic aging-related ion channels TRPV1 and ORAI1 by constituents of the fruits of Foeniculum vulgare

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Ultraviolet (UV) exposure due to the solar radiation is the most important cause of extrinsic skin aging (photoaging), which is characterized clinically by deep skin wrinkling and pigmentation. These phenomena are due to the increasing of metalloproteinasases-1 (MMP-1) expression in keratinocytes and tyrosinase activation in melanocytes. In a recent study, it was reported that two Ca²⁺ channels, a transient receptor potential vanilloid type-1 (TRPV1) and a calcium release-activated calcium channel protein 1 (ORAI1), are involved in UV-induced MMP-1 expression and tyrosinase activity, respectively. In the present study, we analyzed whether the fruits of Foeniculum vulgare have inhibitory effects on TRPV1 and ORAI1 using the whole-cell patch clamp technique and intracellular Ca²⁺ measurements. In our electrophysiological study of the extract and its fractions, the methylene chloride and hexane fractions were found to strongly block capsaicin-induced TRPV1 and ORAI1 currents in HEK293T cells overexpressing TRPV1 or a combination of ORAI1 and STIM1. Furthermore, of the 18 compounds isolated from above fractions, trans-anethole in the hexane fraction had inhibitory effects on both ORAI1 and increases in cytoplasmic Ca²⁺ concentrations in response to ORAI1 activation (both by ~70% at 100 μM). Our findings suggest that the fruit extract of F. vulgare provides a possible novel approach for treating and preventing UV-induced skin aging.

Key Words: Foeniculum vulgare, TRPV1, ORAI1, photoaging, trans-anethole

The rhizomes of Cyperus rotundus and its active component valencene inhibit skin photoaging related ion channels, TRPV1 and ORAI1

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Ultraviolet (UV) irradiation deeply penetrates into skin and causes skin inflammation, immune response changes and pigmentation that promote skin photo aging. Recently, accumulated evidence suggests that several calcium ion channels such as transient receptor potential vanilloid 1 (TRPV1) and calcium release-activated calcium channel protein 1 (ORAI1) mediate diverse skin processes including melanogenesis, skin wrinkling and inflammation. The rhizome of Cyperus rotundus (C. rotundus) is a traditional medicinal herb that has been reported to treat inflammatory diseases such as dermatitis and arthritis. However, its effects on UV-induced photo aging related ion channels are still not known. The aim of this study was to evaluate whether C. rotundus extract and its constituents confer antagonistic activity on TRPV1 and ORAI-1. Electrophysiological analysis revealed that the hexane fraction (100 μg/mL) inhibited capsaicin-induced TRPV1 (95 ± 3% at -60 mV) and ORAI1 (89 ± 4% at -120 mV) currents. Furthermore, valencene, which was one of five constituents isolated from the hexane fraction, showed potent inhibitory effects on TRPV1 (69 ± 15% at -60 mV) and ORAI1 (97 ± 2% at -120 mV) currents. Our results provide insight into the potential therapeutic effects of C. rotundus in the contexts of UV-induced photoaging. The therapeutic and cosmetic applications of valencene need further investigation.

Key Words: Cyperus rotundus, TRPV1, ORAI, valencene

Cryopreservation method of isolated adult cardiac myocytes of rat

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Cardiomyocytes in a physiologic condition are useful model for cardiac physiological research. However, there are inevitable problems to isolate cell: 1) need to sacrifice the animal, 2) need to find the appropriate experimental conditions and adequate enzymes, and 3) difficult to maintain the quality of the isolated myocytes in each isolation. Especially, these problems are the biggest obstacles for isolating human cardiomyocytes. To resolve the above problems, cryopreservation method for long-term cell preservation should be established. In this study, we tried to find the cryopreservation method that can store and recover the cardiomyocytes in a physiologic condition. We tested the several cryoprotective agents, the freeze-thawing conditions, the used solution compositions, and the other agents like 2,3-butanediol monoxygen (BDM). The viability and the shape of cardiac myocytes were checked using trypan blue staining. We found dimethyl sulfoxide (DMSO) was the best cryoprotective agents than the others (methanol, formamide, ethanol, ethylene glycol, glycerol). Among the test of different percentage of DMSO, 15 % DMSO condition produced the best cell survival rate. Cell viability is about 7 percent higher when the rat serum was used instead of fetal bovine serum. Freezing cardiomyocytes in ~80°C in deep freezer generated better survival rate than -20°C or -196°C. Using Iscove’s Modified Dulbecco’s Medium (IMDM) for storage solution makes the cell survival rate higher than using Dulbecco’s Modified Eagle’s Medium (DMEM). The survival rate has clearly increased when thawing in 37°C water bath than room temperature. Pretreatment of BDM definitely improved the cell shape and the survival rate. In conclusion, DMSO reduced cell damage from the procedure of freezing or thawing. Using rat serum helped the cell survival rate. IMDM improved the cell yield and the survival rate after the cryopreservation. The higher concentration of glucose and Mg⁺² may contribute for that effect. From the above results, we could obtain more than 75% survival rate after cryopreservation compared to the survival rate of the initial isolation by optimizing the cryopreservation conditions.

Key Words: Cardiomyocyte, Cryopreservation, Cryoprotective agents, DMSO, Cell viability

Unusual acid- and voltage-dependency of a prokaryotic CLC, eCLC-2: A marginal ion channel or broken transporter?

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The CLC superfamily can be classified into Cl- channels and Cl-/H+ antiporters and be found in virtually all organisms. Genetic mutations in the CLC genes are linked to the various diseases such as myotonia, deafness, epilepsy, leukodystrophy, kidney malfunctions and lysosomal storage disease. CLC proteins also play key roles in the physiology of other organisms: NO3- uptake for nitrogen fixation in plants, extreme acid-resistance in enteric bacteria. In enteric bacterium, two ClC proteins, CLC-1 and CLC-2 are both functionally important for surviving extreme acid environment such as in the stomach; doubly knock-out E.coli cannot survive at pH 2.5 (in the stomach), but either one of CLC gene is enough to rescue the KO mutant. Intriguingly, reconstituted ecCLC-2 (and ckCLC-2) shows much lower Cl- transport activity than ecCLC-1, which immediately raise a question: how does ecCLC-2 have such a physiological contribution with much lower activity than its parologue, ecCLC-1? Here, we present a line of evidences, suggesting a plausible explanation: ecCLC-2 is activated below pH 3, where ecCLC-1 begins to shut down, and ecCLC-2 is also activated by transmembrane voltage stimulus to which ecCLC-1 marginally respond. Interestingly, ecCLC-2 swaps 1 H+ with 10 Cl- in the reconstituted membrane and the exchanging stoichiometry can be changed to 1 : 4 (H+/Cl-) with both acidification and transmembrane voltage change. To reveal the operating mechanisms of ecCLC-2, we are currently devoting our time to solve the crystal structure of ecCLC-2 (and ckCLC-2).

**Key Words:** CLC protein, Ion channel, Transporter, Extreme acid-resistance

### P04-35

**Ketamine inhibits KCNQ2/3 channels and modulates excitability in hippocampal dentate gyrus granule cells**

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Recent studies showed that ketamine, an ionotropic glutamatergic NMDAR (N-methyl-D-aspartate receptor) antagonist, produces a fast-acting antidepressant response in patients with major depressive disorder. However, little is known about the effects of ketamine in the regulation of ion channels in the brain. KCNQ channels regulate neuronal excitability and KCNQ channel inhibitor XE991 reverts cognitive impairment. We tested the action of ketamine on KCNQ2/3 channels in HEK293 cells and hippocampal neurons using patch clamp technique. Ketamine inhibits KCNQ2/3 currents heterologously expressed in HEK293 cells. Current inhibition by ketamine was voltage independent but concentration-dependent. The IC50 for current inhibition was 50.7±13.4 μM. The voltage-dependent activation of the channel was not modified. The powerful effects of ketamine on cloned KCNQ channels imply that ketamine action on KCNQ channels didn’t involve NMDAR. The effects of MK801 and DL-2-amino-5-phosphonopentanoic acid (AP-5), NMDAR blockers that are structurally similar to and distinct from ketamine, respectively, were also examined. MK801 had similar inhibitory effects on KCNQ2/3 channels, but AP-5 showed no effects on KCNQ2/3 activity, suggesting the direct effects of ketamine and MK801 on KCNQ2/3 channels. In hippocampal neurons, which endogenously express KCNQ2/3 channels, application of ketamine produced an increase in neuronal excitability and input resistance. Taken together, these data suggest that ketamine is a KCNQ2/3 channel modulator and the modulation of the neuronal excitability by ketamine may contribute to the fast-acting antidepressant action of ketamine.

**Key Words:** depressive disorder, K channel, ketamine

### P04-36

**Voltage gated sodium channel 1.7 as therapeutic target for treatment of neuropathic pain**

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A novel class of voltage gated sodium channel 1.7 (Nav1.7) inhibitors has been identified. Our compounds showed potent human Nav1.7 inhibitory activities with fair subtype selectivity over Nav1.5. Compounds successfully demonstrated analgesic efficacy in animal models comparable to that of the prototype drug gabapentin.

**Key Words:** voltage gated sodium channel, Pain, ion channel
Autocrine insulin stimulates plasma membrane trafficking of KATP channel via PI3K-VAMP2 pathway in MIN-6 cells

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The aim of this study is to know the effects of nitric oxide (NO) on voltage-dependent K⁺ currents in human cardiac fibroblasts. We found three types of voltage-dependent K⁺ currents in human cardiac fibroblasts by whole-cell mode patch clamp techniques, RT-PCR and Western blots: (1) slow oscillation, non-inactivating, and outward rectifying Ca²⁺-activated K⁺ (KCa) currents, (2) fast activating and non-inactivating, or slowly inactivating delayed rectifier outward K⁺ (KDR) currents, and (3) fast activating and fast inactivating transient outward K⁺ (KTO) currents. In whole-cell configuration, 5-nitro-6-acetylenicilnine (SNAP, NO donor) significantly increased KCa, KDR, and KTO currents. KT5720 (protein kinase A blocker) also inhibited the SNAP stimulating effect on KCa and KDR currents but not KTO currents. B-bromo-cAMP (cell-permeable cAMP analogue) and forskolin (adenylate cyclase activator) increased KCa and KTO currents. On the contrary, the stimulating effect of SNAP on KTO currents was not blocked by KT5720. B-bromo-cAMP also did not increase KTO currents. These findings suggest PKG and PKA pathways involved in the SNAP stimulating effect on KCa currents and KTO currents in human cardiac fibroblasts. On the other hand, the SNAP stimulating effect on KTO currents were through PKG pathway but not PKA pathway.

Key Words: Human Cardiac Fibroblast, Nitric oxide, PKA Pathway, PKG Pathway, Voltage-dependent K⁺ currents
Inhibition of N-type Ca\(^{2+}\) currents in rat peripheral sympathetic neurons by imidazoline \(\text{I}_\text{\textsubscript{1}}\), receptors activation

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Agmatine, an imidazoline derivative, suppresses the vasopressor sympathetic outflow to produce hypotension. This effect has been known to be mediated in part by suppressing sympathetic outflow via acting imidazoline \(\text{I}_\text{\textsubscript{1}}\), receptors (IR\(_2\)) at postganglionic sympathetic neurons. But, the cellular mechanism of IR\(_2\)-induced inhibition of noradrenaline (NA) release is still unknown. To investigate this possibility, we investigated the effect of IR\(_2\) on Ca\(^{2+}\) currents (ICa) in isolated neurons of the celiac ganglion (CG), which is involved in the sympathetic regulation of mesenteric artery vascular tone. In the present study, agmatine diminished voltage-gated Ca\(^{2+}\) currents (ICa), measured using the patch-clamp method, in an irreversible manner in rat CG neurons, while, thrombin had little effect on ICa. This agmatine-induced inhibition was nearly completely prevented by ω-CgTx, a potent N-type Ca\(^{2+}\) channel blocker, suggesting involvement of N-type Ca\(^{2+}\) channel in the PAR-2-induced inhibition. In addition, agmatine inhibited ICa in a voltage-independent manner in rat CG neurons. Moreover, agmatine reduced action potential firing frequency measured using the current-clamp method in rat CG neurons and this inhibition of AP firing induced by agmatine nearly completely prevented by ω-CgTx, indicating IR\(_2\) activation may regulate the membrane excitability of peripheral sympathetic neurons through modulation of N-type Ca\(^{2+}\) channels in rat CG neurons. In conclusion, the present findings demonstrate that the activation of IR\(_2\) suppresses peripheral sympathetic outflow by modulating N-type Ca\(^{2+}\) channel activity located in peripheral sympathetic nerve terminals, which appear to be involved in IR\(_2\)-induced hypotension. This research was supported by the Pioneer Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (2012-0009525)

Key Words: Agmatine, IR\(_2\), N-type Ca\(^{2+}\) currents, celiac ganglion

TRPC6 induces hepatic stellate cell activation causing liver fibrosis

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Hepatic stellate cells (HSCs) activation is the leading cause of liver fibrosis and portal hypertension. In response to injury, HSCs are activated by phospholipase-linked receptors such as Gq-protein coupled receptors and receptor tyrosine kinases whose activation evokes Ca\(^{2+}\) influx mediated signaling pathways are implicated directly or indirectly activating HSCs causing de novo expression of α-smooth muscle actin (αSMA) and/or profibrotic ligand TGFβ. However, the molecular identity and underlying mechanism of ROCE involving HSC activation are ill-defined. Here, we report that TRPC6 channel is an essential molecular component of ROCE mediating HSC activation. Among TRPCs, TRPC6 expression was significantly increased in bile duct ligation- and thioacetamide-induced liver cirrhosis animal models. Functionally, TRPC6-stimulated Ca\(^{2+}\) influx was blunted by specific blockade of TRPC6 with the siRNA against TRPC6 and pharmacological inhibitor SKF96365 in cultured human HSCs. Overexpression of TRPC6 by gene delivery in mice induced de novo expression of αSMA and TGFβ suggesting that TRPC6-mediated Ca\(^{2+}\) influx may involve in HSCs activation and liver fibrosis. These results provide a new perspective on the pathogenesis of liver fibrosis and may provide clues for treatment of the liver cirrhosis. This research was supported by Basic Science Research program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2010-0024789)[P04-42(O-2)]

Key Words: TRPC6, liver fibrosis, ROCE, HSC activation

The organellar Ca\(^{2+}\) channel TRPML3 regulates early autophagosome biogenesis by interaction with phosphoinositides

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TRPML3 is a Ca\(^{2+}\) permeable cation channel expressed in multiple organelles including autophagosomes. Although TRPML3 induces autophagy and increases autophagy upon cell stress, how TRPML3 regulates autophagy is not known. By using a fusion protein containing...
by induction of autophagy. These results suggest that TRPML3 is a key
we found that TRPML3-GCaMP6 could be activated by PI3P as well as
initiation of autophagy and enriched in autophagosomes. Moreover,
phosphatidylinositol-3-phosphate (PI3P) which is essential for the
process. Lipid binding assay showed that TRPML3 interacts with
phosphatidylinositol-3-phosphate (PI3P) which is essential for the
initiation of autophagy and enriched in autophagosomes. Moreover,
we found that TRPML3-GCaMP6 could be activated by PI3P as well as
by induction of autophagy. These results suggest that TRPML3 is a key
regulator for autophagy process, activating by PI3P and providing Ca
during early steps of autophagosome formation.

Key Words: TRPML3, phosphoinositide, Autophagy, GCaMP6

P04-44

 Trafficking-dependent N-glycan structure regulates cell surface expression of potassium channel Kv3.1b
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The potassium ion channel Kv3.1b, member of the third group of
maturely glycosylated voltage-gated ion channel family, allows high
frequency firing of neurons through a controlled modulation of
outward currents when functional and physiologically expressed on
the cell surface. N-glycosylation is known to regulate several functions
different ion channels including trafficking to the cell surface,
targeted localization, gating, and stability. However, the mechanisms
of N-glycosylation-dependent function to Kv3 channels remain to
be elucidated. Here, we show the principal roles of glycosylation at
specific asparagine sites to the diverse functions of the potassium
channel Kv3.1b. We observed that the N-glycosylation at N229, similar
to wild-type, predominantly mediates the cell-surface trafficking and
localization of Kv3.1b proteins whereas high quantities of wild-type
(WT) and N229-glycosylated Kv3.1b channel proteins reach the cell
surface. Both N220-glycosylated and unglycosylated Kv3.1b channel
proteins do also reach the cell surface but in very minute amounts. Mass
spectrometric analyses revealed a complex GlcNAc2Man3GlcNAc2Fuc1 as
the predominant glycan composition of N229-glycosylated Kv3.1b
proteins; as compared to Man8GlcNAc2 for N220-glycosylated Kv3.1b
proteins which are of the high-mannose type. Additionally, all forms of
ER-retained Kv3.1b channel proteins especially of the unglycosylated
types are susceptible to degradation when coexpressed with calnexin,
in comparison to plasma membrane Kv3.1b pools which are generally
resistant, which suggest distinctions in Kv3.1b protein localization. Taken
together, our findings suggest that the various trafficking functions
of the potassium channel Kv3.1b are majorly N229-glycosylation
specific asparagine sites to the diverse functions of the potassium
channel. The phosphorylation subsets of potassium channel
Kv3.1b determine cell background specific differences in function between cerebellum and
cerebrum
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The voltage-gated potassium channel Kv2.1 is highly phosphorylated
in mammalian brain, and its variable phosphorylation sites modulate the
activity-dependent regulation of the channel functions. Previous
our studies reported that the differential phosphorylation subsets of
Kv2.1 affect differences in its physiological properties in different
cell types under basal conditions. Here we found the differences of
Kv2.1 phosphorylation status between cerebellum and cerebrum in
brain. To understand whether these differences are due to different
phosphorylation states of the same sites or the different sets of
phosphorylation sites on Kv2.1 in brain, we used nano-LC tandem mass
spectrometry (nano-LC MS/MS) for the qualitative and quantitative
analysis of phosphorylation of Kv2.1 purified from cerebellum and
cerebrum. We identified a total of 14 phosphorylation sites in
Kv2.1 proteins that exhibits different levels or phosphorylation
sites distributions after oxidant induced brain ischemia. Mutation of the tyrosine phosphorylation sites
(Y686F and Y810F) of Kv2.1 channel results in a decrease of cleaved
PARP-1 level, which indicates the suppression of the neuronal cell
denaturation. In a brain ischemia model, the tyrosine phosphorylation of Kv2.1 is also increased after brain ischemia. A sustained increase of tyrosine
phosphorylation of Kv2.1 was observed for at least 2h after reperfusion. Our results show that the tyrosine phosphorylation of Kv2.1 channel in
brain play a critical role in regulating neuronal ischemia and may be a
potential therapeutic target for brain ischemia.

Key Words: Kv2.1, tyrosine phosphorylation, brain ischemia, oxidative stress
Conclusion: miR-200a and miR-210 overexpression, respectively, on both their proliferation and osteogenic differentiation with that of downregulation of ZEB2 or IGFBP3 in the hADSCs showed similar effects lower activity in the miR-200a- or miR-210-transfected hADSCs than miR-210 target site within the IGFBP3 3’ untranslated region revealed the miR-200a target site within the ZEB2 3’ untranslated region and the analysis of the luciferase reporter activity of the constructs containing the miR-210 target site within the HDAC1 3’ untranslated region revealed lower activity in the miR-210-transfected hADSCs than in control microRNA-transfected hADSCs. The effects of RNA interference–mediated downregulation of HDAC1 on both the proliferation and adipogenic and osteogenic differentiation of hADSCs were similar to those of miR-210 overexpression. Our results indicate that miR-210 regulates the adipogenic and osteogenic differentiation and proliferation of hADSCs through direct targeting of HDAC1.

Key Words: hADSC, adipogenic differentiation, osteogenic differentiation, proliferation, miRNA-210

P05-03(O-12)

mTOR signaling in the insular cortex modulates neuropathic pain

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The insular cortex (IC) has recently been associated with chronic pain, but the underlying molecular mechanisms remain unclear. Because the IC was thought to store pain-related memories, determining the role that translational regulation plays in neuronal plasticity may identify novel targets for controlling chronic pain. The mammalian target of rapamycin (mTOR) is known to control mRNA translation and influence synaptic plasticity and dendritic growth. There have been many studies that have investigated mTOR signaling at the spinal level, but mTOR signaling in the IC in neuropathic pain remains unknown. Therefore, we investigated the role of mTOR signaling in the modulation of neuropathic pain and assessed the potential therapeutic effects of rapamycin, an inhibitor of the mTORC1, in the IC of neuropathic rats. Adult male Sprague-Dawley rats were used for neuropathic surgery, and the development of neuropathic pain was evaluated by measuring mechanical allodynia. Western blot analysis and microinjection of rapamycin into the IC were performed on post-operative day 3 (POD 3). Microinjection of rapamycin into the IC reduced mechanical allodynia and altered the activation of mTOR signaling, which is activated by nerve injury. Furthermore, rapamycin inhibited the development of synaptic plasticity via downregulation of postsynaptic density protein 95 (PSD95). These findings suggest that inhibition of supraspinal mTOR signaling may be a critical molecular mechanism that modulates neuropathic pain. Therefore, rapamycin may be a potential therapeutic agent for the treatment of chronic pain. This research was supported by the Basic Science Research Program through the National Research Foundation (NRF) funded by the Ministry of Science, ICT & Future Planning (No.20150219897).

Key Words: Neuropathic pain, mTOR, insular cortex, rapamycin, synaptic plasticity
P05-04
Nerve injury-induced neuroplasticity in the insular cortex contribute to pain hypersensitivity

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The insular cortex (IC) is involved in important functions linked with pain and emotion. According to recent reports, neural plasticity in the brain including the IC can be induced by nerve injury and may contribute to chronic pain. Protein kinase Mζ (PKMζ) is considered to maintain the late phase of long-term potentiation (L-LTP). This study was conducted to determine the role of PKMζ in the IC which may be involved in the modulation of neuropathic pain. Behavioral test for neuropathic pain development, immunohistochemistry (IHC) for zif268, analgesia test after ζ-pseudosubstrate inhibitory peptide (ZIP, a selective inhibitor of PKMζ) injection, and immunoblotting of PKMζ, phospho-PKMζ, GluR1 and GluR2 subunits of AMPA receptor after ZIP injection were performed. IHC data showed that zif268 expression significantly increased after nerve injury. Mechanical allodynia was significantly decreased by ZIP microinjection into the IC. The analgesic effect lasted for 12 hours. Moreover, the levels of GluR1, GluR2 and, p-PKMζ were decreased after ZIP microinjection. These results suggest that peripheral nerve injury induces neural plasticity related to PKMζ and ZIP has potential effects for relieving chronic pain. This research was support by the Basic Science Research Program through the National Research Foundation (NRF) funded by the Ministry of Science, ICT & Future Planning (No. 2015021989)

Key Words: PKMζ, insular cortex, neuronal plasticity, ZIP, neuropathic pain

P05-05
Alteration of cardiac hypertrophic marker gene expression by PCB 126 and PCB 77

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Polychlorinated biphenyls (PCBs) and other halogenated aromatic hydrocarbons elicit a variety of adverse biological effects on the cardiovascular systems of mammalian, piscine and avian species. However, there are a limited number of studies on hypertrophic marker gene induction by these persistent organic pollutants (POPs) in the heart. We compared the effects of two PCB congeners, 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) and 3,3′,4,4′,5′-pentachlorobiphenyl (PCB 126) on cytotoxicity and gene expression related with cardiac hypertrophy using primary culture of rat adult ventricular myocytes, cytotoxicity assay, and real-time RT-PCR. PCB 126 and PCB 77 increased cytotoxicity, and PCB 77 had ~ 2-fold higher potency than PCB 126. PCB 126 at 10 μM increased the expression of hypertrophic marker genes, ANP and BNP, and decreased the related gene, SERCA2A. PCB 77 at 1–10 μM increased the expression of the hypertrophic marker genes, ANP and BNP, and decreased the related genes, SERCA2A and PLB. We explored the possible mechanism underlying the PCB 126 and PCB 77-induced cardiac hypertrophy by examining gene expression related with TRPC-PKG signaling. PCB 126 increased the expression of RCAN and TRPC1, but decreased PDE5A. PCB 77 increased the expression of RCAN, TRPC1, TRPC3, and TRPC6, but didn’t change the expression of PDE5A. 8Br-cGMP, a PKG activator, blunted PCB126- and PCB 77-induced increase of gene expressions of ANP, BNP, and RCAN, however, TRPC3 blocker, pyrazole, failed to negate the PCB126 and PCB 77-induced increase of gene expressions of ANP and BNP. The present data indicate that the environmental toxicants, PCBs, can modulate the expression of genes coding for programmes of cellular differentiation and stress (ANP and BNP) and induce cardiac hypertrophy by the mechanism related with RCAN, PKG, and TRPC.

Key Words: cardiomyocytes, cytotoxicity, hypertrophy, PCB 126, PCB 77

P05-06
Impaired cholesterol homeostasis increases the secretion of beta-amyloid peptide in Familial Alzheimer’s disease-associated presenilin mutant

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Alzheimer’s disease (AD) is a major neurodegenerative disorder characterized by the accumulation of β-amyloid peptide (Aβ) and formation of neurofibrillary tangles. The highly amyloidogenic 42-residue Aβ (Aβ42) is the first species to be deposited in both sporadic and familial AD (FAD). PS mutations lead to several key cellular phenotypes, including alterations in proteolysis of β-amyloid precursor protein (APP) and Ca2+ entry. It is also reported that PS mutant elevates cholesterol levels due to the upregulated expression of CYP51, which plays a critical role for the cholesterol synthesis (Tomboli et al., 2008 Molec. Biol., vol, pages?). Since elevated cholesterol is a risk factor for AD, it may contribute to the increased Aβ production in PS1 mutant cells. In this study, we tested whether there exists a functional link between the impaired cholesterol homeostasis and the elevated Aβ levels in PS mutant cell. We confirmed that the expression of CYP51, and cholesterol level were elevated in CHO cells transfected with PS1 delta E9 mutant, compared to cells transfected with PS1 wild type (WT). A CYP51 specific inhibitor, tebuconazole, decreased the cholesterol level in PS1 delta E9 cells to the comparable level with PS1 WT cells, and significantly reduced secreted Aβ42 from PS1 delta E9 cells. It suggests that the elevated cholesterol in PS1 delta E9 cells is directly linked to the increased Aβ production. When cholesterol was depleted by incubating cells with lipid depleted serum, larger amount of Aβ42 was decreased in PS1 delta E9 cells than in PS1 WT cells. Combined together, our results demonstrate that the elevated cholesterol in PS1 mutant contributes to the increased Aβ42 production and the pathology of a genetic basis of AD.

Key Words: Alzheimer’s disease, β-amyloid peptide, Familial AD (FAD), Presenilin, Cholesterol

P05-07
Trichostatin A inhibits Angiotensin II-induced Hypertension in Vasocontraction and Blood Pressure via Inhibiting p66shc and Reactive Oxygen Species

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**P05-08**

**Regulation of basal autophagy and Aβ clearance by TRPM7**

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Autophagy is a conserved process for degradation of cytoplasmic components using lysosomal machinery, and the dysfunction of autophagy is related to many neurodegenerative diseases including Alzheimer’s disease (AD). As a ubiquitous Ca2+ channel, TRPM7 channel underlies the constitutive Ca2+ influx, and related to many neurodegenerative diseases. Since intracellular Ca2+-level is known to regulate autophagy, we set out to test whether Ca2+ influx through TRPM7 channel regulates the basal autophagy. When TRPM7 channel expression is elevated, basal autophagy and AMPK phosphorylation (a main regulator for autophagy by Ca2+) are increased. In contrast, basal autophagy and AMPK phosphorylation were decreased when TRPM7 channel expression is down-regulated via shRNA and specific TRPM7 blocker. Recently, autophagy has been implicated as the Aβ clearance mechanism. We have reported that the activation of TRPM7 channel is chronically suppressed by the presence of familial AD mutants via PI3K/Akt/mTOR pathway. Consistent with close relationship between TRPM7 channel activity and autophagy, we demonstrated that the basal autophagy is down-regulated via AMPK phosphorylation in P51D9E9 mutant cells. In these mutant cells, PI3K/Akt pathway is over-activated and AMPK phosphorylation is inhibited. Moreover, AMPK and mTOR/mTORC1 pathway is activated by down-regulating TRPM7 using specific shRNA. Combined together, these results suggest that TRPM7 channel contributes Aβ clearance via regulating basal autophagy.

**Key Words:** autophagy, TRPM7, PI3K, beta-amyloid

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**P05-09**

**The 18-kDa translocator protein inhibits vascular cell adhesion molecule-1 expression via inhibition of mitochondrial reactive oxygen species**

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Translocator protein 18 kDa (TSPO) is a mitochondrial outer membrane protein and is abundantly expressed in a variety of organ and tissues. To date, the functional role of TSPO on vascular endothelial cell activation has yet to be fully elucidated. In the present study, the phorbol 12-myristate 13-acetate, an activator of protein kinase C (PKC), was used to induce vascular endothelial activation. Adenoviral TSPO overexpression inhibited PMA-induced vascular cell adhesion molecule-1 (VCAM-1) and intracellular cell adhesion molecule-1 (ICAM-1) expression in a dose dependent manner. PMA-induced VCAM-1 expressions were inhibited by Mito-Tempo, a specific mitochondrial antioxidant, and cyclosporine A, a mitochondrial permeability transition pore inhibitor, implying on an important role of mitochondrial reactive oxygen species (ROS) on the endothelial activation. Moreover, adenoviral TSPO overexpression inhibited mitochondrial ROS production and manganese superoxide dismutase expression. On contrasts, gene silencing of TSPO with siRNA increased PMA-induced VCAM-1 expression and mitochondrial ROS production. Midazolam, a TSPO ligands, inhibited PMA-induced VCAM-1 and mitochondrial ROS production in endothelial cells. These results suggest that mitochondrial TSPO can inhibit PMA-induced endothelial inflammation via suppression of VCAM-1 and mitochondrial ROS production in endothelial cells.

**Key Words:** TSPO, ROS, VCAM-1, Mitochondria, Vascular endothelium

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**O-GlcNAcylation-induced GPAT Expression is Critical for Anti-apoptosis under Hypoxia**

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Oxygen signaling is critical for stem cell regulation, and oxidative stress-induced stem cell apoptosis decreases the efficiency of stem cell therapy. Hypoxia activates O-linked β-N-acetylglucosaminyltransferase (O-GlcNAcyltransferase) of stem cells, which contributes to regulation of cellular metabolism as well as cell fate. Our study investigated the role of O-GlcNAcylation via glucosamine in the protection of hypoxia-induced apoptosis of mouse embryonic stem cells (mESCs). Hypoxia increased mESCs apoptosis in a time-dependent manner. Moreover, hypoxia also slightly increased the O-GlcNAc level. Glucosamine treatment further enhanced the O-GlcNAc level and prevented hypoxia-induced mESC apoptosis, which was suppressed by O-GlcNAc transferase inhibitors. In addition, hypoxia regulated several lipid metabolic enzymes while glucosamine increased expression of glycerol-3-phosphate acyltransferase-1 (GPAT1), a lipid metabolic enzyme producing...
Expression and Autophagy of CDK2 and CDK4 hyperphosphorylation through Regulation of Aβ-Induced mTOR Activation is Important for Tau

**P05-11**

Amyloid β-Induced abnormal Autophagolysosome formation leading defective mitochondrial accumulation causes neuronal cell death

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Recent studies support that mitochondria became a significant controller affecting the cell fates in aging related diseases such as Alzheimer’s disease (AD). Mitochondria are dynamic organelles changing their morphology which is tightly related to mitochondrial function. Mitochondrial dysfunction is one of causative factor inducing neuronal cell death. Therefore, we investigated the effect of Aβ on mitochondrial dynamics regulating cellular functions and maturation of autophagy pathway. In this report, Aβ induced neuronal cell death in a dose-dependent manner, which was accompanied with increase in caspase-9 and -3 activities. Consistently, the length of mitochondria are highly dependent on the concentration of Aβ showing excessive mitochondrial fragmentation. Aβ increased the mRNA and protein expression of pro-fission protein, Drp1 and Fis1. Whereas, pro-fusion protein (Opa1 and Mfn2) did not significantly affected by Aβ. Furthermore, we found abnormal autophagolysosome formation using Acridine orange staining which has been decreased the red-to-green ratio. These results indicate that lysosomal degradation of dysfunctional mitochondria is lacking. Taken together, the disruption of autophagosome-lysosome fusion leads to accumulation of damaged mitochondria causing neuronal cell death.

**Key Words:** Amyloid β, mitochondria, Fis1, neuronal cell death

**P05-12**

Aβ-Induced mTOR Activation is Important for Tau hyperphosphorylation through Regulation of Expression and Autophagy of CDK2 and CDK4

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Alzheimer’s Disease (AD) is neurodegenerative disorder induced by Aβ resulting in Tau hyperphosphorylation, which is associated with neuronal cell apoptosis. As there has been no defined therapeutic target for AD, we investigated critical signaling pathway regulating Aβ-induced apoptosis in SK-N-MC. In our results, Aβ increased cleaved caspase 3 expression and apoptosis in a dose-dependent manner. We also demonstrated that Aβ increased ROS generation, followed by HIF-1α expression. In addition, Aβ stimulated mTOR phosphorylation, which is inhibited by HIF-1α siRNA transfection. Our results show that Aβ-induced mTOR activation increased CDK2 and CDK4 mRNA expressions, but not CDK1. Moreover, we confirmed that inhibition of autophagy by Aβ-induced mTOR activation increased CDK2 and CDK4 accumulation, which are blocked by autophagy inducer. mTOR-induced CDKs upregulation contributed to Tau hyperphosphorylation. Furthermore, we confirmed that both mTOR and CDKs inhibition and mTOR-independent autophagy induction prevented Aβ-induced neuronal apoptosis. Especially, mTOR inhibition had more protective effect than either CDKs inhibition or autophagy induction. In conclusion, we demonstrated that Aβ-activated mTOR by HIF-1α regulated both transcription and autophagy of CDK2 and CDK4 which are essential for tau hyperphosphorylation leading neuronal cell apoptosis.

**Key Words:** Amyloid beta, mTOR, CDK, Alzheimer’s Disease

**P05-13**

Essential Role of Vibrio (V.) vulnificus VvpE in Promoting the Pyroptosis of Intestinal Epithelial Cells

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In the present study, we investigate the cellular mechanism of Vibrio (V.) vulnificus, VvpE with regard to host cell death and the inflammatory response of human INT-407 cells. The recombinant protein (r) VvpE caused cytotoxicity mainly via necrosis coupled with IL-1β production. The necrotic cell death induced by rVvpE is highly susceptible to the knockdown of ANXA2 (full?) and the sequestration of membrane cholesterol. We found that rVvpE induces the recruitment of NOX2 (full?) and NCF1 (full?) into membrane lipid rafts coupled with ANXA2 to facilitate the production of ROS (Full?) and phosphorylation of NF-κB. rVvpE induced hypomethylation and region-specific transcriptional occupancy by NF-κB in the IL-1β promoter and has ability to induce pyroptosis via NLRP3 inflammasome. In a mouse model, the mutation of the vvpE gene negated the pro-inflammatory responses and maintained the physiological levels of the proliferation and migration of enterocytes. These results demonstrate that VvpE induces the hypomethylation of the IL-1β promoter and the transcriptional regulation of NF-κB through lipid raft-dependent ANXA2 recruitment and ROS signaling to promote IL-1β production in intestinal epithelial cells.
Key Words: Eph, EphB2, Stem cell niche, Umbilical cord blood

P05-14

EphB2-ephrinB2 signaling-induced Nanog expression is critical for maintaining the differentiation potential of umbilical cord blood derived mesenchymal stem cells

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Eph (full name)/ephrin system as a possible regulator of stem cell expression is critical for maintaining the pluripotency genes in maintaining MSCs properties. In addition, the differentiation potential of UCB-MSCs into adipogenic, chondrogenic, and osteoblastogenic lineages was reduced by EphB2 silencing. Notably, EphB2-facilitated Nanog expression contributed to increasing the expression of Dnmt1 and the Dnmt1-induced hypermethylation of p21 promoter. These findings identify the EphB2 signaling as a target of enhancing therapeutic benefits in regard to maintaining UCB-MSCs functions. In conclusion, the EphB2-ephrinB2 signaling regulates Nanog expression to support the differentiation potential of UCB-MSCs.

Key Words: Ephrin, EphB2, Stem cell niche, Umbilical cord blood derived mesenchymal stem cell, Nanog

P05-15

Cdo regulates surface expression of the Kir2.1 K+ channel in myoblast differentiation

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Kir2.1-associated membrane hyperpolarization is required for myogenic differentiation. However the molecular regulatory mechanisms modulating Kir2.1 channel activities in early stage of myogenesis are largely unknown. A cell surface protein, Cdo includes a component of multiprotein cell surface complexes to promote myogenesis. In this study, we investigate the crosstalk between Cdo and Kir2.1 channels in myoblast differentiation. Cdo depleted or deficient myoblasts show defects in differentiation without a clear correlation with Kir2.1 protein levels. Interestingly, Cdo-depleted or deficient myoblasts exhibit a declined Kir2.1 channel activity, correlating with decreased differentiation. Kir2.1 is coprecipitated with Cdo which correlated with the increased membrane-resident Kir2.1. Cdo is known to be associated with various signaling pathways including p38MAPK, Akt and ERK/ Stim1/Ca2+ pathways leading to activation of MyoD, NFATc3 and downstream target genes in myoblast differentiation. We found that the inward rectifying K+ currents induced upon differentiation were sensitive to p38MAPK inhibition and it seems to be due to Kir2.1 surface trafficking. These data suggest that Cdo-mediated signaling might be involved in regulation of Kir2.1 trafficking and activation.

Key Words: Kir2.1, Cdo, p38MAPK

P05-16

Anti-adhesive activity of the ethanol extracts of Ulmus davidiana var japonica in cultured endothelial cells

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Background/Objectives: Ulmus davidiana var japonica Rehder (UD) has long been used for traditional folk medicine. This study is designed to investigate the anti-adhesive activity of UD and its underlying mechanisms in the cultured endothelial cells. Subjects/Methods: The dried root bark of UD was extracted with 80% ethanol. The anti-adhesive activity of the ethanol extracts of UD (UDE) was investigated in cultured human umbilical vein endothelial cells (HUVEC) and HEK293 cells with stable transfected with VCAM-1-luc. The anti-adhesive activity was evaluated with monocyte-endothelial cell adhesion and vascular cell adhesion molecule-1 (VCAM-1) expression. Promotor activity of VCAM-1 is visualized with in vivo optical imaging system.

Results: The exposure of UDE (3~30 μg/ml) for 24 h showed no cytotoxicity in HUVECs. UDE (3~30 μg/ml) treatment significantly inhibited TNF-a-induced monocyte adhesion and VCAM-1 expression in HUVECs. Luciferase activity of VCAM-1 promoter is increased by the TNF-a, its activity was inhibited with UDE. Also, UDE induced TNF-a-induced ROS generation, NF-kB nuclear translocation, and IkBα degradation in HUVECs. Conclusion: Our results indicate that the UDE inhibited TNF-a-induced monocyte adhesion in endothelial cells, suggesting that UD may be potentially useful to vascular endothelial inflammation.

Key Words: Ulmus davidiana var japonica, endothelial cells, vascular cell adhesion molecule-1, monocyte adhesion

P05-17

FBXO11 represses cellular response to hypoxia by destabilizing hypoxia-inducible factor-1α mRNA

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Background: Recent studies have shown that hypoxia-inducible factor (HIF)-1α is stabilized by proteasomal degradation following oxygen deprivation. FBXO11 is a new E3 ubiquitin ligase that targets HIF-1α for degradation.

Results: FBXO11 represses cellular response to hypoxia by destabilizing HIF-1α mRNA.
The transcriptional factor hypoxia-inducible factor-1α (HIF-1α) is induced under hypoxia and plays crucial roles in cancer progression and angiogenesis. Protein arginine methyltransferases (PRMTs), 11 isoforms of which have been identified so far, modulates the functions of diverse proteins by catalyzing arginine methylation in post-translational level. PRMT9 (alternatively named FBXO11) and PRMT11 (FBXO10) are expected to have the E3 ubiquitin ligase activity through their F-box domains as well as the methyltransferase activity. Given previous studies examining roles of 8 PRMT isoforms (PRMT1-8) in the HIF-1 signaling pathway, PRMT1 and PRMT5 were demonstrated to regulate HIF-1α expression in opposite ways. We herein examined if FBXO10 and FBXO11 participate in the HIF-1 signaling pathway. Consequently, the siRNA-mediated knockdown of FBXO11 facilitated HIF-1α expression in various cancer cells and HIF-1-driven gene expressions, but the FBXO10 knockdown did not. Mechanistically, FBXO11 was found to inhibit de novo synthesis of HIF-1α protein by destabilizing HIF-1α mRNA. Since a FBXO11 mutant lacking F-box failed to reverse the HIF-1α expression by FBXO11 knockdown, the FBXO11 regulation of HIF-1α may be attributed to the ubiquitination of some proteins controlling HIF-1α mRNA stability. Considering the oncogenic roles of HIF-1α, FBXO11 is suggested to act as a tumor suppressor and also to be a potential target for cancer therapy.

Key Words: FBXO11, Hypoxic signaling, HIF-1α, mRNA stability

P05-18

Fatty acid modulates nitric oxide synthase activity in hypertensive rat atrium

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Atrial fibrillation (AF) is the most common cardiac arrhythmias. Hypertension (HTN) and hyperlipidemia (obesity) are the major risk factors for the initiation and the recurrence of AF. In cardiac myocytes, nitric oxide (NO) from constitutive nitric oxide synthases (eNOS & nNOS) is well established to prevent arrhythmogenesis and contractile dysfunction under stress. So far, whether and how fatty acids affect cardiac NO activities which are involved in the pathogenesis of AF is not known. Since high plasma level of palmitic acid (PA), one of the saturated fatty acids, is associated with increased incidence of AF, we aim to investigate: 1) whether PA supplementation affects the protein expressions of eNOS and nNOS in rat atrial myocardium; 2) whether PA regulates phosphorylations of nNOS and eNOS; 3) whether total protein or phosphorylation of NOSs are changed by PA in angiotensin II-induced hypertrophy. Our result showed that PA (100 μM, 1 hr) failed to affect total protein levels of eNOS in left atrial (LA) tissue in both groups. In contrast, PA tended to increase eNOS-Ser1177 in sham rats but not affect total protein levels of nNOS in left atrium, left ventricular myocytes, NOS, palmitic acid.

Key Words: Fatty acid, Nitric oxide synthase, Hypertension

P05-19

TGFβp targeting peptide evaluation

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TGFβp (full name?) is an extracellular matrix protein, and secreted from several cells, including fibroblasts. It supports cell adhesion, migration, proliferation of various cells. It is also reported that TGFβp is increased in the tumor. We hypothesized that TGFβp is a biomarker of tumor, and if it is so, we would like to detect TGFβp in tumor using TGFβp targeting peptide. We identified S18 peptide by T7 DMID phage display. The phage, we used, is DMID (designed modular immunodiagnostics) protein scaffold fused into the capsid. Seven random peptide sequences from a peptide library were displayed in the exposed loop region of the protein scaffold for specific selection of target protein. We found 4 candidates of TGFβp binding peptides by T7 DMID phage display and validated the binding specificity using ELISA. One of them is S18. We cloned and purified DMID-S18 in E.coli expression system and tested its specificity against TGFβp. We provided an evidence that S18 recognizes TGFβp in dose-dependent manner. Its binding is mediated by the fasciclin domain in TGFβp. It specifically binds to Fastatin, 4th fasciclin domain of 4 fasciclin domains in TGFβp. We will check whether S18 detects TGFβp in tumor site in vivo model. If it works well, we will develop it as a diagnostic marker of tumor.

Key Words: TGFβp, Designed modular immunodiagnostics, T7 phage display, tumor

P05-20(O-4)

The regulatory role of phosphodiesterase 4 inhibitor rolipram in lipopolysaccharides-induced signaling in submandibular glands

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Innate immunity is triggered after microbial invasion in response to conserved structures present in the groups of microorganism such as lipopolysaccharides (LPS). Salivary glands were exposed to LPS in bacterial invasion and induced inflammatory signals. However, it is unclear LPS-induced intracellular Ca2+ signaling and reactive oxygen species (ROS) formation in salivary glands. Additionally, we elucidate the anti-oxidative role of rolipram as phosphodiesterase 4 inhibitor

Key Words: Phosphodiesterase 4, Rolipram, LPS, Salivary glands

S 74 The 67th Annual Meeting of The Korean Physiological Society
in LPS-induced signaling. Primarily isolated mouse submandibular glands (SMG) and human salivary submandibular glands cell line (HSG) were measured Ca$^2+$ signals by fura-2, AM fluorescence imaging technique and the levels of ROS production by quantification of DCFDA fluorescence. Our results revealed that LPS induced Ca$^2+$ signaling and ROS production in SMG, which expressed toll-like receptor 4. The treatment of rolipram blocked LPS-induced Ca$^2+$ increase and ROS production in SMG. Application of histamine as an inflammatory agonist mediated Ca$^2+$ increase and ROS production, also attenuated by rolipram in both SMG and HSG cells. Our study showed that inflammatory signals can be diminished by rolipram and may provide potential therapeutic strategy for LPS-induced inflammation or other inflammatory signals in salivary glands.

**Key Words:** rolipram, lipo polysaccharides, calcium signaling, reactive oxygen species, submandibular glands

**P05-21**

**TRPC6 as a critical regulator in osteoclastogenesis**

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The transient receptor potential canonical type 6 (TRPC6) channel is a Ca$^2+$-permeable nonselective cation channel and widely expressed in brain, smooth muscle containing tissues, kidney, and so on. TRPC6 channels are permeable for Ca$^2+$ than for Na$^+$ and are directly activated by diacylglycerol and regulated by specific tyrosine or serine phosphorylation. However, the role of TRPC6 in Ca$^2+$ signaling during osteoclastogenesis is not well known. In the present work, we investigated the functional role of TRPC6 channel in bone metabolism using TRPC6 knockout (TRPC6$^{-/-}$) mice. Depletion of TRPC6 markedly decreased the bone density of the tibias. However, TRPC6 deletion did not affect osteoblast formation. RANKL-induced intracellular Ca$^2+$ oscillations were generated 24 h after RANKL treatment in the TRPC6$^{-/-}$ bone marrow-derived macrophages (BMMs). Finally, RANKL treatment of TRPC6$^{-/-}$ BMMs significantly increased induction of multinucleated cell formation and bone resorption. These results suggest that TRPC6 is a critical negative regulator in osteoclasts differentiation.

**Key Words:** TRP channel, Calcium signaling, osteoclastogenesis, RANKL, bone

**P05-22**

**Homer2/3 modulate RANKL-induced NFATc1, osteoclastogenesis and bone metabolism**

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Ca$^2+$ signaling and NFATc1 activation are essential for RANKL-induced osteoclastogenesis through the induction of Ca$^2+$ oscillation, calcineurin activation, and translocation of NFATc1 into the nucleus. Homer proteins are scaffold proteins that have been proposed to modulate multiple Ca$^2+$ signaling channels and proteins, including inositol 1,4,5-triphosphate receptors, ryanodine receptors, transient receptor potential channels, and NFAT family of transcription factors in skeletal muscle myocytes and T cells. However, the role of Homer proteins in Ca$^2+$ signaling during osteoclast differentiation is not known. In the present work, we investigated the role of Homer2 and Homer3 in bone metabolism using Homer2/Homer3 (Homer2/3) double-knockout (DKO) mice. Deletion of Homer2/3 markedly decreased the bone density of the tibias, resulting in bone erosion. However, Homer2/3 deletion did not affect osteoblast formation and RANKL-induced Ca$^2+$ oscillation. Rather, 48 hours RANKL treatment of Homer2/3 DKO bone marrow-derived monocytes/macrophages (BMMs) facilitated greatly osteoclast differentiation through increased NFATc1 expression and translocation of NFATc1 into the nucleus. Notably, the interaction of Homer proteins with NFATc1 was inhibited by RANKL treatment, but restored by cyclosporine A treatment to inhibit calcineurin. Finally, RANKL treatment of Homer2/3 DKO BMMs significantly increased ~3.0-fold induction of multinucleated cells formation. These findings suggest that Homer2/3 regulate NFATc1 function by interacting with NFATc1 to sequester it in the cytosol and thus modulate the NFATc1 pathway and RANKL-induced osteoclastogenesis and bone metabolism.

**Key Words:** Homer protein, bone metabolism, osteoclastogenesis, Calcium signaling

**P05-23**

**Osmo-mechanosensitive TRP channels regulate Ca$^2+$-mediated RANKL expression in mouse osteoblastic cells**

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Mechanical stress plays an important role in the regulation of bone turnover. However, the intracellular mechanisms of mechanical stress under osteoblast differentiation and proliferation are not well understood. In this study, we investigated the effects of osmo-mechanosensitive transient receptor potential (TRP) channels-induced calcium signaling in primary mouse osteoblasts and MC3T3-E1 cells. Hypotonic stress induced significant increases of RANKL mRNA expression but not OPG. In addition, hypotonic stress-induced increases of intracellular calcium concentration ([Ca$^2+$]) and RANKL expression persisted in the presence of non-specific Ca$^2+$ channel blockers or Ca$^2+$-free bath solution. Furthermore, we examined hypotonic stress-induced effects on agonists and antagonists of osmo-mechanosensitive TRP channels in order to determine the cellular mechanism of hypotonic stress-mediated increases on [Ca$^2+$] and RANKL. We found that antagonists of TRPV4 and TRPM3 decreased hypotonic stress-mediated increases on [Ca$^2+$] and protein expression levels of RANKL and NFATc1. We also identified that hypotonic stress-induced effects reduced by the genetic suppression of TRPV4 and TRPM3. Taken together, our results indicate that hypotonic stress activates the expression of RANKL and NFATc1 by [Ca$^2+$] increases through TRPV4 and TRPM3 in osteoblasts. These effects may be important for the differentiation and proliferation of bone cells on bone remodeling that are mediated via mechanosensitive TRP channels.

**Key Words:** TRP channel, osteoblast, mechanical stress, Calcium signaling, RANKL
P05-24

Endothelin stimulates inflammatory bone loss in periodontitis

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Periodontitis is a very common oral inflammatory disease and results in the destruction of supporting connective and osseous tissues of tooth. Although the etiology is still unclear, Gram-negative Porphyromonas gingivalis in subgingival pockets has been thought as one of the major etiologic agent. It has been known that endothelin is involved in the occurrence and progress of various inflammatory process and diseases. However, functional roles of endothelin in periodontitis are still unclear. In this study, we explored cellular and molecular mechanisms of ET-1 actions in periodontitis using human gingival epithelial cells (hGECs) and human gingival fibroblasts (hGFs). ET-1 and ET-A, but not ET-B, were abundantly expressed in both hGECs and hGFs. Stimulation of hGECs with P. gingivalis LPS increased the expression of ET-1 and ETA suggesting the activation of endothelin signaling pathway. Production of pro-inflammatory cytokines, IL-1β, IL-6, and IL-8 was significantly enhanced by exogenous ET-1 treatment in both hGECs and hGFs. Moreover, ET-1 augmented the number of multilamellar osteoclasts implicating the acceleration of alveolar bone loss. Together, our study showed that activation of ET-1/ET, signaling pathway by P. gingivalis may exacerbate periodontitis by stimulating production of pro-inflammatory cytokines in hGECs and hGFs and provoking the alveolar bone loss through the increment of multilamellar osteoclasts at the same time. To directly examine the endothelin antagonism as a potential therapeutic approach for periodontitis, the inhibitors for ET receptors will be applied to the animal periodontitis model. Infiltration of immune cells, production of pro-inflammatory cytokines, and alveolar bone loss will be evaluated.

Key Words: Endothelin, inflammation, periodontitis, human gingival epithelial cells

P05-26

Calcium ion regulates WNK/OSR1/NKCC1 pathway in HSG cell-line

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Cell volume homeostasis is important to cell survival. Our body strictly maintains the osmosis in the body fluids for keeping the cell volume. Sodium-Potassium-Chloride co-transporter 1 (NKCC1) is the key components of volume maintaining process by using the chloride ion transport. When cells are located in the hypotonic condition, chloride ion is getting into the cytosol, and when cells are located in the hypertonic condition, chloride ion is coming out to the extracellular fluids, and cell reduce cytosol osmotic concentration. In the present study, we found that HSG cell-line expressed molecules participated in WNK/OSR1/NKCC pathway, such as Wnk1, Wnk4, OSR1, SPAK, and NKCC1. In the hypotonic stimulation, and it was synchronized with the phosphorylation of OSR1. Interestingly, when we inhibited hypotonic-induced [Ca2+]i increase with non-specific Ca2+ chelator by using human salivary gland (HSG) cell-line as a model. Finally, through this process, NKCC1 activity also reduced to maintain the cell volume in the HSG cell-line. These results indicate that Ca2+ may affect to regulate WNK/OSR1 pathway and NKCC1 activity in the HSG cell-line, and this is the first demonstration that indicates upstream Ca2+ regulation of WNK/OSR1 pathway in the intact cell.

Key Words: Calcium signaling, NKCC1, WNK/OSR
P05-27

Hypotonic stress induces RANKL via transient receptor potential melastatin 3 (TRPM3) and vanilloid 4 (TRPV4) in human PDL cells

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Bone remodeling occurs in response to various types of mechanical stress. The periodontal ligament (PDL) plays an important role in mechanical stress-mediated alveolar bone remodeling. However, the underlying mechanism at the cellular level has not been extensively studied. In this study, we investigated the effect of shear stress on the expression of bone remodeling factors, including receptor activator of nuclear factor-kappa B (NF-kB) ligand (RANKL) and osteoprotegerin (OPG), and its upstream signaling pathway in primary human PDL cells. We applied hypotonic stress to reproduce shear stress to PDL cells. Hypotonic stress induced the mRNA and protein expression of RANKL but not OPG. It also increased intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(i\)). Extracellular Ca\(^{2+}\) depletion and non-specific plasma membrane Ca\(^{2+}\) channel blockers completely inhibited the increase in both [Ca\(^{2+}\)]\(i\), and RANKL mRNA expression. We identified the expression and activation of transient receptor potential melastatin 3 (TRPM3) and vanilloid 4 (TRPV4) in PDL cells. Pregnenolone sulfate (PS) and 4α-phorbol 12, 13-didecanoate (4α-PDD), which are agonists of TRPM3 and TRPV4, augmented Ca\(^{2+}\)\(i\) influx and RANKL mRNA expression. Both pharmacological (2-aminoethoxydiphenyl borate [2-APB], ruthenium red [RR], ononetin [Ono], and HC 067047 [HC]) and genetic (small interfering RNA [siRNA]) inhibitors of TRPM3 and TRPV4 reduced the hypotonic stress-mediated increase in [Ca\(^{2+}\)]\(i\), and RANKL mRNA expression. Our study shows that hypotonic stress induced RANKL mRNA expression via TRPM3 and TRPV4-mediated extracellular Ca\(^{2+}\)\(i\) influx and RANKL expression. This signaling pathway in PDL cells may play a critical role in mechanical stress-mediated alveolar bone remodeling.

Key Words: Hypotonic stress, calcium signaling, RANKL, TRP channels, human periodontal ligament cells

P05-28

Induction of IL-6 and IL-8 by activation of thermosensitive TRP channels in human PDL cells

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The oral cavity is often exposed to not only diverse external pathogens but also dramatic temperature changes. In this study, we investigated the effect of thermal stress on PDL cells with a focus on the inflammatory responses and bone homeostasis. The PDL cells were isolated from healthy premolar extracted for orthodontic reasons, and investigated the effect of thermal stress on PDL cells. Pathogens but also dramatic temperature changes. In this study, we examined the receptors activated by exogenous bacterial pathogens (Lipopolysaccharide and peptidoglycan) and allergens (German cockroach extract and house dust mite) as well as these pathogenic mediators-induced effects on the intracellular Ca\(^{2+}\)\(i\) signaling in human PDL fibroblasts. Moreover, we evaluated the expression of pro-inflammatory cytokines (Interleukin (IL)-1β, IL-6, and IL-8) and bone remodeling mediators (receptor activator of NF-κB ligand and osteoprotegerin) and intracellular Ca\(^{2+}\)-involved effect. Bacterial pathogens and allergic mediators induced increased expression of pro-inflammatory cytokines, and these results are dependent on intracellular Ca\(^{2+}\). However, bacterial pathogens and allergic mediators did not lead to increased expression of bone remodeling mediators, except lipopolysaccharide-induced effect on receptor activator of NF-kB ligand expression. These experiments provide evidence that a pathogens and allergens-induced increase in [Ca\(^{2+}\)], affects the inflammatory response in human PDL fibroblasts.

Key Words: Calcium signaling, human periodontal ligament fibroblasts, inflammation

P05-29

Bacterial PAMPs and allergens trigger increase in [Ca\(^{2+}\)]\(i\)-induced cytokine expression in human PDL fibroblasts

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An oral environment is constantly exposed to environmental factors and microorganisms. The periodontal ligament (PDL) fibroblasts within this environment are subject to bacterial infection and allergic reaction. However, how these condition affects PDL fibroblasts has yet to be elucidated. PDL fibroblasts were isolated from healthy donors. We examined using reverse transcription-polymerase chain reaction and measuring the intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(i\)). This study investigated the receptors activated by exogenous bacterial pathogens (Lipopolysaccharide and peptidoglycan) and allergens (German cockroach extract and house dust mite) as well as these pathogenic mediators-induced effects on the intracellular Ca\(^{2+}\)\(i\) signaling in human PDL fibroblasts. Moreover, we evaluated the expression of pro-inflammatory cytokines (Interleukin (IL)-1β, IL-6, and IL-8) and bone remodeling mediators (receptor activator of NF-kB ligand and osteoprotegerin) and intracellular Ca\(^{2+}\)-involved effect. Bacterial pathogens and allergic mediators induced increased expression of pro-inflammatory cytokines, and these results are dependent on intracellular Ca\(^{2+}\). However, bacterial pathogens and allergic mediators did not lead to increased expression of bone remodeling mediators, except lipopolysaccharide-induced effect on receptor activator of NF-kB ligand expression. These experiments provide evidence that a pathogens and allergens-induced increase in [Ca\(^{2+}\)], affects the inflammatory response in human PDL fibroblasts.

Key Words: Calcium signaling, human periodontal ligament fibroblasts, inflammation

P05-30

Corn Silk Extract Prevents Carrageenan-Induced Inflammatory Edema by Suppressing Expression of P-Selectin Glycoprotein Ligand-1

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Corn silk extract (CSE) has been used as traditional medicine for edema, cystitis, gout, kidney stones, nephritis and prostatitis. Although CSE was shown to be effective in oxidative stress, inflammation and diabetes, preventive effect of CSE is not known well. So, we have investigated
the preventive effect of CSE in carrageenan-induced inflammatory edema. CSE administered orally for a week not only suppressed initial formation of edema but also enhanced recovery through inhibiting infiltration of immune cells. Pretreatment of CSE to human umbilical vein endothelial cells (HUVECs) for a day has shown no effect on the monocyte-endothelial adhesion. However, pretreatment of CSE to THP-1 cells inhibited adhesion between monocytes and endothelial cells. Expression of lymphocyte function-associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4) on THP-1 cells was not changed by CSE. Whereas P-selectin glycoprotein ligand-1 (PSGL-1), involved in affinity between LFA-1 and intercellular adhesion molecule-1 (ICAM-1), was significantly reduced by CSE. These results suggest that CSE prevents inflammatory edema through the suppression of PSGL-1 expression on monocytes.

Key Words: Corn silk, Inflammation, Edema, Adhesion, PSGL-1

P05-31

Airborne allergens induce protease activated receptor-2 mediated production of inflammatory cytokines in human gingival epithelium

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In reaching the airways inhaled allergens pass through and contact with the oral mucosa. Although they are often responsible for initiating asthmatic attacks, it is unknown whether airborne allergens can also trigger chronic inflammation of gingival epithelial cells leading to chronic periodontitis. In this study, we investigated the inflammatory responses of human gingival epithelial cells (HGECs) to airborne allergens, particularly German cockroach extract (GCE) with a focus on calcium signaling. HGECs isolated from healthy donors were stimulated with GCE. Intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) was measured with Fura-2-acetoxymethyl ester (Fura-2/AM) staining. Expression of inflammatory cytokines interleukin (IL)-8, IL-1β, IL-6, and NOD-like receptor family, pyrin domain-containing (NLRP) 3 was analyzed using reverse transcription-polymerase chain reaction (RT-PCR). GCE promoted increase in the [Ca\(^{2+}\)]\(_i\) in a dose-dependent manner. Depletion of endoplasmic reticulum (ER) Ca\(^{2+}\) by the ER Ca\(^{2+}\) ATPase inhibitor thapsigargin (Tg), but not the depletion of extracellular Ca\(^{2+}\), abolished the GCE-induced increase in [Ca\(^{2+}\)]\(_i\). Treatment of phospholipase C (PLC) inhibitor (U73122) or 1,4,5-trisinositolphosphate (IP3) receptor inhibitor (2-APB) also prevented GCE-induced increase in [Ca\(^{2+}\)]\(_i\). Protease activated receptor (PAR)-2 activation mainly mediated the GCE-induced [Ca\(^{2+}\)]\(_i\) increase and enhanced the expression of IL-8, NLRP3, IL-1β, and IL-6 in HGECs. GCE activates PAR-2, which can induce PLC/IP3-dependent Ca\(^{2+}\) signaling pathway, ultimately triggering inflammation via the production of pro-inflammatory cytokines in HGECs.

Key Words: Inflammation, calcium signaling, PAR2, human gingival epithelial cells

P05-32

Macrophages programmed by apoptotic cells inhibit epithelial-mesenchymal transition in lung alveolar epithelial cells via PGE2, PGD2, and HGF

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Apoptotic cell clearance results in the release of growth factors and the action of signaling molecules involved in tissue homeostasis maintenance. Previously, we demonstrated that macrophages exposed to apoptotic cells counteract TGF-β1-induced epithelial-mesenchymal transition (EMT) in lung epithelial cells. Here, we investigated how macrophages programmed by apoptotic cells inhibit the TGF-β1-induced EMT process in lung alveolar epithelial cells. Exposure of macrophages to cyclooxygenase (COX-2) inhibitors (NS-398 and COX-2 siRNA) or RhoA/Rho kinase inhibitors (Y-27632 and Rhōs siRNA) and LA-4 cells to antagonists of prostaglandin E2 (PGE2) receptor EP4 (AH-23848), PGD2 receptors (DP1 [BW-A868C] and DP2 [BAY-u3405]), or the hepatocyte growth factor (HGF) receptor c-Met (PHA-665752), reversed EMT induction by the conditioned medium. Additionally, we found that apoptotic cell instillation inhibited bleomycin-mediated EMT in primary mouse alveolar type II epithelial cells in vivo. Our data suggest a new model for epithelial cell homeostasis, by which the anti-EMT programming of macrophages by apoptotic cells may control the progressive fibrotic reaction via the production of potent paracrine EMT inhibitors.

Key Words: EMT, TGF-β1, PGE2, PGD2, HGF

P05-33

Diverse effects of a 445 nm diode laser on isometric contraction of the rat aorta

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The usefulness of visible lasers in treating vascular diseases is controversial. It is probable that multiple effects of visible lasers on blood vessels and their unclear mechanisms have hampered the usefulness of this therapy. Therefore, elucidating the precise actions and mechanisms of the effects of lasers on blood vessels would provide insight into potential biomedical applications. Here, using organ chamber isometric contraction measurements, western blotting, patch-clamp, and en face immunohistochemistry, we showed that a 445 nm diode laser contracted rat aortic rings, both by activating endothelial nitric oxide synthase and by increasing oxidative stress. In addition to the effects on the endothelium, the laser also directly relaxed and contracted vascular smooth muscle by inhibiting L-type Ca\(^{2+}\) channels and by activating protein tyrosine kinases, respectively. Thus, we conclude that exposure to 445 nm laser might contract and dilate blood vessels in the endothelium and smooth muscle via distinct mechanisms.

Key Words: Laser, e-NOS, Aorta, L-type Ca channel

P05-34

Suberoylanilide hydroxamic acid enhances apoptotic effect of TNF-α in human lung cancer cells via TNFR1 upregulation

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The usefulness of visible lasers in treating vascular diseases is controversial. It is probable that multiple effects of visible lasers on blood vessels and their unclear mechanisms have hampered the usefulness of this therapy. Therefore, elucidating the precise actions and mechanisms of the effects of lasers on blood vessels would provide insight into potential biomedical applications. Here, using organ chamber isometric contraction measurements, western blotting, patch-clamp, and en face immunohistochemistry, we showed that a 445 nm diode laser contracted rat aortic rings, both by activating endothelial nitric oxide synthase and by increasing oxidative stress. In addition to the effects on the endothelium, the laser also directly relaxed and contracted vascular smooth muscle by inhibiting L-type Ca\(^{2+}\) channels and by activating protein tyrosine kinases, respectively. Thus, we conclude that exposure to 445 nm laser might contract and dilate blood vessels in the endothelium and smooth muscle via distinct mechanisms.

Key Words: Laser, e-NOS, Aorta, L-type Ca channel
Suberoylanilide hydroxamic acid (SAHA) is a histone deacetylase (HDAC) inhibitor to have an anti-cancer effect. In the present study, we evaluated the anti-growth effect of SAHA in lung cancer (A549, SK-LU-1, HCC-95, HCC-1588, NCI-H460, NCI-H1299, Calu-6, HCC-33 and NCI-H69) and human small airway epithelial cells (HSAEC). SAHA inhibited the growth of lung cancer cells and induced apoptosis in these cells. However, this agent did not affect cell growth and apoptosis in HSAEC. All the tested caspase inhibitors markedly prevented lung cancer cell death induced by SAHA. Treatment with TNF-α and SAHA synergistically enhanced apoptosis in lung cancer cells, which was accompanied by caspase-8 activation. In addition, SAHA increased the expression of TNF-α receptor 1 (TNFR1) in lung cancer cells. The down-regulation of TNFR1 suppressed apoptotic cell death in TNF-α and SAHA-treated lung cancer cells. In conclusion, SAHA inhibited the growth of lung cancer cells via caspase-dependent apoptosis. SAHA also enhanced apoptotic effect of TNF-α in human lung cancer cells through TNFR1 upregulation and caspase-8 activation. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2008-0062279) and supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2013006279).

Key Words: Suberoylanilide hydroxamic acid, Apoptosis, Tumor necrosis factor alpha, Lung cancer

P05-35

Hydroquinone intensifies the death of valproic acid-treated SK-LU-1 cells

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Valproic acid (VPA) is an inhibitor of histone deacetylase (HDAC). It has been reported that shows an anti-cancer effect on various cancer cells. Hydroquinone (HQ) as an autophagy inhibitor can regulate many biological events such as apoptosis. In the present study, we evaluated the effect of VPA and HQ on apoptosis and autophagy in lung cancer cells (A549, SK-LU-1, NCI-H460 and Calu-6). VPA inhibited the growth of lung cancer cells. However, lung cancer SK-LU-1 cells were the most resistant to VPA. This drug induced apoptosis, which was accompanied by the loss of mitochondrial membrane potential (MMP; ΔΨm), PARP-1 cleavage and caspase-3 activation in lung cancer cells except SK-LU-1 cells. In addition, VPA led to autophagy, as evidenced by LC3B increase and p62 decrease in lung cancer cells. Interestingly, the levels of LC3B were already increased in VPA-untreated SK-LU-1 cells. Treatment with HQ enhanced cell death and the loss of MMP in VPA-treated SK-LU-1 cells. In conclusion, VPA induced apoptosis and autophagy in lung cancer cells. Autophagy might be a therapeutic target in anticancer drug resistance. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (No. 2008-0062279) and supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2013006279).

Key Words: Valproic acid, Apoptosis, Autophagy, Lung cancer

P05-36

Differential Expression of Taste Receptors in Tongue Papillae

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Taste is important to survive and to maintain quality of life of animals. Several species of mammals, including human, can detect sweet, bitter, sour, salty and umami taste. Sweet or umami taste helps animals to find nutrients such as carbohydrates or amino acids, whereas bitter taste prevents animals to intake probable toxic substances. Tongue has 4 kinds of papillae which are filiform, fungiform (FU), foliate (FO) and circumvallate papilla (CV). Tongue papillae except filiform papilla include taste buds. Taste sensitivities of these papillae are different each other. Although the reason of the different taste threshold of the taste papillae is not known yet, it might be due to the differential expression of taste receptors. This study was performed to determine the expression levels of taste receptors in FU, FO and CV. DBA2 mice of 42-60-day-old were used. Messenger RNAs were extracted from the murine epithelial tissues including FU, FO and CV. Cloned DNAs were synthesized by reverse transcription. Quantitative PCRs were performed to determine mRNA expression levels of taste receptors. Expression levels of taste receptors were calculated as relative that to GAPDH. Results of qPCR revealed that the relative expression levels and patterns were different in FU, FO and CV. All three type I taste receptors were expressed in FU, FO and CV. All 35 kinds of type II taste receptors were more expressed in FU and CV than in FO. Expression levels of Tas2r108 and Tas2r137 were highest in all tested papilla. The different physiological taste thresholds in tongue papillae may due to the different expression levels and patterns of taste receptors, at least in part.

Key Words: taste receptor, fungiform papilla, foliate papilla, circumvallate papilla, qPCR

P05-37

Expression of Bitter Taste Receptor Tas2r108 mRNA in Murine submandibular gland

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Mammals have 3 pairs of major salivary glands, the parotid, submandibular, and sublingual glands. Saliva secretion of these glands is involved in digestion as well as in protection of teeth and oral mucosa. The different expression of taste receptors in tongue papillae may due to the differential expression levels and patterns of taste receptors, at least in part. Although the reason of the different taste threshold of the taste papillae is not known yet, it might be due to the differential expression of taste receptors. In the present study, we evaluated the expression of Tas2r108 mRNA in mouse salivary glands. We used 42-60 days old DBA2 mice. The expression of Tas2r108 mRNA was detected in all tested salivary glands. Interestingly, the levels of Tas2r108 mRNA were highest in submandibular gland. This result suggests that the taste papillae is not known yet, it might be due to the differential expression of taste receptors. The objectives of the present study are to investigate whether acinar or ductal cells of the submandibular gland express Tas2r108. In this study, male 42-60 days old DBA2 mice were used. Messenger RNAs were extracted from the submandibular gland for generating digoxigenin (DIG) labeled-cRNA probes. These probes were transcribed in anti-sense and sense orientation using T7 RNA polymerase. To estimate these probes
concentration, dot blot was performed using labeled probes. ISH was performed on murine submandibular gland to detect Tas2r108 mRNA. Anti-sense was visualized by dot blot in order to dilute DIG labeled-cRNA probes. ISH results showed that the anti-sense probes labeled acinar and duct cells in the submandibular gland, whereas no staining was visible in sense controls. Interestingly, the expression levels of Tas2r108 were higher in acinar cells than in ductal cells. These results suggest that Tas2r108 may play a role in primary secretion than in ductal modification of saliva composition in the submandibular gland.

Key Words: bitter taste receptor, Tas2r108 mRNA, submandibular gland, RT-PCR, in situ hybridization

P05-38

A monoclonal antibody against transmembrane proteins of human umbilical vein endothelial cells is a potential inhibitor of endothelium-dependent relaxation in rat aorta

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In previous study, we produced antibodies from rat immunized by transmembrane proteins of human umbilical vein endothelial cells (HUVECs). However, unanswered question remains still about vascular function of the antibodies. The current study explored vasoreactivity, especially focused on vascular contractility, of a functional antibody that is expressed on plasma membrane of HUVECs. These findings suggest that monoclonal A-7 antibody may act as an inhibitor on endothelium-intact and -denuded aorta. Immunocytochemical test showed that A-7 alleviated Ach-increased expression of ACh receptor on the plasma membrane of HUVECs. These findings suggest that monoclonal A-7 antibody may act as an inhibitor on endothelium-dependent vasorelaxation to Ach, probably in part through downregulation of Ach receptor expression.

Key Words: Antibody, Plasma membrane protein, Acetylcholine receptor, Vasorelaxation

P05-39(O-3)

TGF-β1-induced apoptosis via Nox4 is mediated by ERK1/2-mTOR1 activation in podocytes

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TGF-β, a pleiotropic cytokine, accumulates during kidney injuries and results in chronic renal diseases. We have previously reported that TGF-β1 induces selective upregulation of mitochondrial Nox4 playing critical roles in podocyte apoptosis. Here, we investigated the regulatory mechanism of Nox4 upregulation by mammalian target of rapamycin (mTOR) activation on TGF-β1-induced apoptosis in podocytes. TGF-β1 treatment markedly increased phosphorylation of mTOR and its downstream target p70S6k and 4EBP1. Blocking TGF-β1 receptor-I by SB431542 completely blunted phosphorylation of mTOR, p70S6k and 4EBP1. simTOR and adenosinal constructs overexpressing wild type (WT), constitutively active (CA) or kinase-dead (KD) were used to deduce the role of mTOR in Nox4 upregulation by TGF-β1. Inhibition of mTORC1 by low dose of rapamycin or siRNA mediated knockdown of p70S6k protected podocytes through attenuation of Nox4 protein expression and subsequent oxidative stress-induced apoptosis by TGF-β1. Pharmacological inhibition of MEK/ERK cascade, but not PI3K-Akt pathway, abolished TGF-β1-induced mTOR activation. Inhibition of neither ERK1/2 nor mTORC1 reduced the TGF-β1-stimulated increase of Nox4 mRNA level, however, significantly inhibited total Nox4 expression, ROS generation and apoptosis induced by TGF-β1. Moreover, siRNA mediated double knockdown of Smad2/3 or siSmad4 completely suppressed ERK-mTOR activation by TGF-β1. Our data suggest that TGF-β1 increases translation of Nox4 protein level through Smad2/3-ERK1/2-mTOR axis and this pathway is independent of transcriptional regulation of Nox4 by Smad2/3. Activation of this pathway plays a crucial role in ROS generation and mitochondrial dysfunction leading to podocyte apoptosis. Therefore, inhibition of ERK1/2-mTOR pathway could be a therapeutic and preventive target against proteinuric and chronic kidney diseases.

Key Words: TGF-β1, Smad2/3, mTOR, NADPH Oxidase 4, ERK1/2, podocytes

P05-40

Scoparone inhibits PDGF-BB-induced vascular smooth muscle cells migration via inactivation of mitogen-activated protein kinases signaling pathway

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Vascular smooth muscle cells (VSMCs) migration and proliferation are key processes in the neo-intima formation that occurs in atherosclerosis and restenosis. These events are potently stimulated by platelet-derived growth factor (PDGF), which is induced in various types of cells including platelets, endothelial cells, and macrophages under physiological or pathophysiologic conditions. Scoparone (6,7-dimethoxycoumarin) is known to vasorelaxant and inhibit proliferation at high dose in VSMCs. However, the effect of scoparone on VSMCs migration has not been investigated. In the present study, we examined whether scoparone affects migration in VSMCs. Scoparone dose-dependently suppressed PDGF-BB-induced migration in VSMCs. It inhibited the PDGF-BB-induced phosphorylations of mitogen-activated protein kinases (MAPKs), p38 MAPK and extracellular signal-regulated kinase (ERK) 1/2. Moreover, scoparone inhibited PDGF-BB-induced sprout outgrowth in rat aortas. These results indicate that scoparone inhibits migration by suppressing the phosphorylations of p38 MAPK and ERK 1/2 in VSMCs. Therefore, scoparone may be a potential agent for prevention of pathogenesis such as vascular restenosis or atherosclerosis.

Key Words: Scoparone, Vascular smooth muscle cells, Migration, Platelet-derived growth factor, Restenosis, Atherosclerosis
P05-41

Nafamostat mesilate induces protective effects against TNF-α-induced vascular endothelial cell dysfunction by inhibiting reactive oxygen species production

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Nafamostat mesilate (NM) is a serine protease inhibitor with anticoagulant and anti-inflammatory effects. NM has been used in Asia for anticoagulation during extracorporeal circulation in patients undergoing continuous renal replacement therapy and extra corporeal membrane oxygenation. Oxidative stress is an independent risk factor for atherosclerotic vascular disease and is associated with vascular endothelial function. We investigated whether NM could inhibit endothelial dysfunction induced by tumor necrosis factor-α (TNF-α). Human umbilical vein endothelial cells (HUVECs) were treated with TNF-α for 24 h. The effects of NM on monocyte adhesion, vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) protein expression, p38 mitogen-activated protein kinase (MAPK) activation, and intracellular superoxide production were then examined. NM (0.01–100 μg/mL) did not affect HUVEC viability; however, it inhibited the increases in reactive oxygen species (ROS) production and p66shc expression elicited by TNF-α (3 ng/mL), and it dose dependently prevented the TNF-α-induced upregulation of endothelial VCAM-1 and ICAM-1. In addition, it mitigated TNF-α-induced p38 MAPK phosphorylation and the adhesion of U937 monocytes. These data suggest that NM mitigates TNF-α-induced monocyte adhesion and the expression of endothelial cell adhesion molecules, and that the anti-adhesive effect of NM is mediated through the inhibition of p66shc, ROS production, and p38 MAPK activation.

Key Words: Nafamostat Mesilate, ICAM-1, VCAM-1, Reactive Oxygen Species, p66shc

P05-42

HN1 Promotes Tumorigenicity through Activation of the SREBP-1 and -2 Lipogenic Signaling Pathway in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death in the world and its overall 5-year survival rate is less than 12%. Although it has been reported that HN1 is expressed in various cancers, the functional significance of HN1 in HCC is not clearly identified. We have studied the importance of HN1 function in hepatocellular carcinoma cell lines, HepG2 and SNU449. HN1 was highly expressed in human HCC cells. Knockdown of HN1 significantly inhibited the proliferation of HCC cells and decreased expression of Poly ADP-ribose polymerase (PARP) and Caspase-9 as well as increased expression of cleaved-caspase-9 and cleaved-PARP with the silencing of HN1 showed the incidence of apoptosis of human HCC cells. The number and size of the HCC colonies were found to be diminished by silencing of HN1. Knockdown of HN1 significantly inhibited the invasion and metastasis of HCC cells. The mRNA and protein levels of vimentin, β-catenin and UPA were significantly decreased in HN1 knockdown HCC cells. To further investigate the role of HN1 in HCC cell, we performed gene expression profiling. Statistical analyses of gene expression data from HN1 silencing HCC cells revealed that 130 genes were significantly upregulated, while 379 genes were downregulated. Putative gene networks showed that the expressions of SREBP-1 and -2 which regulate the lipogenic signaling pathway were significantly suppressed by HN1 silencing. We confirmed that knockdown of HN1 significantly inhibited the protein levels of SREBP-1 and -2 expression in HCC cells. Using clinical data from HCC patients, gene expression profiling data revealed that overexpression of HN1 was significantly associated with tumor aggressiveness and poor prognosis in patient with HCC. In vivo xenograft animal study, HN1 knockdown significantly inhibited the tumor weight and growth. Tunel assay also showed that HN1 knockdown significantly induced cell apoptosis in xenograft animal models. In conclusion, HN1 promotes the proliferation and invasion of HCC cells in part through the activation of SREBP-1 and -2 lipogenic signaling pathway. Therefore, our results suggest that targeting HN1 may constitute a therapeutic strategy for HCC.

Key Words: HN1, hepatocellular carcinoma cells, metastasis, cell proliferation, SREBP-1, SREBP-2

P05-43

TonEBP/NFAT5 suppresses adipogenesis via modulation of mitotic clonal expansion during early phase of differentiation in 3T3-L1 cells

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Obesity resulting from excessive accumulation of white adipose tissue is closely related to the chronic diseases such as diabetes, hyperlipidemia, and hypertension. White adipose mass is determined by the number and size of adipocytes. The differentiation of adipocyte can be divided into two broad stages. Determination phase results in the conversion of the stem cell to a preadipocyte. The committed cells undergo terminal differentiation manifested by formation of lipid droplets as well as adipocyte specific protein. TonEBP/NFAT5 belongs to the Rel family of transcription factors and plays important roles in the development and maintenance of kidney. However, recent reports suggest that TonEBP/NFAT5 function is not limited to the renal medulla. Although the functions of TonEBP/NFAT5 during chondrogenesis and myogenesis are reported recently, its role in the adipogenesis is not well known. In this study, we analyzed the role of TonEBP/NFAT5 in adipogenesis using 3T3-L1 cells. Mouse 3T3-L1 cell line is widely used as an in vitro model for studying terminal adipocyte differentiation. TonEBP/NFAT5 protein expression was dramatically reduced during adipocyte differentiation of 3T3-L1 cells. RNAi-mediated knock down of TonEBP/NFAT5 facilitated adipogenesis. Whereas sustained expression of TonEBP/NFAT5 protein using adenovirus suppressed the formation of lipid droplet and the expression of FABP4, marker for terminal differentiated adipocytes. Also, TonEBP/NFAT5 inhibited the expression of PPARγ, master regulator of terminal adipocytes. Inhibited adipogenesis by TonEBP/NFAT5 regulates in the early phase of the adipocyte differentiation process via modulation of mitotic clonal expansion and insulin signaling pathway. These results suggest that TonEBP/NFAT5 may be an important regulatory factor in the differentiation of adipocytes.

Key Words: TonEBP/NFAT5, adipogenesis, mitotic clonal expansion
P05-44  
**Sirtuin 6 inhibits proliferation and invasion of hepatocellular carcinoma cells**  
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Sirtuin6 (SIRT6) has been reported to be dynamic in its chromatin binding in response to stimuli resulting in altering the transcriptional landscape of tumor development. Despite SIRT6 has been link to involve in tumorigenesis, the molecular mechanisms underlying SIRT6 protein downregulation in human cancers remain unknown. In this study we aimed to investigate the functional significance of SIRT6 in hepatocellular carcinoma (HCC). SIRT6 was highly expressed in human HCC cells. Overexpression of SIRT6 significantly inhibited the proliferation of HCC cells whereas knockdown of SIRT6 significantly increased the proliferation of HCC cells. In colony formation assay showed that the colony numbers were diminished by overexpression of SIRT6 and increased expression of cleaved-caspase-9 and cleaved-PARP. On the other hands, knockdown of SIRT6 in HCC cells did not change the apoptotic related protein levels. In addition, overexpression of SIRT6 significantly inhibited the invasion and metastasis of HCC cells whereas knockdown of SIRT6 induced increase the invasion and metastasis abilities of HCC cells with time dependent manner. In addition, overexpression of SIRT6 significantly decreased the protein levels of vimentin, β-catenin, and uPA whereas knockdown of SIRT6 in HCC cells induced increase the protein levels of UPA, vimentin, and twist. P-β-catenin levels was increased by overexpression of SIRT6 and was diminished by knockdown of SIRT6. Together, SIRT6 regulates the proliferation and invasion of HCC cells and may plays as a tumor suppressor.

**Key Words:** SIRT6, hepatocellular carcinoma cells, metastasis, cell proliferation, β-catenin

P05-45  
**Ursolic Acid inhibits the growth of human esophageal squamous cell carcinoma cells by inducing autophagy**  
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Autophagy is a phenomenon that involved in tumorigenesis. It has been reported that autophagy can kill tumors and thus the activation of the nonapoptotic autophagic cell death program is emerging as a potential cancer therapy. Ursolic acid (UA) is a natural phytochemical anticancer agent. It has been shown that UA inhibits tumor growth and has anti-cancerous property in several human cancers. However, the important biological function of UA on human esophageal squamous cell carcinoma (ESCC) has not been explored. Our endeavor from this study is to discover anti-tumorigenic property of UA in ESCC cells. The result of MTT assay showed that UA significantly decreased the viability of ESCC (TE-8 and TE-12) cells in a dose-dependent manner. Colony numbers and sizes from the ESCC were found to be diminished with a dose and time dependent manner in treatment of the UA. UA significantly induced apoptosis of ESCC cells. The Poly ADP-ribose polymerase (PARP) and Caspase-3 protein levels were significantly decreased and the cleaved-caspase-3 and cleaved-PARP protein levels were significantly increased with a dose dependent manner. Autophagy was induced by UA in ESCC cells. After exposure to 30μM of UA for 24 hr, there were a large accumulated vacuoles in cytoplasm and displayed punctuated staining of LC3, a marker of autophagosome. Induction of autophagy was confirmed by measuring of LC3 protein levels. UA significantly increased the protein levels of LC3II, a processed form of LC3 by in a dose dependent manner. Taken together, our results indicate that UA induces ESCC cell death by inducing autophagy.

**Key Words:** ursolic acid, esophageal squamous cancer cells, autophagy, LC3, apoptosis

P05-46  
**CTHRC1 Stimulates Growth and Metastasis in Esophageal Adenocarcinoma Cells by Activation of the β-catenin/c-Myc Signaling Pathway**  
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Despite many attempts to understand the biology of EAC, the biological mechanisms of EAC progression remain elusive. In the present study, we investigated the underlying molecular mechanisms by which CTHRC1 regulates growth and metastasis in EAC cells. Knockdown of CTHRC1 significantly diminished the growth rates of EAC cells (BE3 and OE33) by MTT assay. Apoptotic proteins were significantly increased by knockdown of CTHRC1 in EAC cells. Cleaved-caspase9 and cleaved-PARP were significantly increased after silencing of CTHRC1 in EAC cells. Knockdown of CTHRC1 significantly diminished the metastasis of EAC cells by matrigel invasion assay. The mRNA and protein levels of vimentin, twist, MMP9, and uPA were significantly decreased in CTHRC1 knockdown EAC cells. In addition, knockdown of CTHRC1 in EAC cells significantly reduced levels of β-catenin and c-Myc, but increased p-β-catenin level. Therefore, CTHRC1 regulates the growth and invasion/metastasis of EAC cells through activation of the β-catenin/c-Myc pathway. Our results suggest that targeting CTHRC1 may constitute a potential therapeutic strategy for EAC.

**Key Words:** esophageal adenocarcinoma cells, CTHRC1, β-catenin/ c-Myc, growth, metastasis

P05-47  
**Effect of Macrophage on Induction of Gefitinib Resistance in EGFR Mutated Non Small Cell Lung Cancer Cells**  
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It is well known that tumor-associated macrophages (TAMS), which are abundant in the microenvironment of several tumors, including non-small-cell lung cancer (NSCLC), secrete pro-tumorigenic factors that contribute to cancer progression. However, there is no evidence indicating the involvement of macrophage in inducing drug resistance
in case of lung cancer. To see the effect of macrophage in induction of resistance to tyrosine kinase inhibitors (TKI), epidermal growth factor receptor (EGFR) mutated cells (PC9 and HCC827) were co-cultured with macrophage and then treated with TKI (Erlotinib and Gefitinib). PC9 and HCC827 cells co-cultured with macrophage were much more resistant to erlotinib and gefitinib than those cultured alone. Macrophage can induce cancer cells to enhance migration and invasion via secretion of soluble factors. Therefore we prepared THP-1 cells derived macrophage conditioned medium (CM), and then treated to the PC9 cells. Enhanced migration and invasion of PC9 cells were confirmed upon induction with macrophage CM. Gefitinib induced apoptosis, DNA fragmentation, and cleaved of apoptotic protein PARP and caspase-3 were markedly reduced in macrophage CM treated PC9 cells. U937 cells derived macrophage CM also showed inducibility of Gefitinib resistance. Whereas, THP-1 and U937 derived monocyte CM had no effect on Gefitinib resistance indicating these induction of gefitinib resistance is specific to soluble factors secreted from macrophage. From these results, we can conclude that soluble factors secreted from macrophage induce EGFR TKIs resistance as well as migration and invasion in EGFR mutated NSCLC cells.

Key Words: Macrophage, NSCLC, gefitinib

P05-48

Gas6/Mer signaling induces transactivation of LXRα-target gene arginase 2 and vascular endothelial growth factor via STAT1 transcription factor in macrophages

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Mer plays a central role in intrinsic inhibition of the inflammatory response by immune cells. Previously, we demonstrated that the Mer signaling increases the transcriptional liver X receptor (LXR) α/β activity to promote the resolution of acute sterile inflammation. Here we aimed to understand the downstream pathway of growth arrest-specific protein 6 (Gas6)/Mer signaling leading to LXR expression and transcriptional activity in mouse bone-marrow derived macrophages (BMDM). We examined the role of signal transducer and activator of transcription1 (STAT1), which acts as an enhancer of LXR expression and LXR-mediated transcription of alternative activation markers, such as arginase 2 (Arg2) and vascular endothelial growth factor (VEGF) in BMDM. Exposure of BMDM to Gas6-enhanced phosphorylation of STAT1. Gas6-induced STAT1 phosphorylation was inhibited in BMDM from Mer-/- mice or by the specific inhibitor of PI3K, or Akt. Gas6-induced LXR mRNA and protein expression was reduced in BMDM from STAT1-/- mice or BMDM in the presence of STAT1 specific inhibitor, fludarabine. Gas6-induced transcriptional activity from the liver X receptor element (LXRE) promoter in RAW 264.7 cells was completely inhibited by fludarabine. Moreover, enhanced mRNA and protein expression of LXR’s target genes, such as Arg2, VEGF, ABCG1 and ApoE, by Gas6 was also reversed in BMDM from STAT1-/- mice or BMDM and RAW 264.7 cells pretreated with fludarabine. Our data suggest that Gas6/Mer signaling leads to increased transcriptional LXR activity and its target genes related to lipid and cholesterol metabolism as well as the anti-inflammatory response via STAT1.

Key Words: Mer, LXR, bone marrow-derived macrophages, PI3K/Akt, STAT1

P05-49

Nafamostat mesilate attenuates transient focal ischemia/reperfusion-induced brain injury via the inhibition of endoplasmic reticulum stress

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Nafamostat mesilate (NM), a serine protease inhibitor, has a broad range of clinical applications that include use as an anticoagulant during hemodialysis in cerebral hemorrhage patients, as a hemoperfusion anticoagulant for patients with intravascular coagulation, hemorrhagic lesions, and hemorrhagic tendencies, and for the improvement of acute pancreatitis. However, the effects of NM on acute cerebral ischemia have yet to be investigated. Thus, the present study utilized a rat model in which transient middle cerebral artery occlusion (MCAO) was used to induce ischemic injury to investigate the effects of NM on infarct volume and histological and biological changes. NM (1 mg/kg) was intravenously administered prior to and after the MCAO procedure. Compared to control rats, the administration of NM significantly decreased infarct size and the extent of brain edema after the induction of focal ischemia via MCAO. Additionally, NM treatment attenuated MCAO-induced neuronal degeneration and activation of microglia and astrocytes. NM treatment also inhibited the MCAO-induced expression levels of glucose-regulated protein 78 (GRP78), CATT/EBP homologous protein (CHOP), and p-eukaryotic initiation factor 2α (eIF2α), which are endoplasmic reticulum (ER) stress markers, in the cerebral cortex. The present findings demonstrate that NM exerts neuroprotective effects in the brain following focal ischemia via, at least in part, the inhibition of ER stress.

Key Words: Nafamostat mesilate, cerebral ischemia, MCAO, ER stress

P05-50

Statin pretreatment inhibits LPS-induced EMT via the downregulation of TLR4 and NF-κB in hBECs

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Epithelial-mesenchymal transition (EMT) of biliary epithelial cells (BECs) plays an important role in biliary fibrosis. Lipopolysaccharide (LPS) promotes EMT in BECs. This study investigated the effects of simvastatin on the LPS-induced EMT in BECs. Following exposure to 1 μg/mL LPS for 5 days, the mRNA and protein levels of E-cadherin decreased, while those of vimentin increased. The TLR4 mRNA levels increased after a 5-day exposure to LPS or TGF-β1 (5 ng/mL). Compared with the BECs treated with LPS alone, co-treatment with simvastatin plus LPS induced a remarkable increase in E-cadherin expression and a slight decrease in vimentin expression. The LPS-induced TLR4 expression was slightly decreased by co-treatment with simvastatin and LPS. In the proliferation analysis, LPS-induced BEC growth was remarkably inhibited by simvastatin (1 μM) treatment. With regard to BEC morphology, compared with BECs pretreated with simvastatin before LPS exposure (preSL), BECs treated with LPS (postSL) or co-treated with LPS plus simvastatin (LS) demonstrated additional EMT characteristics (cell morphology changes from a round shape to a
**P05-51**

**Regulation of Autophagy by Rapamycin has inhibition cardio-toxicity role in Doxorubicin-Induced Cardiac Progenitor/Stem cells Dysfunction**

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**Background** Although doxorubicin (DOXO) is widely used for chemotheraphy against various solid cancer and childhood cancer, but using the DOXO is limited by serious cardiac toxicity through loss of cardiomyocyte. Recently reported researches suggested that endogenous cardiac stem/progenitor cells (eCPC) play important roles in cardiomyocyte homeostasis. Furthermore, most recently reported research suggested that DOXO occurred eCPC depletion. However, these underlying mechanisms have not been fully demonstrated. In addition, autophagy has emerging signaling pathway for regulation of cellular bioactivities, such as proliferation, differentiation and senescence. Thus, in this study, we first examined whether autophagy signaling regulation could rescue to DOXO-mediated eCPC dysfunction. **Method & Results** For this study, c-kit positive eCPCs were isolated from infant-derived cardiac tissues as previously reported. To determined optimal DOXO concentration in eCPC, we used eCPC viability using MTS assay. As shown result, over the 500nM of DOXO treatments were significantly reduced eCPC viability. Next, immunoblotting was used to detect expression of regulaclcin(SMP30, calcium regulator protein), mTOR, and LC3 (autophagy maturation related protein). SMP30 and LC3 expressions were time dependently increased after DOXO treatment in eCPC. However, mTOR expressions were significantly increased after treatment with DOXO in eCPC. Next, we examined whether administered with rapamycin (mTOR inhibitor) could rescue SMP30 and LC3 expression. After treatment with rapamycin, reduced SMP30 and LC3 expressions were significantly increased in DOXO-induced eCPC. Additionally, intracellular Ca2+ levels were analyzed by Fluor-8 assay, and reduced Fluor-8 level in DOXO-treated eCPC groups were significantly reduced fluorescence intensities after treatment with rapamycin. **Conclusion** From the above results, rapamycin could be rescue autophagy formation and SMP30 expression DOXO-treated eCPC through mTOR inhibition and intracellular Ca2+ handling. Thus, rapamycin might be suppressive effects of DOXO-mediated cardiotoxicity through autophagy signaling regulation in eCPC. **Key Words:** Endogenous cardiac stem/progenitor cells, autophagy, cardiotoxicity, doxorubicin, rapamycin

**P05-52**

**O-8**

**Serum protein Fetuin-B is involved in immune cells and vascular smooth muscle cells-linked atherosclerotic plaque stability**

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**Coronary artery disease frequently progresses in an abrupt fashion, and the occlusion of vessels develops rapidly, which is largely related to thrombosis resulting from the disruption of atherosclerotic plaque. It is generally known that the disruption of atherosclerotic plaque can be associated with the stability of atherosclerotic plaque that is implicated with responses in various cell types including immune cells and vascular smooth muscle cells (VSMCs). However, influenceable risk factor for plaque rupture-linked plaque stability remains unclear. In this study, we investigated proteins expressed differentially in serum from patients with acute myocardial infarction (AMI) and stable angina using a proteomic analysis and identify the new molecule fetuin-B, which was up-regulated in the AMI group.**

**Key Words:** Acute myocardial infarction, Stable angina, Atherosclerotic plaque, Fetuin-B

**P05-53**

**O-8**

**DJ-1 contributes to sphingophosphorylcholine-induced differentiation of human mesenchymal stem cells into smooth muscle cells**

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**Human mesenchymal stem cells (hMSCs) have a self-renewal and a differentiation capacity to diverse cell types such as chondrogenic, adipogenic and myogenic cells. Sphingophosphorylcholine (SPC) is known to induce differentiation of hMSCs into smooth muscle cells (SMCs). In the present study, we investigated correlation between SMC differentiation and its related proteins in SPC-stimulated hMSCs. We analyzed the proteins expressed differentially in SPC-stimulated hMSC using proteomics techniques and found that the oxidized form of DJ-1 protein was predominantly altered in hMSCs in response**
Platelet-derived growth factor, Apoptosis and therapeutic strategy of vascular restenosis. BB-treated VSMCs. This study may provide useful information for migration and also stimulated the induction of apoptosis in PDGF-
demonstrate that LPLI may induce the inhibition of proliferation and LPLI reduced PDGF-BB-evoked aortic sprout outgrowth. These findings treated with PDGF-BB were enhanced by exposure to LPLI. In addition, Activations of caspase3 and Bax, as well as p38 MAPK, in VSMCs LPLI stimulated apoptotic induction in VSMCs in the presence of PDGF-
VSMCs. PDGF-BB-increased migration in VSMCs was inhibited by LPLI. Moreover, Ang II significantly induced the translocation of cytoplasmic APE/Ref-1 into nuclear fraction in RASMCs. The knockdown of APE/Ref-1 with small interference RNA abolished the overexpression of S1PR1 in response to Ang II. H3 histone acetylation and APE/Ref-1 binding at the S1PR1 promoter were increased in RASMCs treated with Ang II. In addition, Ang II-induced migration was suppressed by AT1 and S1PR1 inhibitors in RASMCs. These results indicate that Ang II may stimulate the epigenetic regulation of S1PR1 expression via H2O2-mediated APE/Ref-1 translocation, which may consequently be involved in the Ang II-induced VSMC migration. Key Words: Angiotensin II, Vascular smooth muscle cell, Sphingosine-1-phosphate receptor, APE/Ref-1, Histone modification, Migration

Inhibition of Pi transport across plasma and mitochondrial membrane prevents high phosphate-induced vascular calcification
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Inorganic phosphate (Pi) is very crucial for cell signaling and energy metabolism. However, hyperphosphatemia in chronic kidney disease (CKD) patients or even high normal range of plasma Pi level in non-CKD individuals is associated with serious cardiovascular complications including medial calcification, left ventricular hypertrophy and positively correlated with cardiovascular events. But the underlying mechanisms of Pi-induced these toxicities have been still debated. Thus, we have investigated whether cellular and mitochondrial Pi uptake followed by reactive oxygen species (ROS) generation act as a critical role in high Pi-induced vascular calcification in a rat aortic smooth muscle cell line, A7r5. Type III Na+/Pi cotransporters (PiT-1/2), the predominant plasmaemmal Pi transporters expressed in A7r5 cells, were up-regulated both in total protein levels and surface abundance.
by high Pi incubation. Using patch clamp technique, we observed that Pi induced a Na\(^+\)-dependent inwardly rectifying current in A7r5 cells as well as in PIT-1 overexpressed HEK cells. Cellular uptake of Pi elicited cytosolic alkalization which facilitated Pi transport into mitochondrial matrix. Increased mitochondrial Pi uptake accelerated superoxide generation, upregulation of osteogenic genes and calcific changes in A7r5 cells. Vascular calcification by high Pi was prevented by mitochondrial ROS scavenger. Inhibition of Pi transport by PIT-1/2 knockdown or pharmacologic blocking of mitochondrial Pi transport restored all these pathogenic changes by high Pi. High Pi activated ERK/mTOR signaling, inhibition of which abolished osteogenic gene upregulation and vascular calcification. Taken together, we propose that mitochondrial oxidative stress, Pi transport across plasma and mitochondrial membranes and ERK/mTOR signaling could be therapeutic targets for Pi-induced vascular calcification and cardiovascular morbidities.

**Key Words:** plasma membrane phosphate transporter PIT-1/2, mitochondrial phosphate transport, ERK, mTOR, vascular calcification

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**P05-57**

**Cul3-KLHL22 E3 ubiquitin ligase and TWIST target anterior gradient-2 and regulate tumor progression**

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Anterior gradient-2 (AGR2) is a well-known pro-oncogenic/metastatic factor that is overexpressed in multiple types of cancer. In this study, we elucidated novel regulatory mechanisms of AGR2. We found that Twist1, a basic helix-loop-helix transcription factor, enhanced AGR2 promoter activity. Additionally, chromatin immunoprecipitation assays indicated that Twist1 bound directly to the AGR2 promoter through the E-box. Silencing of AGR2 by shRNA inhibited the proliferation, migration, and colony formation of MCF7 cells. These data indicated that Twist1 was critical for AGR2 activity and that AGR2 may be a potential tumor biomarker. Next, we identified a novel Culillin 3 (Cul3)-Bric-a-brac/Tramtrack/Broad complex (BTB) adaptor protein, Cul3-Kelch-like protein (KLHL) 22 E3 ligase. KLHL is a BTB domain adaptor protein that assembles with Cul3; the role of KLHL22 in cancer biology is still largely unknown. Our studies showed that KLHL22 bound directly to AGR2 through Kelch domains and ubiquitinylated AGR2. Additionally, Cul3-KLHL22 E3 lysine polyubiquitinylated AGR2 through lysine 6-linked ubiquitin chains and downregulated the expression of AGR2 and the downstream proteins cathepsin B and D. Importantly, KLHL22 inhibited the migration and colony-forming capacities of MCF7 breast cancer cells. Finally, in a mouse xenograft model of breast cancer, KLHL22 significantly inhibited tumor growth. Taken together, our data suggested that the Cul3-KLHL22-mediated ubiquitination signal inhibited AGR2 expression and breast cancer progression.

**Key Words:** Anterior gradient-2, Cul3-KLHL22 E3 ligase, tumorigenesis

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**P05-58**

**Engineered M13 Phage as a Novel Therapeutics to enhance Endothelial Progenitor Cell-based Neovascularization**

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Enhancement of transplanted EPC survival, proliferation, differentiation and migration at the ischemic region is significantly important to the EPC therapy. To enhance EPC function, EPC therapy was constantly studied in many different ways. But M13 phage was not in used in EPC therapy. In this study, we fabricated genetically engineered M13 phages with two functional peptides, RGD peptide and SDKP peptide, on their minor and major coat proteins and treated on EPCs to improve the EPC function. Next, Engineered M13 phage treated on EPC to enhance EPC function before transplantation in mouse hind limb ischemia. Consequently, EPC proliferation was increased by stimulating cyclin D expression. In addition, engineered M13 phage enhanced survival, migration and differentiation on EPC via Akt and ERK activation. In vivo study used mouse hind limb ischemia model, engineered M13 phage treated EPC transplantation group was significantly improve blood perfusion. Histological analysis suggested that engineered M13 phage treated EPC proliferation, survival and differentiation was improved in ischemic hind limb by confirming caspase-3, PCNA, CD31 antibodies. Genetically engineered M13 phage is a promising candidate for the development of EPC therapy for hind limb ischemia treating due to its promising structural features and advantages. We showed that the engineered M13 phage were able to support EPC proliferation and differentiation as well as EPC survival in ischemic region. Genetically engineered M13 phage will be a useful platform for EPC therapy in various ischemic diseases.

**Key Words:** M13 phage, neovascularization, therapy, EPC

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**P05-59**

**Tat-biliverdin reductase A protects insulin-producing INS-1 cells from islet amyloid polypeptide (IAPP)-induced apoptosis by alleviating oxidative and endoplasmic reticulum stresses**

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Islet amyloid polypeptide (IAPP) is a major component of pancreatic amyloid deposit, which is a characteristic histopathological finding for type 2 diabetes mellitus (T2DM). IAPP in amyloid deposit has been closely associated with the β cell degeneration, and the extent of its deposition correlates negatively with β cell mass in the T2DM. We recently developed a cell-permeable fusion protein, Tat-biliverdin reductase A (Tat-BLVR)A and investigated the anti-inflammatory effects in macrophage cells. In this study, we transduced Tat-BLVR into INS-1 rat insulinoma cells and examined its protective effect against IAPP-induced cell apoptosis. Tat-BLVR was successfully delivered into INS-1 cells in time- and dose-dependent manner and was maintained within the cells for at least 48 h. Exposure of cells to IAPP-induced apoptotic cell death determined by MTT assay and Hoechst staining. Pre-treatment with Tat-BLVR increased the survival of INS-1 cells exposed to IAPP in a dose-dependent manner. Tat-BLVR markedly decreased IAPP-induced production of reactive oxygen species and malondialdehyde. These protective effects of Tat-BLVR against IAPP were well correlated with the changes in the levels of signaling mediator molecules of cell apoptosis/survival (Bcl-2, Bax, caspase-3, PARP, JNK, and Akt) and endoplasmic stress (CHOP, ATF-4, BIP, XBP-1, caspase-12). These
results showed that the transduced Tat-BLVRA efficiently prevented IAPP-induced cell apoptosis of INS-1 cells by alleviating oxidative and endoplasmic reticulum stresses. Further, these results suggested that Tat-mediated BLVRA transduction may be a potential therapeutic strategy to prevent β cell loss in patients with T2DM.

Key Words: Type 2 diabetes mellitus, β Cell apoptosis, IAPP, Transduction, Tat-BLVRA

P06-01

Absence of hypoxic augmentation of vascular constriction in the femoral artery from eNOS deficient mice

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Previously we have reported that hypoxia augments the agonist-induced contraction of skeletal arteries (HVC) from rats. As for the mechanism, hypoxic inhibition of eNOS expressed in the arterial myocytes was suggested. To further prove the novel role of muscular eNOS in skeletal artery, we investigate HVC in the femoral arteries (FAs) from wild type (WT), hetero (+/-), and null (-/-) eNOS knockout mice. Absolute contractile force under 80 mM KCl-induced depolarization (80K) was lower in (-/-) than WT and (+/-) FAs. Phenylephrine (Phe)- or Ang II-induced contraction of FAs normalized to the 80K-contraction was higher in (+/-) and (-/-) than WT. Immunohistochemical assay of FAs demonstrated, in addition to the strong endothelial eNOS, weak but certain expression of eNOS in the medial layer of FAs. The medial expression of eNOS was not observed in (+/-) and (-/-) FAs as well as WT carotid arteries (CAs). Consistently, hypoxia (3 % PO2) largely augmented Phe-induced contraction in WT FAs while not in (+/-), (-/-) FAs. WT CAs did not show the HVC. NOS inhibitor, L-NAME (0.1 mM), also augmented Phe-contraction in endothelium-denuded WT FAs while not in WT CAs. Taken together, the muscular expression of eNOS in skeletal arteries contributes to intrinsic attenuation of alpha-adrenergic vasoconstriction. The counterbalancing effect is effectively alleviated under hypoxia, resulting HVC under the sympathetic stimulation, which might play a role in maintaining the blood pressure under emergency.

Key Words: Hypoxia, eNOS, smooth muscle, skeletal artery, knockout mouse

P06-02

Augmented vascular reactivity and hypoxic pulmonary vasconstriction in monocrotaline-induced pulmonary arterial hypertension rats

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Pulmonary arterial hypertension (PAH) is a progressive and eventually lethal disease caused by vascular proliferation, increased vascular resistance and remodeling of pulmonary arteries (PA). Monocrotaline (MCT) is a pyrrolizidine alkaloid phytotoxin which is widely used for developing pulmonary arterial hypertension (PAH-MCT) rat model caused by injury of pulmonary endothelial cells; however, the pulmonary arterial contractility of the MCT-induced PAH rat model has not been fully understood yet. Here we investigate the effects of vasoactive agonists and the response of PA to hypoxia. The hypoxic pulmonary vasoconstriction (HPV) was analyzed using ventilated/perfused (VP) lungs. Histological study revealed the vascular remodeling (i.e. medial thickening of PA) and right ventricle hypertrophy 3 weeks after application of MCT to rats. The basal pulmonary arterial pressure (PAP) and the increase of PAP by raised perfusion flow rate (up to 40 ml/min) were significantly higher in PAH-MCT model. Furthermore, high K+ (40 mM KCl) and Angiotensin II-induced PAP were higher in PAH-MCT rats. Different from the loss of HPV in chronic hypoxia-induced PAH model, the hypoxia-induced PAP increase in VP lungs was not impaired in the PAH-MCT rats. An application of NO synthase inhibitor (L-NAME) induced PAP increase that was higher in PAH-MCT than control rats. The decreased compliance of PA might underlie the higher responses to agonists and contractile conditions. Despite the toxicological effect of MCT on the pulmonary endothelium, the regenerated endothelial function (e.g. NOS) might partly counterbalance the severe contraction and PAP increase in the PAH-MCT rats.

Key Words: Pulmonary arterial hypertension, Hypoxic pulmonary vasoconstriction, Monocrotaline, Vascular reactivity

P06-03

Smooth Muscle Cell Genome Browser: Enabling the Identification of Novel Serum Response Factor Target Genes

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Genome-scale expression data on the absolute numbers of gene isoforms offers essential clues in cellular functions and biological processes. Smooth muscle cells (SMCs) perform a unique contractile function through expression of specific genes controlled by serum response factor (SRF), a transcription factor that binds to DNA sites known as the CArG boxes. To identify SRF-regulated genes specifically expressed in SMCs, we isolated SMC populations from mouse small intestine and colon, obtained their transcriptomes, and constructed an interactive SMC genome and CArGome browser. To our knowledge, this is the first online resource that provides a comprehensive library of all genetic transcripts expressed in primary SMCs. The browser also serves as the first genome-wide map of SRF binding sites. The browser analysis revealed novel SMC-specific transcriptional variants and SRF target genes, which provided new and unique insights into the cellular and biological functions of the cells in gastrointestinal (GI) physiology. The SRF target genes in SMCs, which were discovered in silico, were confirmed by proteomic analysis of SMC-specific Srf knockout mice. Our genome browser offers a new perspective into the alternative expression of genes in the context of SRF binding sites in SMCs and provides a valuable reference for future functional studies.
P06-04

Serum Response Factor Is Essential for Prenatal Gastrointestinal Smooth Muscle Development and Maintenance of Differentiated Phenotype

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Background/Aims: Smooth muscle cells (SMCs) characteristically express serum response factor (SRF), which regulates their development. The role of SRF in SMC plasticity in the pathophysiological conditions of gastrointestinal (GI) tract is less characterized.

Methods: We generated SMC-specific Srf knockout mice and characterized the prenatal lethality phenotype using ultrasound biomicroscopy and histological analysis. We used small bowel partial obstruction surgeries and primary cell culture using cell-specific enhanced green fluorescent protein (EGFP) mouse lines to study phenotypic and molecular changes in SMCs by immunofluorescence, Western blotting, and quantitative polymerase chain reaction. Finally we examined SRF change in human rectal prolapse tissue by immunofluorescence.

Results: Congenital SMC-specific Srf knockout mice died before birth and displayed severe GI and cardiac defects. Partial obstruction resulted in an overall increase in SRF protein expression. However, individual SMCs appeared to gradually lose SRF in the hypertrophic muscle. Cells expressing low levels of SRF also expressed low levels of platelet-derived growth factor receptor alpha (PDGFR low) and Kit67. SMCs grown in culture recapoprted the phenotypic switch from differentiated SMCs to proliferative PDGFR low cells. The immediate and dramatic reduction of Srf and Myh11 mRNA expression confirmed the phenotypic change. Human rectal prolapse tissue also demonstrated significant loss of SRF expression. Individuals SMCs down-regulate SRF to transition into proliferative PDGFR low cells that may represent a phenotype responsible for their plasticity. These findings demonstrate that SRF also plays a critical role in the remodeling process following GI injury.

Key Words: Gastrointestinal tract, Platelet-derived growth factor receptor alpha, Rectal prolapse, Serum response factor, Smooth muscle cell

P06-06

Sildenafil is effective to enhance the proliferation of skeletal myoblasts

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Sildenafil is a specific inhibitor of phosphodiesterase type 5 and clinically used to treat erectile dysfunction and pulmonary artery hypertension because of its vasodilatation effect due to the relaxation of smooth muscle cells. In cardiac muscle, the cardioprotective effects of sildenafil have been reported. The effectiveness of sildenafil on skeletal muscle has been controversial. In skeletal muscle, sildenafil reduces the cellular damage and muscle fatigue. However, sildenafil also induces muscle cell necrosis and apoptosis. Therefore, the effectiveness of sildenafil on skeletal muscle cells is unknown. In the present study, the efficacy of sildenafil on skeletal muscle cells was examined using mouse primary skeletal myoblasts and myotubes. Sildenafil was effective to enhance the proliferation of myoblasts and there was no macroscopic change in the shape of myotubes.

Key Words: skeletal muscle, sildenafil

P06-05

Loss of Cdo leads to alteration in N-cadherin and connexin with intercellular coupling defects and cardiomyopathy

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Dysregulation of adherens and gap junctional proteins, N-cadherin and Connexin 43 (Cx43) is associated with cardiomyopathy and fibrosis. A cell surface protein Cdo interacts with N-cadherin/β-catenin mediating cell adhesion signaling in skeletal myogenesis however its role in cardiomyocyte junctions is unknown. Here we report that Cdo is essential in regulation of cardiomyocyte coupling via modulation of N-cadherin and Wnt/β-catenin signaling. Cdo-deficient mice exhibit marked fibrosis and reduced cardiac function with shortened QTc intervals. Cdo-deficient cardiomyocytes exhibit elevated N-cadherin levels and Cx43 accumulation at lateral borders, accompanied by altered gap junction coupling which is rescued by wildtype but not by an N-cadherin binding-deficient Cdo. Additionally, Cdo deficiency also derepresses Wnt/β-catenin signaling which elevates N-cadherin and Collagen I expression. Conversely, Wnt signaling activation in turn inhibits Cdo expression in cardiac cells, suggestive of a feedback loop. Taken together, Cdo deficiency leads to alterations in intercellular coupling, contributing to fibrosis and cardiac remodeling.

Key Words: N-cadherin, Connexin 43, Cardiomyopathy, Cdo

P06-07

Interaction between mitsugumin 29 and TRPC3 participates in regulating calcium transients in skeletal

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Effect of mitsugumin 29 and TRPC3 on intracellular calcium levels have not been examined. In the present study, sildenafil have been reported. The effectiveness of sildenafil on skeletal muscle, sildenafil reduces the cellular damage and muscle fatigue. However, sildenafil also induces muscle cell necrosis and apoptosis. Therefore, the effectiveness of sildenafil on skeletal muscle cells is unknown. In the present study, the efficacy of sildenafil on skeletal muscle cells was examined using mouse primary skeletal myoblasts and myotubes. Sildenafil was effective to enhance the proliferation of myoblasts and there was no macroscopic change in the shape of myotubes.

Key Words: skeletal muscle, sildenafil
P06-08

Inhibition of nNOS facilitates myofilament disarray and cardiac hypertrophy in Ang II-induced hypertensive rat

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Previous reports using neuronal nitric oxide (nNOS) gene knockout mice suggest that nNOS may be essential in the preservation of left ventricular (LV) structure and contractile function following post-infarction-induced heart failure. Recently, we have shown that the protein expression and the activity of nNOS are up-regulated in hypertensive rat heart and exert protective roles against sustained pathologic stimulation. However, underlying cellular mechanisms of nNOS remain unclear. Accordingly, we aim to investigate myocardial phenotypes following chronic nNOS inhibition in sham and angiotension II (Ang II)-induced hypertensive rats (Ang II). Co-infusion of nNOS inhibitor S-Methyl-L-thiocitrulline (SMTC, 28 ng/kg/min) with Ang II (125 ng/kg/min) showed a decrease in systolic blood pressure in SHR treated with TUDCA. Sixteen-week old male SHRs and WKYs were treated with TUDCA (100 mg/kg/day, IP (taurine-conjugated ursodeoxycholic acid, TUDCA). Sixteen-week old male SHRs and WKYs were treated with TUDCA (100 mg/kg/day, IP injection) or PBS (control, 300 μL/day, IP injection) for two weeks. There was a decrease in systolic blood pressure in SHR treated with TUDCA. The pressure-induced myogenic tone was significantly increased.

Key Words: NOS, myocardial, hypertrophy

P06-09

Signaling pathway and physiological role of WNK1 in mouse skeletal muscle

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WNK (with-no-lysine [K]) kinases are serine/threonine protein kinases with an atypical placement of the catalytic lysine. While WNK1 is highly expressed in skeletal muscle, however, signaling pathways and physiological role of WNK1 in skeletal muscle have been ill-defined. WNK1 and WNK2, not WNK4 are expressed in mouse skeletal muscle. WNK1 is downstream effector of insulin and IGF-1 receptor signaling. Insulin stimulates WNK1 via phosphoinositide-3-kinase-Akt/PI3K signaling cascade in differentiated C2C12 mouse skeletal muscle cell-line. The WNK1 expression is significantly decreased in db/db mice, a hyperinsulinemic type II diabetic model compared to that of wild type mice. Furthermore, an expression of downstream effectors of insulin signaling including GLUT4 and is markedly reduced in skeletal muscle of db/db mice. These results suggest that WNK1 function as downstream effector of insulin signaling and regulate glucose transport in skeletal muscle providing new insights for increased susceptibility to insulin resistance and diabetes in skeletal muscle. [This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2013R1A1A2060764)]

Key Words: WNK1, Skeletal muscle, Insulin

P06-10

Inhibition of Endoplasmic Reticulum Stress Normalizes Augmented Myogenic Responses in Coronary Arteries of the Spontaneously Hypertensive Rats

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Endoplasmic reticulum (ER) stress has been shown to play a critical role in the pathogenesis of cardiovascular complications. However, the role and mechanisms of ER stress in hypertension remain unclear. Thus, we hypothesized that enhanced ER stress contributes to the maintenance of hypertension in spontaneously hypertensive rats (SHRs). We investigated this hypothesis by suppressing ER stress in SHRs and their normotensive controls, Wistar-Kyoto rats (WKYs) with ER stress inhibitor (taurine-conjugated ursodeoxycholic acid, TUDCA). Sixteen-week old male SHRs and WKYs were treated with TUDCA (100 mg/kg/day, IP injection) or PBS (control, 300 μL/day, IP injection) for two weeks. There was a decrease in systolic blood pressure in SHR treated with TUDCA. The pressure-induced myogenic tone was significantly increased.

Key Words: nNOS, myofilament, hypertrophy
whereas endothelium-dependent relaxation was significantly attenuated in SHRs compared with WHYs. Interestingly, treatment of ER stress inhibitor normalized myogenic responses and endothelium-dependent relaxation in SHRs. These data were associated with an increase in expression or phosphorylation of ER stress markers (Bip, CHOP, ATF6, XBP1, IRE1, and eIF2a) in SHRs, which were normalized by TUDCA treatment. Furthermore, phosphorylation of myosin light chain was increased in SHRs, which was reduced by the treatment of TUDCA. In conclusion, ER stress inhibition decreases systolic blood pressure and normalizes myogenic response and endothelium-dependent relaxation in SHRs. Moreover, ER stress inhibition normalizes expression or phosphorylation of ER stress markers, and phosphorylation of myosin light chain in SHRs. Therefore, we suggest that ER stress could be a potential target for hypertension.

Key Words: myogenic tone, endothelium-dependent relaxation, coronary artery, hypertension, ER stress

P06-11(O-6)

Does eNOS-palmitoylation involve in palmitic acid-enhanced cardiac inotropy in rat cardiac myocyte?

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Background and aim: Palmitic acid (PA) is a predominant metabolic substrate for cardiac β-oxidation. Our recent results have shown that PA increases contraction of cardiac myocytes, however, the underlying mechanisms remain unclear. Palmitoylation is an important post-translational modification that affects the translocation and the activity of target proteins in a variety of cell types including cardiomyocytes. Since endothelial nitric oxide synthase (eNOS) is known to be palmitoylated and the activity of eNOS is essential in fatty acid-dependent β-oxidation in muscle, we aim to identify whether eNOS is palmitoylated by PA and the involvement of eNOS-palmitoylation in PA-regulation of cardiomyocyte contraction. Results: Our results showed that palmitic acid (PA, 100 μM) significantly increased eNOS palmitoylation but reduced nitric oxide (NO) production 22.12% in LV cardiomyocytes. Pre-treatment of LV myocytes with an inhibitor of palmitoylation, 2-bromopalmitic acid (2BP, 100 μM) significantly reduced eNOS palmitoylation and increased NO production. Inhibition of nNOS with S-methyl-L-thiocitrulline (SMTC, 100 mM) reduced greater myocyte contraction as compared with vehicle. Conclusion: Our results showed that PA, 100 μM, significantly increased eNOS palmitoylation and decreased NO production. PA at 100 μM increased the phosphorylation of eNOS Ser1177 at Thr67, indicating the possibility that impaired eNOS-NO signaling is involved in the greater and abnormal myocyte contraction. Inhibition of constitutive NOS (eNOS and neuronal NOS, nNOS) with Nu-Nitro-L-arginine methyl ester (L-NAME, 1 mM) and S-methyl-L-thiocitrulline (SMTC, 100 mM) maintained greater myocyte contraction or [Ca2+]i in NF+ISO but significantly increased the occurrence of DACs. Treatment of LV myocytes with nebivolol (100 nM-1 μM) following NF+ISO attenuated myocyte contraction and reduced diastolic/peak amplitudes of [Ca2+]i in NF+ISO but significantly increased the occurrence of DACs. Reduced NO production in NF+ISO markedly increased the occurrence of DACs. Inhibition of constitutive NOS (eNOS and neuronal NOS, nNOS) with Nebivolol abolished DOCA-induced DACs in NF, Similarly, cordycepin (50 μM-100 μM) was an adenosine mimetic and exerts anti-adrenergic effect, reduced DACs in NF+ISO without changing myocyte contraction. Nebivolol abolishes DACs following beta-adrenergic stimulation with metabolic substrates supplemented. Similar results of nebivolol and cordycepin suggest that NO-signaling in the protective role of nebivolol needs further investigation.

Key Words: nebivolol, fatty acid, arrhythmias, nitric oxide

P06-12

Beta1-adrenergic receptor antagonist and nitric oxide stimulator, nebivolol, prevents spontaneous contraction induced by metabolic substrates in rat cardiomyocytes

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Nebivolol, a β1-adrenergic receptor antagonist and nitric oxide (NO) stimulator, has been implicated in the treatment of heart failure, atrial fibrillation and hypertension. Recently, we have established an in vitro model of metabolic syndrome, where metabolic substrates induce delayed after-contractions (DACs) in left ventricular (LV) myocytes from rat heart after beta-adrenergic stimulation with isoproterenol (ISO), a precursor for ventricular arrhythmias. Here, we aim to investigate whether nebivolol affects the occurrence of DACs in this model with supplementation of metabolic substrates in normal Tyrode’s (NF). Our results showed that NF increased basal and ISO-stimulation of LV myocyte contraction and induced DACs. The effects of NF were mirrored by increases in the diastolic/peak amplitudes of Ca2+ transients ([Ca2+]i) and facilitated time constant of [Ca2+]i decay (tau). Furthermore, NF significantly reduced the phosphorylation of endothelial nitric oxide synthase at Ser1177, indicating the possibility that impaired eNOS-NO signaling is involved in the greater and abnormal myocyte contraction. Inhibition of constitutive NOS (eNOS and neuronal NOS, nNOS) with Nω-Nitro-L-arginine methyl ester (L-NAME, 1 mM) and S-methyl-L-thiocitrulline (SMTC, 100 mM) maintained greater myocyte contraction or [Ca2+]i in NF+ISO but significantly increased the occurrence of DACs. Treatment of LV myocytes with nebivolol (100 nM-1 μM) following NF+ISO attenuated myocyte contraction and reduced diastolic/peak amplitudes of [Ca2+]i. Importantly, nebivolol abolished ISO-induced DACs in NF. Similarly, cordycepin (50 μM-100 μM) was an adenosine mimetic and exerts anti-adrenergic effect, reduced DACs in NF+ISO without changing myocyte contraction. Nebivolol abolishes DACs following beta-adrenergic stimulation with metabolic substrates supplemented. Similar results of nebivolol and cordycepin suggest that NO-signaling in the protective role of nebivolol needs further investigation.

Key Words: nebivolol, fatty acid, arrhythmias, nitric oxide

P06-13

Angiotensin IV protects cardiac reperfusion against via AT4R by inhibiting apoptosis and inflammation

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Angiotensin IV (Ang IV) is formed by aminopeptidase N (APN) from angiotensin III (Ang III) by removing the first N-terminal amino acid. Angiotensin IV (Ang IV) is formed by aminopeptidase N (APN) from angiotensin III (Ang III) by removing the first N-terminal amino acid. Angiotensin IV protects cardiac reperfusion against via AT4R by inhibiting apoptosis and inflammation. Byung Mun Park1, Seung Ah Cha1, Sun Hwa Lee2, Byung Hyun Park2, Yuen Kuichang2, Suhn Hee Kim1

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Ang IV attenuated I/R-induced increases in plasma creatine kinase (CPK) and lactate dehydrogenase (LDH) concentrations, and infarct size. I/R also caused increases in Bax, caspase-3 and caspase-9 protein levels, and a decrease in Bcl-2 protein level in ventricles, which were attenuated by pretreatment with Ang IV. Co-treatment with AT4R antagonist or inhibitors of downstream signaling pathway including phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR) attenuated Ang IV-induced changes in CPK and LDH levels, infarct size, and apoptosis-related proteins. Furthermore, I/R increased the expression of TNF-α, MMP-9, VCAM-1, and NF-κB protein levels, which were attenuated by the pretreatment with Ang IV. After co-treatment with AT4R antagonist and inhibitors of downstream signaling pathway, the inflammatory protein levels were increased. Therefore, these results suggest that Ang IV has cardioprotective effect against I/R injury by inhibiting apoptosis and inflammation via AT4R and PI3K-Akt-mTOR pathway. supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No 2008-0062279). 

**Key Words:** Angiotensin IV, ischemia-reperfusion, apoptosis, inflammation

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**P06-14**

**Cereblon gene dysfunction improves cardiac performance and mitochondrial energy metabolism in mice**

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Cereblon (CRBN) is a protein interacting with calcium-activated potassium channels. Mutation in this protein causes mild mental retardation in humans. Recent studies have suggested the novel function of the protein as an AMPK inhibitor through a direct interaction with AMPKα1 subunit. Disruption in the gene enhances hepatic AMPK activity and halts high-fat diet induced obesity and insulin resistance in mouse model. This study aims to determine the effect of the knockout of CRBN in hearts and its relevance to mitochondria. The body weight, heart rate and heart/body ratio of Control (CRBN+/+) and CRBN KO (CRBN−/−) models (8 weeks) were examined. Echocardiography was used to assess in vivo cardiac functions of animals. To evaluate mitochondrial function, cardiac mitochondria of CRBN+/+ and CRBN−/− were isolated and examined for their ATP contents and ATP production rate, ROS production rate, oxygen consumption rate (OCR) and membrane potential (ΔΨm). Body weight, heart weight and heart/body ratio were not significantly different between CRBN+/+ and CRBN−/− mice. Echocardiography showed enhanced cardiac contractility in CRBN−/− mice as evidenced by increased ejection fraction (%) and fractional shortening (%). Results of the mitochondrial studies showed that basal ATP contents and substrate/ADP-stimulated ATP production rates were significantly higher in CRBN−/− mice than CRBN+/+. Moreover, basal H2O2 level and rotenone-induced ROS production rates were significantly lower in CRBN−/− mice than CRBN+/+. OCR and ΔΨm in both groups were maintained at similar levels. These results suggest CRBN is an important mitochondrial functional regulator which links cytosol to mitochondrial energy metabolic signaling.

**Key Words:** CRBN, cardiac function, mitochondria

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**P06-15**

**DQAsome, a Mitochondria targeting carrier, shows cardiac toxicity via suppressing cardiac Ca2+ signaling**

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DQAsomes (dequalinium-based liposome-like vesicles) are mitochondria-targeted vesicular pharmaceutical nanocarrier systems. They have been designed for the delivery of DNA and low-molecular weight molecules to mitochondria within living mammalian cells. Although targeting ability of DQAsomes is well known, it has shown lower stability with cell toxicity. To overcome its low-stability and cellular toxicity, we newly developed modified-DQAsomes (DQA0 and DQA80) by using different combination of DOPE and DOTAP molecules. Their mitochondria targeting efficiency, effect on whole heart and isolated cardiac myocyte and effect on mitochondrial function were extensively tested and compared with original DQAsome. As results, all DQAsomes successfully targeted to mitochondria in perfused heart and intraventricular injected hearts. DQAsome and DQA0 showed significant cardiac toxicity which impaired cardiac output, ventricular cell contraction and mitochondrial oxygen consumption rate at doses of 2 or 20 ug/mL. However, DQA80 did not significantly affect the cardiac output, single cardiac myocyte contraction and mitochondrial oxygen consumption. Our results conclude that modified DQAsome-DQA80 significantly improve the targeting efficiency without cardiac and mitochondrial toxicity. DQA80 is the suitable mitochondria targeting carrier which will be used for delivery of DNA and low-molecular weight molecules to mitochondria in clinical application.

**Key Words:** DQAsome, Heart, Calcium, Mitochondria

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**P06-16**

**The difference between vascular smooth muscle contraction and relaxation in four different aortic regions and their aortic parameters in rats**

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Abstract **Objective:** The aortic aneurysm is a common disease with dysfunction of vascular contraction and relaxation. It is mainly found in the abdominal and thoracic aorta but also found in the arch and ascending aortic region to a lesser extent. However, the pathological cause of spatial specificity of aortic aneurysm is unclear. To understand this spatial specificity, we tested whether different aortic regions respond differently to contracting and relaxing stimulations. Furthermore, we tested whether there are expressional differences in contractile protein components between the ascending, arch, thoracic and abdominal regions of the aorta. **Methods:** Aortic isometric tension and effect of Phenylephrine (Phe) and acetylcholine (Ach) were measured for the four different aortic regions in Wistar rats. Histological studies of the four different aortic tissues were performed using Hematoxylin-Eosin, Masson’s Trichrome stains for collagen and Verhoeff’s stains for elastin.To investigate collagen mRNA and protein expressions, real-time PCR and western blot method was used. **Results:** The Phe-
dose-dependent contraction in aortic strips was significantly different. The ascending aorta showed significantly higher contraction than the three other aortic regions. The Achinduced relaxation in thoracic aortic regions was significantly lower than the three other aortic regions. In the histological study, we observed that the shape of the ascending and archaortic lumens were elliptic, but the abdominal and thoracic aortic lumens were circular. The elliptic areas were divided into thin and thick tunica media. The thickness between thin and thick tunica media area was significantly different in the ascending and arch aorta. The amounts of collagen mRNA and protein expression in the ascending and archaortic segments are less than in the thoracic and abdominal aortic wall. Verhoff’s stain showed that the lamellar of elastin in the ascending aortic segments was greater than in the thoracic and abdominal aortic tunica media wall. Conclusion: These data suggest that the thoracic aorta has lower relaxibilty with higher intracellular collagen contents which may relate with higher occurrence of aneurysm in this aortic region.

Key Words: Ascending, Arch, Thoracic, Abdominal, collagen fiber, elastic fiber

P06-17

Role of Formyl Peptide Receptors on Mobilization of Peripheral Blood Stem Cells in Myocardial Ischemia Injury
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Increasing evidence suggests that circulating bone marrow-derived stem cells promote repair of ischemic tissues. However, the role of FPR2 in mobilization of bone marrow-derived stem cells and repair of myocardial infarction has not been explored. This study was undertaken to investigate the role of FPR2 on mobilization of bone marrow stem cells and repair of myocardial infarction. WKYMVm, which is a specific agonist for FPR2, was administered in a murine model of acute myocardial infarction and the percentages of subpopulations (CD34+/CD133+, CD45−/CD34+, CD45−/CD133+) of peripheral blood stem cells (PBSCs) in peripheral blood were quantified by fluorescence-activated cell sorter analysis. Intraportal injection of WKYMVm stimulated mobilization of CD34+/CD133+ or CD45−/CD34+ PBSCs with a peak stimulation on day 4. Moreover, WKYMVm administration prevented tissue damage and improved cardiac function. In mice transplanted with bone marrow derived from GFP transgenic mice, WKYMVm stimulated homing of GFP-positive bone marrow cells into infarcted heart and formation of GFP-positive blood vessels. WKYMVm-induced mobilization of PBSCs and repair of infarcted heart were abrogated in FPR2-knockout mice, but not in FPR1-knockout mice. Furthermore, WKYMVm-induced mobilization of PBSCs and repair of infarcted heart were completely abrogated in wild type mice transplanted with bone marrow from FPR2-knockout mice, but not in FPR2 knockout mice transplanted with bone marrow from wild type mice. These results suggest that FPR2 is a new receptor regulating mobilization of PBSCs from bone marrow into peripheral blood and FPR2 activation can be beneficial for therapy of myocardial infarction.

Key Words: mobilization, formyl peptide receptor, stem cells, myocardial infarction

P06-18

Antihypertensive effects of fermented garlic extract through NO-cGMP-PKG pathway in SHR
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Hypertension can cause a variety of complications and serious problem to threaten the lives and health directly. Garlic (Allium sativum L.) has long been used as an antihypertensive and has been reported to have antioxidant, anti-thrombotic, anti-inflammatory and anti-cancer effects. The aim of the present study was to investigate the effect of fermented garlic extract (FGE), which contains high level of stable nitrite, on blood pressure and its mechanism in spontaneously hypertensive rats (SHR). Acute feeding of FGE reduced systolic blood pressure (SBP) showing the peak level at 30 min and recovery to control level within 2 to 3 hr depending on dosage. Chronic feeding of FGE for 2 weeks reduced significantly SBP, right ventricular hypertrophy and BNP mRNA expression. The expressions of endothelial nitric oxide synthase (eNOS) and protein kinase G (PKG) proteins in aortic tissues were significantly increased and aortic cGMP concentration was also increased by chronic feeding of FGE. The anti-hypertensive effect as well as increased eNOS and PKG protein expressions by FGE feeding were attenuated by ODQ, a soluble guanylyl cyclase (sGC) inhibitor. By intake of FGE, the relaxation response of thoracic aorta to acetylcholine and sodium nitroprusside was significantly accentuated in Wistar-Kyoto rats (WKY) and tended to accentuate in SHR without significance. FGE also reduced SBP in WKY. Therefore, FGE with high nitrate have antihypertensive effect through eNOS, sGC, PKG and cGMP pathway in SHR. supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No 2008-0062279).

Key Words: fermented garlic extract, hypertension, nitrite, eNOS, cGMP

P06-19

Echinochrome A inhibits vascular smooth muscle cell phenotype changing
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Phenotype modulation of vascular smooth muscle cells (VSMCs) plays an important role in the pathogenesis of various vascular diseases including atherosclerosis. Platelet-derived growth factor (PDGF) initiates the various biological effects that contribute to VSMC phenotype changing in progression of atherosclerosis. Here we report that echinochrome A (Ech A) which is a naphthoquinoid pigment from sea urchins, has inhibits effect of the VSMC phenotype changing. Increased synthetic states of VSMC by PDGF-BB were initiated with osteopontin (OPN), and under the Ech A treatment, synthetic states of VSMC exhibited were decreased. Increased VSMC proliferation by PDGF-BB was attenuated by Ech A pretreatment in a dose and time dependent manners. Furthermore, under the Ech A treatment, VSMC exhibited decreased phosphorylation of protein kinase B (Akt) and mTOR. Taken together, Ech A treatment may inhibits VSMC’s phenotype changing by PDGF-BB via Akt and mTOR signaling pathways. Therefore, Treatment of Ech A may be a potential therapeutic strategy for the prevention of atherosclerosis.
P06-20

The effect of microRNA-34c on angiogenesis capacity of high glucose-insulted mesenchymal stem cells

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Rationale: MicroRNAs (miR) are actively involved in the regulation of the physiological function of stem cells. Angiogenesis of stem cells are affected by diabetic stress, and we studied the role of miR in high glucose-stressed MSCs. Materials and Methods: We found miR-34c was induced by high glucose in MSCs. Stem cell factor (SCF) is the targets of miR-34c, and was studied in human bone marrow mesenchymal stem cells (BMSCs). In vitro angiogenesis was assessed by Matrigel assay. Myocardial infarction (MI) was induced in nude mouse, and BMSCs were injected 7 days later. Results: In vitro angiogenesis assay showed that miR-34c impaired tube formation of BMSC, and SCF was confirmed as a target of miR-34c. In miR-34c transfected BMSCs, the levels of mRNA and protein of SCF were decreased. Additionally, SCF knockdown by siRNA resulted in the blockade of in vitro angiogenesis. Kruppel-like factor 4 (KLF4) was unexpectedly induced by both SCF knockdown and miR-34c overexpression in BMSCs. In KLF4-overexpressed BMSCs, tube formation was completely blocked, while the level of SCF was not changed. When KLF4 was knockdowned by siRNA, miR-34c failed to inhibit tube formation in BMSCs. From these results, miR-34c was suggested to target SCF to inhibit angiogenesis, and KLF4 might be a downstream effector of SCF in BMSCs. In order to determine whether the therapeutic potential of BMSCs was influenced by miR-34c, mouse MI model was used. BMSCs were transfected with miR-control or miR-34c and injected into the myocardium. Cardiac fibrosis was 18.2±4.7% in miR-34c-BMSC group and 10.0±1.8% in miR-con-BMSC group. Fluorescence immunostaining for vWF revealed decreased blood vessel density in the miR-34c-BMSC group as compared with the miR-con-BMSC group. Capillary density was also smaller in the miR-34c-BMSC group than in the miR-con-BMSC group. Collectively, miR-34c negatively regulated the angiogenic potential through inhibition of SCF, and subsequent induction of KLF4 in BMSCs. Conclusion: Our results show that the angiogenic activity of BMSCs is finely regulated by miR-34c-SCF-KLF4 axis which is a potent translational target for anti-angiogenesis.

Key Words: Mesenchymal Stem Cells, Angiogenesis, Myocardial infarction, High glucose, MicroRNA-34c

P07-01

Epigallocatechin-3-Gallate Rescues LPS-impaired Adult Hippocampal Neurogenesis through Suppressing the TLR4-NF-κB Signaling Pathway in Mice

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Adult hippocampal dentate granule neurons are generated from neural stem cells (NSCs) in the mammalian brain, and the fate specification of adult NSCs is precisely controlled by the local niches and environment, such as the subventricular zone (SVZ), dentate gyrus (DG), and Toll-like receptors (TLRs). Epigallocatechin-3-gallate (EGCG) is the main polyphenolic flavonoid in green tea that has neuroprotective activities, but there is no clear understanding of the role of EGCG in adult neurogenesis in the DG after neuroinflammation. Here, we investigate the effect and the mechanism of EGCG on adult neurogenesis impaired by lipopolysaccharides (LPS). LPS-induced neuroinflammation inhibited adult neurogenesis by suppressing the proliferation and differentiation of neural stem cells in the DG, which was indicated by the decreased number of Bromodeoxyuridine (BrdU)-, Doublecortin (DCX)- and Neuronal Nuclei (NeuN)-positive cells. In addition, microglia were recruited with activatingTLR4-NF-κB signaling in the adult hippocampus by LPS injection. Treating LPS-injured mice with EGCG restored the proliferation and differentiation of NSCs in the DG, which were decreased by LPS, and EGCG treatment also ameliorated the apoptosis of NSCs. Moreover, pro-inflammatory cytokine production induced by LPS was attenuated by EGCG treatment through modulating the TLR4-NF-κB pathway. These results illustrate that EGCG has a beneficial effect on impaired adult neurogenesis caused by LPS-induced neuroinflammation, and it may be applicable as a therapeutic agent against neurodegenerative disorders caused by inflammation.

Key Words: Epigallocatechin-3-gallate, Neuronal Inflammation, Neural stem cells, Adult Neurogenesis, TLR4, NF-κB signaling

P07-02

The effect of BD1047 in CCL2 mediated microglia activation in zymosan induced hyperalgesia in rats

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Although intrathecal blockage of sigma-1 receptor (Sig-1R) produces a potent anti-nociception through neuronal regulation in several pain models, it is unclear interactions between neuron and microglia under inflammatory condition. Here we are aimed to address anti-nociceptive mechanism of BD1047 (a selective Sig-1R antagonist) through regulation of chemokine CCL2 mediated microglia activation. Intraplantar injection of zymosan in rats elevated spinal microglia activation with phosphorylated p38 (p-p38), and increased CCL2 expression in dorsal root ganglion (DRG) but not in spinal neurons and glia. Intrathecal blockage of CCL2 reduced zymosan-induced hyperalgesia (evoked by thermal and mechanical stimuli) accompanying spinal Fos elevation as well as microglia/p-p38 activation. In spinal cord slice patch-clamp, incubation of CCL2 significantly increased inward current and p-p38 expression, which was reversed by pretreatment of microglia inhibitor (minocycline). RT-PCR and immunohistochemical study revealed that Sig-1R was predominantly located in DRG, which was overlapped with CCL2. In DRG primary culture, zymosan dose-dependently increased secretion and synthesis of CCL2 with reversed by BD1047. Oral administration of BD1047 dose-dependently inhibited zymosan-evoked hyperalgesia as well as CCL2 elevation, microglia/ p-p38 activation. Taken together, our results indicated that anti-
nociception of Sig-1R antagonist in inflammatory pain was mediated by the blockade of CCL2 induced microglia activation in the spinal level.

Key Words: sigma-1 receptor, zymosan, CCL2, microglia, hyperalgesia

**P07-03**

Repetitive motor cortex stimulation for the chronic neuropathic pain

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Electrical stimulation of the motor cortex is used for reducing spontaneous pain behaviors in animal model of neuropathic pain, but the mechanism of action is still unclear. Previous our report show the pain behaviors are associated with abnormal inhibition in the inhibitory nucleus zona incerta and motor cortex stimulation (MCS) produces antinociception by activating the incertothalamic pathway. We hypothesized that the antinoceceptive effects of MCS are due to enhanced long term potentiation (LTP) signaling in the anterior cingulate cortex (ACC). To test this hypothesis, we used a rodent model of neuropathic pain and performed 30 min MCS (50 µA, 50 Hz; 300 µs pulses) for consecutive 10 days. The behavioral tests were performed before and after MCS. We found that MCS reduced mechanical threshold immediately after MCS and repetitive MCS suppressed pain-like behavior up to 3 weeks. Whether MCS contribute the pain-related LTP or not, the zeta inhibitory peptide (ZIP inhibits PKMz) was injected in the ACC. The comparison of ZIP and vehicle injection, ZIP injection with MCS did not show the mechanical threshold changes. These results support our hypothesis and suggest that MCS produces the synaptic change in the ACC area and mediates the LTP. This research was supported by the Basic Science Research Program through the National Research Foundation (NRF) funded by the Ministry of Science, ICT & Future Planning (No. 2015021989).

Key Words: motor cortex stimulation, anterior cingulate cortex, neuropathic pain, ZIP, behavioral test

**P07-04**

Maresin 1 inhibits TRPV1 in temporomandibular joint (TMJ)-related trigeminal nociceptive neurons and TMJ inflammation-induced synaptic plasticity in the trigeminal nucleus

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In the trigeminal system, disruption of acute resolution processing may lead to uncontrolled inflammation and chronic pain associated with the temporomandibular joint (TMJ). Currently, there are no effective treatments for TMJ pain. Recently, it has been recognized that maresin 1, an endogenous pro-resolution lipid mediator that is derived from the addition of docosahexaenoic acid to macrophages, is a potent analgesic for somatic inflammatory pain without noticeable side effects in mice and a potent endogenous inhibitor of transient receptor potential vanilloid 1 (TRPV1) in the somatic system. However, the molecular mechanisms underlying the analgesic actions of maresin 1 on TMJ pain are unclear in the trigeminal system. Here, by performing TMJ injection of a retrograde labeling tracer DiI (a fluorescent dye), I showed that maresin 1 potently inhibits capsaicin-induced TRPV1 currents and neuronal activity via G i-coupled G-protein coupled receptors in TMJ-related trigeminal nociceptive neurons. Further, maresin 1 blocked TRPV1 agonist-evoked increases in spontaneous excitatory post-synaptic current (sEPSC) frequency and abolished TMJ inflammation-induced sEPSC increases (frequency and amplitude) in the trigeminal nucleus. These results demonstrate the potent actions of maresin 1 in regulating TRPV1 in TMJ-related trigeminal nociceptive neurons and TMJ inflammation-induced synaptic plasticity in the trigeminal nucleus. Therefore, these new findings suggest that maresin 1 may serve as a novel endogenous inhibitor for treating TMJ-inflammatory pain in the orofacial region.

Key Words: temporomandibular joint, maresin 1, trigeminal ganglion neuron, TRPV1, synaptic plasticity

**P07-05**

Neuroprotective Effects of Okadaic Acid Following Oxidative Injury in Organotypic Hippocampal Slice Culture

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Oxidative stress produces neurotoxicity often related with various CNS disorders. A phosphatase inhibitor enhances the actions of the signaling kinases. Protein kinases mediated-action shows the neural protection in brain injury. Phosphatase inhibitor, okadaic acid (OA), may enhance the protection effect and benefit to improve neuronal plasticity in post-injury. Thus, we investigated that the protein phosphatase inhibitor affects neuroprotective signaling and neuroplastic changes in hippocampus after oxidative injury. Electrophysiological and biochemical assays were used to observe changes in synaptic efficacy following electrical and/or pharmacological manipulation of synaptic function. Neuronal cell death, as assessed by propidium iodide (PI) uptake, was reduced by OA treatment (24 and 48 h) compared with KA treatment. The pattern of DCFH-DA fluorescence in hippocampal slices corresponded well with PI uptake. The phospho-AKT/AKT ratio showed that the level of phospho-AKT was significantly increased in the OA-treated group. Furthermore, the OA-treated group exhibited significantly increased expression of SOOD compared with the KA-only group. Optical imaging revealed that KA treatment tended to delay the latency of electrical stimulation and decrease the amplitude of optical signals of synaptic activity. These results suggest that OA may protect hippocampal neurons against oxidative stress and the survived neurons may functional to synaptic plasticity changes.

Key Words: hippocampal slice culture, okadaic acid, oxidative injury, optical imaging, synaptic plasticity

**P07-06**

NDL-PCBs inhibit store-operated Ca2+ entry

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Polychlorinated biphenyls (PCBs) are ubiquitous pollutants which accumulate in the food chain. Recently, several molecular mechanisms by which non-dioxin-like (NDL) PCBs mediate neurodevelopmental and neurobehavioral toxicity have been elucidated. However, although the G-protein coupled receptor (GPCR) is a significant target for neurobehavioral disturbance, our understanding of the effects of PCBs on GPCR signaling remains unclear. In this study, we investigated the effects of NDL-PCBs on GPCR-mediated Ca2+ signaling in PC12 cells. We found that ortho-substituted 2,2',6-trichlorinated biphenyl (PCB19) caused a rapid decline in the Ca2+ signaling of bradykinin, a typical Gq- and phospholipase C-coupled GPCR, without any effect on its inositol 1,4,5-trisphosphate production. PCB19 reduced thephagocytin-induced sustained cytosolic Ca2+ levels, suggesting that PCB19 inhibits SOCE. The abilities of other NDL-PCBs to inhibit store-operated Ca2+ entry (SOCE) were also examined and found to be of similar potencies to that of PCB19. PCB19 also showed a manner equivalent to that of known SOCE inhibitors. PCB19-mediated SOCE inhibition was confirmed by demonstrating the ability of PCB19 to inhibit the SOCE current. These results imply that one of the molecular mechanism by which NDL-PCBs cause neurobehavioral disturbances involves NDL-PCB-mediated inhibition of SOCE, thereby interfering with GPCR-mediated Ca2+ signaling.

Key Words: Polychlorinated biphenyl, non-dioxin-like, G-protein coupled receptor, Ca2+ signaling, store-operated Ca2+ entry

P07-07

The effect of ultrasound stimulation on neurogenesis

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Adult neurogenesis is a process involving the generation, development and integration of new neurons in the brain, and it is increased under pathological stimulation, such as traumatic brain injuries. In physiological conditions, neural progenitor cells are involved in the formation of long-term memories. It is reported that non-harmful stimulation, such as random noise, increases learning and memory. Ultrasound can promote tissue regeneration via improvement of blood circulation, stimulation of angiogenesis and acceleration of wound healing and enhancement of ultimate mechanical strength. Effects of ultrasound on the proliferation and differentiation of other stem cells have gained attention. However, the effect of neurogenesis is not studied well. In this reports, we hypothesized that ultrasound stimulation causes induced neural stem cells(NCSCs) proliferation, differentiation and astrocyte activation. To examine that, we checked IGF-1 and IGFIR expression on NSCs after ultrasound stimulation to 8 weeks old male rat. We also checked that apoptosis and proliferation near subventricular zone(SVZ), IGFIR expression, not IGF-1, is increased on NSCs. Apoptosis of neural stem cell (NSC)/neural progenitor cell(NPC) is also decreased. Taken together, we make the conclusion that ultrasound stimulation on brain can cause neurogenesis, therefore, ultrasound treatment can be used as an efficient and cost-effective method to enhance neurogenesis.

Key Words: Neural Stem cell, Neurogenesis, Ultrasound, Astrocyte, IGF-1, IGFIR

P07-08(O-7)

Necrotic cells Influence Migration and Proliferation of Glioblastoma cells through NF-κB/IL-8 Signaling

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Glioblastoma multiform (GBM), derived from astrocytes, is the most common adult primary intracranial tumor. GBM has a very poor prognosis fatal with a median survival of less than 14 months. Remarkable property of GBM is diffuse infiltration into normal brain parenchyma, rapid growth and central necrosis. However, the effect of these necrotic tissues on GBM growth and metastasis is poorly understood at present. In this study, we examined the biological significance of the existence of necrotic tissues through exploring the molecular mechanisms underlying signaling network between necrotic tissues and GBM cells. Scratch wound healing assay showed that the migration of GBM cell line CRT-MG was significantly enhanced by treatment of necrotic cells. Co-culture with necrotic cells induced IL-8 secretion in CRT-MG in dose-dependent manner. Immunohistochemical analysis for IL-8 in human GBM tissues, showed that positively stained cells were mainly distributed along necrotic core. Necrotic cells induced NF-κB activation and its DNA binding to IL-8 promoter, leading to enhanced IL-8 production and secretion in GBM cells. Our study demonstrates that when GBM cells are exposed and stimulated by necrotic cell, the migration and proliferation of GBM cells are enhanced and facilitated through NF-κB/IL-8 signaling pathway.

Key Words: Glioblastoma multiform(GBM), necrosis, IL-8

P07-09

Utilizing Ultrasound to Transiently Increase Blood-Brain Barrier Permeability, Modulate of the Tight Junction Proteins, and Alter Cytoskeletal Structure

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The central nervous system is protected by the blood-brain barrier (BBB). The tight junction (TJ) proteins claudin-5 and zonula occludens-1 (ZO-1) as well as the cytoskeletal component F-actin play key roles in maintaining homeostasis of the BBB. Increases in BBB permeability may be beneficial for the delivery of pharmaceutical substances into the brain. Therefore, here, we assessed the use of ultrasound to induce transient enhancement of BBB permeability. We used fluorescein isothiocyanate (FITC)-dextran 40 to detect changes in the membrane permeability of bEnd.3 cells during ultrasound treatment. Ultrasound increased FITC-dextran 40 uptake into bEnd.3 cells for 2–6 h after treatment; however, normal levels returned after 24 h. An insignificant increase in lactate dehydrogenase (LDH) leakage also occurred 3 and 6 h after ultrasound treatment, whereas at 24 h, LDH leakage was indistinguishable between the control and treatment groups. Expression of claudin-5, ZO-1, and F-actin at the messenger RNA (mRNA) and protein levels was assessed with real-time polymerase chain reaction and western blotting. Ultrasound induced a transient decrease in claudin-5 mRNA and protein expression within 2 h of treatment; however, no significant changes in ZO-1 and F-actin expression were observed. Claudin-5, ZO-1, and F-actin immunofluorescence demonstrated that the cellular structures incorporating these proteins were transiently impaired by ultrasound. In conclusion, our ultrasound technique can temporarily increase BBB permeability without cytotoxicity to exposed cells, and the method can be exploited in the delivery of drugs to the brain with minimal damage.

**Key Words:** Blood-brain barrier (BBB), Tight junction protein, Ultrasound, Permeability, cytotoxicity.

### P07-10

**PAMAM dendrimer-conjugated TA attenuates mechanical allodynia by inhibiting spinal cord microglia activation**

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Neuropathic pain is a pathological pain with allodynia and hyperalgesia that is caused by sensory neuron damage such as peripheral nerve injury (PNI). The activation of spinal cord microglia is critical for the development and maintenance of neuropathic pain after PNI. Our previous study showed that triamcinolone acetonide (TA) inhibits microglia activation. However, TA has a limitation in clinical application due to its off-target side effects. To obviate this problem, we developed polyamidoamine (PAMAM) dendrimer-conjugated TA (D-TA), which supposedly delivers TA specifically into microglia. PAMAM dendrimer is a sphere-like shape nano-molecule. In this study, we show that PAMAM-dendrimer is selectively delivered into spinal cord microglia. Intrathecal D-TA injection inhibited nerve injury-induced spinal cord microglia activation. D-TA administration reduced mRNA expression of proinflammatory cytokines, such as Nox2, IL-1β, TNFα, and IL-6 in spinal cord after PNI. In addition, D-TA administration significantly attenuated PNI-induced mechanical allodynia. Conclusively, our data demonstrate that D-TA attenuates neuropathic pain after PNI by inhibiting spinal cord microglia activation, suggesting a therapeutic implication for the treatment of neuropathic pain.

**Key Words:** Neuropathic pain, Microglia, Dendrimer, microglia

### P07-12

**Spinal leptin enhances NMDA receptor-mediated tactile hypersensitivity via the reactive oxygen species-phosphatidylinositol 3-kinase (ROS-Pi3K) pathway in neuropathic rats**

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Increasing evidence supports the notion that both microglia and satellite glial cell (SGC) activation play important roles in the development of neuropathic pain after peripheral nerve injury, yet neither the activation mechanisms nor their relative contributions to neuropathic pain have been elucidated. To address this issue, we generated SGC-specific Ikkβ conditional knock-out mice in which IKK/NF-κB-dependent proinflammatory SGC activation is abrogated. In these mice, nerve injury-induced proinflammatory gene expression and macrophage infiltration into the DRG were severely compromised. Likewise, nerve injury-induced spinal cord microglia activation and pain hypersensitivity were significantly attenuated in these mice compared to control mice. However, macrophages recruited into the DRG per se have minimal effects on spinal cord microglia activation suggesting a direct causal effect of SGC activation on spinal cord microglia activation. As an underlying mechanism, we found that SGC activation induces St3gal2 expression in sensory neurons and a subsequent increase in ganglioside GT1b in their axon in the dorsal horn. Studies using St3gal2 knock-out mice indicated that aberrant GT1b increase in the spinal cord is required for the nerve injury-induced spinal cord microglia activation and pain hypersensitivity. Finally, GT1b induced pain-mediating gene expression in primary microglia via direct binding to microglial toll-like receptor 2 (TLR2). Taken together, we present a novel mechanism for spinal cord microglia activation in nerve injury-induced neuropathic pain that is dependent on SGC activation, GT1b increase in the dorsal horn, and activation of microglial TLR2.

**Key Words:** Neuropathic pain, Microglia, Satellite glia, Ikkβ kinase, ganglioside
Recent studies have shown that leptin (an adipocytokine) played an important role in influencing neuropathic pain. It was revealed that leptin enhanced NMDA-induced spinal neuronal excitation. We have previously displayed that upregulation of phosphatidylinositol 3,4,5-triphosphate (PIP3) levels via reactive oxygen species (ROS) in the dorsal horn was involved in tactile hyperalgesia seen in neuropathic rats. In the present study, we investigated whether leptin aggravated NMDA receptor-mediated neuropathic pain behavior and, if so, whether this leptin-induced effect was mediated through the ROS-phosphatidylinositol 3-kinase (PI3K) pathway. Tactile hyperalgesia of the hind paw, evaluated by measuring paw withdrawal threshold upon the application of von Frey hairs, was induced using naïve rats either by lumbar 5 spinal nerve ligation (LS SNL) or by intrathecal (i.t.) administration of leptin or glutamate. The LS SNL-induced tactile hyperalgesia was attenuated by i.t. administration of leptin antagonist, NMDA antagonist MK-801, ROS scavenger alpha-phenyl-N-tetra- butyl nitron (PBN), or PI3K inhibitor LY294002. When intrathecally administered in naïve rats, both leptin and glutamate induced tactile hyperalgesia. Leptin and glutamate administered together induced more severe tactile hyperalgesia than glutamate alone. Leptin-induced tactile hyperalgesia was attenuated by MK801. Both leptin-induced and glutamate-induced tactile hyperalgesia were attenuated by either ROS scavenger PBN or LY294002. The results suggested that spinal leptin enhanced NMDA receptor-mediated tactile hyperalgesia, via the ROS-PI3K pathway, in the neuropathic state. The research was supported by a grant from the Korea Health technology R & D Project, Ministry of Health & Welfare, Republic of Korea (A120254).

**Key Words:** leptin, NMDA receptors, reactive oxygen species, phosphatidylinositol-4,5-bisphosphate 3-kinase, neuropathic pain

### P07-13

**Spinal D-serine induces increase in GluN1 phosphorylation and nociception via nNOS activation in mice: involvement of sigma-1 receptors**

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We have recently demonstrated that increased D-serine in the spinal cord by sigma-1 receptor (Sig-1R) activation mediates neuropathic pain in mice. Here we examine the role of D-serine on the enhancement of NMDA receptor function and nociception via increase in phosphorylation of GluN1 subunit (pGluN1) and nNOS activation, NMDA-induced pain behaviors were assessed for a 10-min period after intrathecal (i.t.) NMDA administration. Neuropathic pain was produced by chronic constriction injury (CCI) of sciatic nerve in mice. Mechanical allodynia (MA) and thermal hyperalgesia (TH) were evaluated in CCI-mice. Western blotting and NADPH-diaphorase staining were performed to assess the changes in pGluN1, GluN1 expression and nNOS activation in the spinal cord. I.t. administration of the D-serine degrading enzyme, DAAO attenuated the facilitation of NMDA-induced nociception occurred by the Sig-1R agonist, PRE084. Exogenous D-serine facilitates NMDA-induced nociception with a dose-dependent manner and increases in PKC-dependent pGluN1 expression, which were attenuated by pretreatment with the nNOS inhibitor, 7-nitroindazole. In CCI-mice, i.t. administration with exogenous D-serine during the induction phase of neuropathic pain restored MA and pGluN1 expression suppressed by the Sig-1R antagonist, BD1047. The serine racemase inhibitor, LOS or DAAO treatment increased the ratio of phosphorylated nNOS to nNOS expression and decreased the number of NADPH-diaphorase-positive neurons in the spinal cord dorsal horn of CCI-mice. This treatment also attenuated CCI-induced MA and pGluN1 expression, which were restored by the NO donor, SIN-1. I.t. administration with 7-nitroindazole dose-dependently attenuated CCI-induced MA and pGluN1 expression. By contrast, D-serine and nNOS signaling had no effect on CCI-induced TH and GluN1 expression. Collectively, spinal D-serine modulates nNOS activation and NO-induced increase in PKC-dependent pGluN1 expression, and ultimately contribute to the Sig-1R-induced pain facilitation and the peripheral nerve injury-induced induction of chronic neuropathic pain.

**Key Words:** D-serine, Sigma-1 receptor, neuronal NOS, GluN1 phosphorylation, neuropathic pain

### P07-14

**Astrocyte gap junction contribute to development of mirror-image mechanical allodynia in peripheral inflammatory rat: Suppressive effect of spinal interleukin-1β on connexin 43 expression**

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Mirror-image pain (MIP) is abnormal pathologic phenomenon which damage on one side of the body can also result in pain from the contralateral unaffected side. Though MIP is known to be mediated by intercellular interactions in CNS, the exact mechanisms underlying the development and modulation of MIP are still unknown. We recently demonstrated that peripheral inflammation induces spinal IL-1β expression which inhibits the astrocyte activation and mediates delayed development of MIP. Here we examined the contribution of spinal IL-1β to astrocyte gap junction and development of MIP. After carrageenan (CA) injection into hindpaw of rats, mechanical allodynia (MA) was evaluated at each time point. Immunohistochemistry and Western blot assay were used to determine the changes of GFAP or connexin (Cx) subtypes expression in the spinal dorsal horn. I.t. injection of carbenuoxolone (CBX; a gap junction decoupler) or Gap26 (Cx43 mimetic peptide) at days 0-3 post-CA injection blocked the development of contralateral MA. The Cx43 and GFAP expression was upregulated after CA injection, which was reversed by I.t. CBX administration. Notably, I.t. injection of interleukin-1 receptor antagonist (IL-1ra) at days 0-3 post-CA injection significantly advanced the appearance of contralateral MA and increased Cx43 and GFAP expression compared to that of control rats. However, I.t. CBX or Gap26 restored IL-1ra-induced contralateral MA. Furthermore, IL-1ra-induced increased expression level of Cx43 and GFAP was reversed by I.t. injection of recombinant IL-1β. These results demonstrated that spinal astrocyte gap junction plays a major role for development of contralateral MA during the early phase of peripheral inflammation. Also, blocking of spinal IL-1β induced the Cx43 expression and astrocyte activation which was ultimately facilitated development of contralateral MA in peripheral inflammatory pain model, suggesting that the relationship between spinal IL-1β and astrocyte gap junction plays an important role in the regulation of induction time of MIP.

**Key Words:** Mirror-image pain, Astrocyte, Gap junction, connexin 43, Interleukin-1β
P07-15

Effects of TCDD exposure on the gonadotropin releasing hormone neurons in mice
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2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most potent toxic environmental pollutant which has adverse effects on reproductive development. Till date little is known about the impact of dioxin in GnRH neuronal development and its role in reproductive physiology at hypothalamic level. Thus, in present study, using whole cell electrophysiology we investigated the effect of various neurotransmitter agonists on gonadotropin releasing hormone (GnRH) neurons in TCDD (10 µg/kg; single dose) exposed prenatal and juvenile mice. GnRH neurons from juvenile offspring of TCDD injected pregnant female mouse on gestational day 15 showed no significant difference in GABAA and kainate receptor mediated neurotransmissions. Single dose of TCDD in juvenile mice showed significant decrease in inward current response of GABA and NMDA receptor mediated and increase in kainate receptor mediated neurotransmission when examined in peri-pubertal age with respect to control. On the other hand, a single dose of TCDD injected on juvenile period showed no significance difference in GABAA receptor mediated responses on adult female over estrous cycle. Whereas, in diestrus and proestrus phase, there was a significant increase in kainate receptor mediated neurotransmission in adult female. These results support that TCDD is a potent environmental pollutant which may directly affect reproductive physiology at hypothalamic level. This research was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2014R1A1A2054241) and (2015R1C1A1A02036793)

Key Words: GnRH neurons, TCDD, Patch clamp

P07-16

Action of calcitriol on NMDA and kainate receptor-mediated actions in juvenile GnRH neurons
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Vitamin D is a versatile signaling molecule which plays a critical role in calcium homeostasis. There are a number of studies showing the genomic action of vitamin D in control of reproduction. However, the quick non-genomic action of vitamin D at hypothalamic level has not been well understood. So, to investigate the effect of vitamin D on juvenile GnRH neurons, excitatory neurotransmitters NMDA (30-µM) and kainate (10-µM) were applied in the absence or the presence of vitamin D3 (10-nM). The NMDA-mediated responses were decreased by VitaD3 in intact and in presence of TTX, a sodium channel blocker with a mean relative inward current being 0.56±0.07 and (0.66±0.07) (p<0.05) respectively. In addition, VitaD3 decreased the frequency of GABAAergic spontaneous postsynaptic currents and spontaneous postsynaptic currents induced by NMDA application with a mean relative frequency of 0.595 ± 0.07 and 0.56±0.09 respectively. Further, VitaD3 decreased the kainite-induced inward currents with a relative inward current 0.69±0.10 (n=5; p<0.05). These results demonstrate that VitaD3 has non-genomic action and partially inhibits the NMDA and the kainite receptor-mediated actions on GnRH neurons suggesting that VitaD3 may regulate HPG axis at the time of pubertal development. This research was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2014R1A1A2054241) and (2015R1C1A1A02036793)

Key Words: GnRH neurons, Vitamin D, Patch clamp

P07-17

Effect of BPA over pre- and post-natal development of Gonadotropin Releasing Hormone Neurons
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Over the course of development, various hormones shape the brain for a time specific physiological events like puberty and reproduction. Further, in present modern age, the manmade pollutants are disrupting proper reproductive development. Taking these scenario into account, it is well established that bisphenol-A (BPA), a monomer of polycarbonate plastic is an endocrine disruptor and is a potential hazard for reproductive physiology. So in this study, using patch clamp technique we examined the agonists of various neurotransmitter receptors on GnRH neurons from the pre- and post-natal BPA exposed mice. In the first set of experiment, neonatal offspring of the BPA (125 mg/Kg) exposed female pregnant mice were examined. Interestingly, pups from BPA exposed mothers showed increased response to GABA (100 µM), kainate (10 µM) and AMPA (10 µM) mediated responses than their respective controls. In contrary, GnRH neurons from BPA injected juvenile mice showed decreased GABAA and kainate receptor mediated responses than their control counterpart parts. Further in another set of experiment gramicidin perforated mode was used to examine the effect of BPA exposure on various neurotransmitter receptor mediated responses on adult GnRH neurons. There were decreased GABA (100 µM), baclofen (10 µM), kainate (10 µM) and AMPA (10 µM) mediated responses in BPA exposed mice than in control counterpart parts. These results suggest that BPA exposure may directly affect GnRH neurons which is the central regulator of hypothalamic pituitary gonadal axis. This research was supported by Basic Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2013R1A1A2058356) and (2014R1A1A2054241)

Key Words: Endocrine disrupting chemicals, Bisphenol-A, GnRH neurons, patch-clamp, GABAergic

P07-18

Loss of Tumor Suppressor PML Promotes Cell Cycle Progression and Proliferation By Enhancing STAT-3 Activity
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P07-19

Necrotic cells Influence Glioblastoma progression through regulating MCP-1 and MIP-3α expression

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Glioblastoma multiform (GBM), a grade IV astrocytoma, is most lethal and common adult primary intracranial tumor. Among the histological properties of GBM, necrosis has been implicated to be a strong predictor of poor prognosis. However, the effect of tumor necrosis on GBM progression is poorly understood at present. In this study, we examined the effect of tumor necrosis on glioblastoma cells through exploring gene transcription and chemokine expression, such as Monocyte Chemoattractant Protein-1 (MCP-1/CCL2) and Macrophage Inflammatory Protein-3 alpha (MIP-3α/CCL20). Chemokine array and ELISA assay showed that CRT-MG human glioblastoma cells secreted several chemokines including MCP-1 and MIP-3α in response to necrotic cells. Expression levels of mRNA of MCP-1 and MIP-3α were increased by treatment of necrotic cells in CRT-MG, well correlated with corresponding protein levels. Further study is in progress to determine the molecular mechanisms underlying the suppressive activity of PML in STAT-3 activation by performing reporter assay.

Key Words: PML, STAT-3

P07-20(O-14)

Generation and regulation of pacemaker activity by TRPC3 channels in nigral dopamine neurons

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Dopamine neurons in the substantia nigra pars compacta (SNc) are slow pacemakers that generate spontaneous action potentials regularly. This regular pacemaking activity regulates the release of basal dopamine to the projection area, such as striatum. Although spontaneous action potentials are essential for maintenance of background dopamine levels and proper functioning of basal ganglia, including the striatum, it is not known what channels are responsible for pacemaking in the midbrain dopamine neurons. Here we report that TRPC3 channels are responsible for pacemaking in the midbrain dopamine neurons. A specific TRPC3 channel blocker, Pyr10, stopped spontaneous firing and following Ca2+ oscillations in dopamine neurons. However, in TRPC3 knockout mice, dopamine neurons showed normal spontaneous firing rate and Pyr10 did not affect spontaneous firing and Ca2+ oscillations at all, suggesting that spontaneous firing in the TRPC3 KO mice is driven by other channels. When TRPC3 channels were blocked by pyr10 with TTX present, neurons hyperpolarized to average -52 mV and then these inhibition of pacemaking were recovered by somatic injection current, suggesting a TRPC3 conductance are constitutively active and lead tonic depolarization. Our results suggest that TRPC3 channels are essential for pacemaking and determination of tonic firing rate in midbrain SNc dopamine neurons.

Key Words: dopamine neuron, pacemaking, TRPC3
P07-22

Treatment With Diluted Bee Venom Reduces Both Spinal Inflammatory Responses And Central Neuropathic Pain Behaviors After Spinal Cord Injury In Rats

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Chemical acupuncture with diluted bee venom (DBV) has been traditionally used in eastern medicine to treat several inflammatory diseases or chronic pain conditions. We have previously shown that DBV had a potent anti-inflammatory and anti-nociceptive efficacy in several rodent pain models. In the present study, we investigated whether the treatment of DBV into Zusanli (ST36) acupoint suppressed intraspinal inflammatory responses as well as allodynic and hyperalgesic behaviors in the spinal cord injury (SCI) model of rats. SCI was induced by T13 spinal cord hemisection after laminectomy. SCI surgery produced acute migration of the neutrophils and the dramatic increment of myeloperoxidase (MPO) activity in the spinal cord lesions at 24 hours following hemisection. In addition, the mechanical allodynic and thermal hyperalgesic behaviors were developed in the bilateral hind paws throughout the 28 days of experiment. Subcutaneous injection (0.25 mg/kg) of DBV was applied into Zusanli acupoint twice a day for five days. DBV treatment significantly suppressed neutrophils infiltration and the MPO activity at 24 hours after hemisection. Moreover, mechanical allodynia and thermal hyperalgesia were relieved throughout the experimental period. DBV injection also showed the facilitated motor function recovery as indicated by the Basso-Beattie-Bresnahan rating score. Finally, spinal glial fibrillary acidic protein (GFAP) expression, a marker for astroglial activation, was also suppressed by DBV injection. These results demonstrated that the repetitive application of DBV into acupoint not only enhanced functional recovery but also reduced acute-inflammatory response and neuropathic pain behavior after SCI. This study suggests that DBV acupuncture can be a potential clinical therapy for management of SCI.

Key Words: Bee venom, Spinal cord injury, Neuropathic pain, Spinal inflammation, Gial fibrillary acidic protein

P07-23

Immunosuppressive effect of estrogen ameliorates pruritic atopic dermatitis in the pubertal female rats

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Atopic dermatitis (AD) that is a chronically relapsing inflammatory skin disease accompanied with chronic pruritus greatly affects the quality of life of afflicted children and their families. Nevertheless, its underlying mechanisms or appropriate remedies remain to be elucidated. Many earlier studies have shown that endogenous estrogens are important modulators of immune system and its function. Gender difference of AD, a preponderance or severity of an adolescent boy compared to girl, has long been recognized. Previously, we developed a rat model of atopic dermatitis produced by subcutaneous injection of capsaïcin within 48 hours after birth. The model showed the cardinal signs of AD from 3rd to 12th postnatal week (PW). In the present study using this model, we investigated the effect of estrogen on the severity of AD during puberty. To meet this aim, we first compared dermatitis, scratching behaviors and serum levels of IgE among the following 4 groups of AD rats; 1) Male group, 2) Female group, 3) Female-OVX (OVX) group that was subjected to ovariectomy at the 3rd PW and 4) Female-OVX-E2 (E2) group that was subjected to ovariectomy followed by an implantation of silastic tubing containing 17β-estradiol (180 μg/μl) under dorsal neck skin at the 3rd PW. The Male and OVX groups showed more severe pruritic dermatitis with higher level of serum IgE, compared to both the Female and E2 groups in which IL-4 and NGF mRNA expression of the lesional skin was relatively reduced but expression of TGF-β and flaggrin mRNA was markedly increased. Thus, our results indicate that estrogen, at least during pubertal female, ameliorates the signs of AD by the modulation of the skin immunity and epidermal barrier functions.

Key Words: Atopic dermatitis, Dermatitis, Estradiol, Ovariectomy, IgE, NGF, Filaggrin

P07-24

Spontaneous firing system of substantia nigra dopamine neurons: proximal dendrites as an accelerator and the soma as a counteract balancer

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Pacemaker activity of highly polarized neurons requires proper spatial organization of excitable elements throughout the somatodendritic compartment. In spontaneously firing dopamine neurons, the pacemaker mechanism composed of intrinsic excitability of the somatodendritic compartment is not clearly understood yet. Here we demonstrate that the dynamic complementary interaction between the stably-oscillating soma and the stochastically-behaving proximal dendritic compartments determines pacemaker activity of the dopamine neuron. Ca2+ spikes occurring in the proximal dendritic compartment having a fast Ca2+ dynamics were highly stochastic and its excitability was higher than the soma. But the dendritic compartment having a fast Ca2+ dynamics were highly stochastic and its excitability was higher than the soma. But the tight electrical-coupling with the soma makes dendritic Ca2+ fluctuations synchronized with the stable somatic Ca2+ oscillations. Local perturbation experiments suggest that the stochastic proximal dendritic regions drive pacemaking activities, but that the electrically-coupled large-compartment soma counteracts the accelerating activities of the proximal dendrites and balances them. This accelerator-counteract balancer model could explain real pacemaker activity and dynamic aspects of glutamate-induced firing diversity in the dopamine neurons.

Key Words: dopamine neuron, pacemaker mechanism, Ca2+ oscillation, somatodendritic balance

P07-25(O-5)

Novel function of histone demethylase of JHDM in spatial learning and memory
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Dynamic changes in histone modification play a role in regulating the gene expression program linked to memory formation. Among them, very little is known about the role of Jumonji-containing histone demethylases which erase methyl group of H3K4, H3K9, H3K27, H3K36, and H4K20- associated with memory formation. Here, we documented the physiological role of JHDM (H3K9 demethylase) in learning and memory. Surprisingly, we found that the JHDM overexpressed transgenic mice displayed enhanced spatial-memory formation and contextual fear conditioning compared to wild-type mice. Conversely, JHDM-deficient mice derived by Lenti-viral vector in hippocampus showed the impairment in hippocampus-dependent memory function. We also observed that overexpression and knockdown of H3K9 demethylase led to changes in expression of neuronal target genes involved in memory formation. Taken together, our results suggest that JHDM has an important role of memory formation in the hippocampus. These findings suggest that JHDM might be a suitable therapeutic avenue for neurodegenerative diseases associated with learning and memory impairment.

Key Words: Jumonji-histone demethylase (JHDM), learning and memory, hippocampus

Hypotaurine action mediated by α-homomeric & αβ-hetromeric glycine receptors in medullary dorsal horn neurons
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Hypotaurine, the immediate precursor of taurine in mammalian tissues is biosynthesized from cysteine in astrocytes and play as an indigenous neurotransmitter. The medullary dorsal horn plays a key site in the processing of orofacial nociceptive input to higher brain areas for orofacial pain perception. Patch clamp technique was used to examine the direct effects of hypotaurine and the receptor types involved in the actions. Under the condition of high chloride pipette solution, hypotaurine induced inward currents at different concentrations (300 μM, 1 mM and 3 mM) were almost blocked by strychnine (2 μM), a glycine receptor antagonist, but not affected by gabazine (3 μM), a synaptic GABAAR receptor blocker, suggesting the involvement of glycine receptors. Further, to figure out the type of glycine receptors activated by hypotaurine, a low concentration of picrotoxin which blocks α-homomeric glycine receptors was applied prior to hypotaurine and glycine. Hypotaurine (300 μM and 1 mM) and glycine (100 μM) induced inward currents were partially blocked by picrotoxin (50 μM). Similarly hypotaurine- and glycine-induced inward currents were also partially blocked by bicuculline (10 μM), which serves as α2 homomeric glycine receptor blocker. Overall, these results indicate that hypotaurine affects SG neuronal activities by α-homomeric and αβ-heteromeric glycine receptors. This research was supported by Basic Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2015R1D1A1A01018700).

Key Words: Hypotaurine, orofacial pain, patch clamp technique, glycine receptors

Role of Neuregulin-2 in synaptogenesis in newborn granule cells
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Neuregulin-2 (NRG2) was identified as a member of proteins containing EGF-like domain. NRG2 is expressed in a few restricted regions in the brain including the hippocampal dentate gyrus (DG) and subventricular zone, where neurogenesis persists during adulthood. Little is understood about the role of NRG2 in developments of newborn neurons. To study the role of NRG2 in synaptogenesis, we infected the newborn granule cells (GCs) in the ex vivo culture of hippocampus with retrovirus encoding microRNA against NRG2 (miNRG2). The miNRG2 was designed to be expressed under the control of Tet-On expression system. We recorded feed-forward GABAergic or glutamatergic postsynaptic current (GPSC or EPSC) evoked by stimulation of inner molecular layer of the DG. Depletion of endogenous NRG2 by treatment of doxycycline (dox) from 4 dpi (day-post-injection) suppressed GPSC amplitude. In contrast, dox treatment from 7 dpi displayed no significant effect on EPSCs, suggesting NRG2 is essential in GABAergic synapse formation but not in its maintenance. Next, we studied the role of NRG2 in glutamatergic synapse formation by treating dox from 7 dpi. Whereas such dox treatment had no effect on GPSC, it lowered both amplitudes of AMPA- and NMDA-EPSCs, and abolished the normal increase in the ratio of AMPA- to NMDA-EPSC. In parallel, dendritic arborization of newborn GCs was reduced. These effects of knockdown were rescued by simultaneous overexpression of the intracellular domain of NRG2. Consistently, pharmacological inhibition of ErbB4, the receptor of Nrg2, suppressed the development of GABAergic synapses, but not glutamatergic synapses. These results suggest that the NRG2-mediated forward and reverse signalings participate in GABAergic and glutamatergic synaptogenesis, respectively.

Key Words: hippocampus, neurogenesis, synaptogenesis, neuregulin

Portal hypertension is associated with the impairment of arterial baroreflex and hypoexcitability of aortic baroreceptor neurons in cirrhotic rats
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Portal hypertension (PH) is a frequent clinical syndrome that is characterized by an increased portal venous pressure, and is most commonly caused by chronic liver disease. Clinical studies have suggested that portal hypertension causes cardiovascular autonomic dysfunction (CAD) including decreased baroreflex sensitivity (BRS) and heart rate variability. In the present study, we examined the time courses of PH and CAD progresses in cirrhotic rats, and whether portal hypertension causes impairment of arterial baroreflex and functional plasticity of the aortic baroreceptor (AB) neurons like liver cirrhosis. In this regard, we produced rats with either PH or liver cirrhosis by a partial portal vein ligation and intraperitoneal injection of thioacetamide (TAA), respectively. Time courses of baroreflex dysfunction and PH development were similar in TAA-induced cirrhotic rats. One week after...
surgery, the portal venous pressure was significantly increased in PH rats compared with sham-operated rats. As assessed by measurement of the heart rate changes during phenylephrine-induced baroreceptor activation, BRS was significantly decreased in PH rats. Under the current clamp mode of the patch-clamp technique, cell excitability was recorded in Di-4 labeled AB neurons. The number of action potential discharge in A- and C-type AB neurons was significantly reduced due to increased rheobase and threshold potential in PH rats compared with sham-operated rats. Real-time PCR and western blotting experiments revealed that NaV1.7, NaV1.8, and NaV1.9 transcripts and proteins were significantly down-regulated in the nodose ganglion neurons from PH rats compared with sham-operated rats. Consistent with these molecular data, TTX-sensitive NaV currents as well as both TTX-sensitive and TTX-resistant NaV currents were significantly decreased in A- and C-type AB neurons, respectively, from PH rats compared with sham-operated rats. Taken together, these data suggest that PH may cause the impairment of arterial baroreflex in cirrhotic rats. Moreover, the cellular mechanisms underlying the PH-induced hypoexcitability of AB neurons include down-regulation of voltage-gated sodium channels. This research was supported by Basic Science Research Program through the National Research Foundation (NRF) funded by the Ministry of Education, Science and Technology (2013R1A1A2013424).

Key Words: liver cirrhosis, portal hypertension, arterial baroreflex, baroreceptor, sodium channel

P07-29
Intraplantar injection of DHEAS or PREGS enhance P2X mediated mechanical allodynia via sigma-1 receptors in rats
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The role of peripheral neurosteroids in nociception and their related mechanisms have not been thoroughly investigated. Since there is emerging evidence that neurosteroids affect P2X mediated membrane current in cellular system, we have determined to investigate the possible modulatory role of dehydroepiandrostosterone sulphate (DHEAS) and pregnenolone sulfate (PREGS) on the P2X mediated pain at the peripheral level. We performed concomitant intraplantar injection of DHEAS or PREGS with αβmeATP and observed paw withdrawal frequency to the innocuous mechanical stimulation in rats. Neurosteroid itself did not produce any detectable changes paw withdrawal frequency. Otherwise, when DHEAS or PREGS co-injected with sub-effective dose of αβmeATP, they dose dependently developed αβmeATP induced mechanical allodynia which was almost totally prevented by TNP-ATP (a P2X antagonist). These results demonstrated that DHEAS and/or PREGS potentiated the activity of P2X receptors which result in the enhancement of αβmeATP induced mechanical allodynia. Subsequently, we investigated the possible action of GABAA, NMDA and sigma-1 receptors, representative neurosteroid’s target receptors, in DHEAS or PREGS + αβmeATP induced mechanical allodynia. As a result, pre-treatment of BD-1047 (a specific sigma-1 antagonist) effectively prevented the facilitatory effects induced by neurosteroids, but muscimol (a GABAA agonist) or MK-801 (a NMDA antagonist) did not affect such potentiation of mechanical allodynia. Overall, we addressed that peripheral DHEAS and/or PREGS potentiated P2X induced mechanical allodynia, and this action was mediated by sigma-1 but not by GABAA nor NMDA receptors.

Key Words: neurosteroid, sigma-1, P2X, mechanical allodynia

P07-30
Investigation of leak channels important for pacemaking in the nigral dopamine neurons
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Dopamine neurons in the midbrain are slow pacemakers that generate spontaneous firing autonomously and regularly. However, it is still not known what ion channels are responsible for pacemaking in dopamine neurons. So far, unidentified Na+-permeable leak channels appear to play a major role in driving pacemaker activity. Since resting membrane potentials of midbrain dopamine neurons are maintained between -55-45 mV far from the equilibrium potential of K+ (EK), there could be a conductance responsible for persistent depolarization of membrane potential. Therefore, we have investigated background Na+-permeable ion channels responsible for maintaining membrane potential depolarized in nigral dopamine neurons, using Ca2+ measurement and patch-clamp techniques. Since extracellular Ca2+ and Na+ can play a key role in determining resting leak conductances, we examined whether extracellular Ca2+ and Na+ influence membrane potentials, firing rates, and inward currents in dopamine neurons. Lowering [Ca2+]e from 2.0 to 0.5mM increased the Na+ leak inward current and heavily affected spontaneous firing rates. A nonselective cation channel blocker for TRPC channels, SKF96365, did not completely block background Na+ conductances. Despite usage of TTX and Cs+ which block Nav and Kv channels, the component of Na+- resistant leak conductances survived. RT-PCR showed the presence of mRNA for NALCN1, a background Na+-leak channel, in dopamine neurons. These results suggest that there could be a TTX- and Cs+-resistant Na+ leak channel controlled by [Ca2+]e and that NALCN could play an important role in the pacemaking of the midbrain dopamine neurons.

Key Words: nigral dopamine neurons, pacemaking, Ca2+, leak channel, NALCN

P07-31
LTP of dendritic spines in nigral dopamine neurons: possible link of reward and burst
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During reinforcement learning, glutamatergic inputs to the midbrain dopamine neurons generate bursts that encode initially reward itself but later cues that inform upcoming reward. However, little is known about the cellular mechanism for bursts. Very recently, we found that dopamine neurons in the substantia nigra pars compacta(SNC) have two morphologically and functionally distinct types of glutamatergic synapses, spine synapses and shaft synapses on the same dendrite. Thus we have explored how these glutamate synapses generate burst firing in nigral dopamine neurons, using high-resolution two-photon confocal microscopy and whole-cell voltage-clamp recordings in the TH-eGFP mouse midbrain slices. By consecutive focal glutamate uncaging pulses on the tip of spine heads or dendritic shafts, similar to physiological release of neurotransmitter glutamate, we found that
stimulation above a certain level increased diameter of spine heads and then increased firing frequency, which was in accord with the defined frequency of bursts. But it failed to increase firing frequency unless spine swelling entailed. After spine enlargement, stimulation with lower pulses evoked burst firing, suggesting that spine enlargement is enough to generate burst firing. These results suggest that spine swelling is able to generate burst firing in dopamine neurons. Therefore, this synaptic plasticity of glutamatergic spine synapses could be a possible link between reward and burst in midbrain dopamine neurons. Key Words: Dopamine neuron, burst, dendritic spine, substantia nigra, two-photon confocal imaging

P07-32

Electroacupuncture alleviates mechanical allodynia via spinal opioidergic and alpha2-adrenergic mechanisms in oxaliplatin- or vincristine-induced neuropathy mice model

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This study investigated whether and how electroacupuncture (EA) determines the antinociceptive effect and related neuronal mechanism in the chemotherapy-induced neuropathic pain in mice. Oxaliplatin (OXA, 10 mg/kg) was intraperitoneally injected on days 0 and 6, and vincristine (VCR, 0.1 mg/kg) was intraperitoneally administered once a day for 7 consecutive days to induce neuropathic pain. EA stimulation (2 Hz, 1-2 mA, 30 min) was applied at the ST36 acupoint bilaterally once in every 2 days. Repeated EA stimulation significantly attenuated OXA- or VCR-induced mechanical allodynia. When compared with gabapentin (GAB, 50 mg/kg, intraperitoneal treatment), EA stimulation appeared at similar results. In a separate set of experiment, the antinociceptive effect of a single EA stimulation 8 days after OXA or VCR treatment was reduced by intrathecal pretreatment with naloxone (NAL, opioid receptor antagonist, 40 ug/kg), idazoxan (IDA, alpha2-adrenoceptor antagonist, 200 ug/kg). Moreover, EA remarkably suppressed the OXA- or VCR-enhanced phosphorylation of NMDA receptor NR1 and NR2B subunit in spinal dorsal horn and intrathecal pretreatment of NAL or IDA blocked the effect of EA. In conclusion, EA stimulation at the ST36 acupoint significantly diminished OXA- or VCR-induced neuropathic pain in mice via the mediation of spinal opioid receptor or alpha2-adrenoceptors.

Key Words: Neuropathic pain, Electroacupuncture, Opioidergic system, Adrenergic system, NMDA receptor

P07-33(O-13)

Agonist-independent activity of mGluR1 underlies homeostatic control of intrinsic excitability via IH in cerebellar Purkinje cells

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Homeostatic plasticity, non-Hebbian form of neural plasticity, is triggered to stabilize neural network when long-lasting changes of neural activity occur. Albeit that homeostatic regulation of the intrinsic excitability is a fascinating model for both pathological condition and physiological plasticity, cellular mechanism of homeostatic regulation is still unclear. Given that type 1 metabotropic glutamate receptor (mGluR1) can monitor neuronal activity which results in plastic changes, the receptor could be one candidate for tuning the neuronal activity in an activity-dependent manner. Here we show that agonist-independent action of mGluR1 induces homeostatic intrinsic excitability via upregulation of the hyperpolarization-activated current (IH). First, we observed that activity-deprivation by chronic treatment of tetrodotoxin (TTX) for 2 days decreased evoked firing rates from cerebellar Purkinje cells (PCs). Interestingly, co-treatment of mGluR inverse-agonist under activity-deprived condition, not neutral antagonist, prevented downregulation of excitability, suggesting that homeostatic intrinsic plasticity required agonist-independent action of mGluR1. Next, we observed elevated IH components, including voltage sag and current density by activity-deprivation hence it was suggested that upregulated IH results in lowered excitability. Indeed, homeostatic upregulation of IH was also rescued by blockade of constitutive mGluR activity with activity-deprived condition. Taken together, this study suggests that mGluR1 is a key player for homeostatic control via modulation of IH.

Key Words: Homeostatic plasticity, Intrinsic excitability, mGluR1, cerebellar Purkinje cells, hyperpolarization-activated current

P07-34

Distinct responses of vagal and splanchnic nerves innervating liver to 5-HT receptor agonists in Guinea pigs

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Background: The primary visceral sensory information from intra-abdominal organs is transmitted to the spinal cord and medulla oblongata via splanchnic nerve and vagus nerve, respectively. However, there has been little study for distribution and function of dual sensory innervation system in intraabdominal organs. Purpose: We aimed at elucidating the distribution of 5-HT receptor subtype, the responsiveness to 5-HT and electrophysiological property of 5-HT response in splanchnic and vagal nerves innervating liver. Method: Guinea pigs(250g) were used. Dye(DiI) was injected in liver under anesthesia then one week later neural cells were extracted from vagal and dorsal root ganglia. RT-PCR and intracellular calcium imaging technique were used to check 5-HT receptor subtypes and 5-HT response in DiI labeled vagal and DRG neurons. We performed gramicidin perforated conventional patch clamp technique to find various electrophysiological characteristics and 5-HT2 & 5-HT3 response in DiI labeled neurons. Result: RT-PCR technique showed that vagal (nodose and jugular) and DRG neural cells had mRNAs for 5-HT subtype 2.3 receptors among seven subtypes of 5-HT receptors. Intracellular calcium imaging revealed that dominantly nodose cells responded to 5-HT. This response was mediated by 5-HT2 &
S-HT3 receptors. In the study of electrophysiological properties nodose neuron showed inward current induced by S-HT and S-HT3 selective agonist but not by S-HT2 selective agonist. **Summary:** (1) Vagal and DRG neurons had mRNAs for S-HT subtype 2,3 receptors in the RT-PCR experiment. (2) Nodose vagal neurons responded to S-HT and these responses are mediated by S-HT2 & S-HT3 receptors in intracellular calcium imaging experiment. (3) Nodose vagal neurons responded to S-HT and S-HT3 selective agonist but not S-HT2 selective agonist in patch clamp recording.

**Key Words:** liver, S-HT, vagus nerve, splanchnic nerve

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**P07-35**

Primary afferents temporally encode the noxious stimulus for pain signaling

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Even though an activation of a primary afferent C-fiber is conceptually assumed to initiate a pain response, there are studies reporting no pain response under the activation of the afferents. One of the strong explanations is the neural network that a fiber’s activation is considered as a single input to central nervous system. However, the network process is not enough to interpret all the complex sensations in animal. Moreover, most primary C-fibers contain various chemoreceptors responding to each agonists. For example, TRPV1 receptors and TRPA1 are expressed commonly on a same fiber’s membrane. Thus, chemical specific processing might take an account to such a modified pain sensation. In this study, the responses and its characteristics of primary afferents for different chemicals have been investigated on ex vivo single fiber recording setup. The time stamps of the evoked action potentials recorded from the skin-nerve preparation from the mice were recorded. A mouse was sacrificed before each experiment, and their hind paw skin including the saphenous nerve was extracted with surgical methods. After the identification of a single fiber on the recording setup, a chemical was applied. As a result, we obtained the responses are mediated by 5-HT2 & 5-HT3 receptors in intracellular calcium imaging experiment. P07-35

**Key Words:** Vestibulo-ocular reflex, cerebellum, purkinje neuron

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**P07-36**

Three distinct cerebellum-dependent eye movement learning in pcp2-cre mice

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Vestibulo-Ocular reflex (VOR), which known as cerebellum-dependent eye movement, is a compensatory eye movement to stabilise an image on retina. To deal with dynamic changes of surroundings, this reflex can adapt to the situation and we call it as “VOR learning”. There are three well-known VOR learning protocols, such as Gain-up, Gain-down and Phase reversal learning, and these three distinct protocols based on different synaptic mechanism. To investigate whether and how one molecule act in this eye movement learning, we prepared Purkinje neuron specific cre-recombinase expression mouse (pcp2-cre mice). Since Purkinje neuron can only provide information to outside of cerebellar cortex, modifying this Purkinje neuron could directly affect to synaptic or intrinsic property of the neuron and finally, VOR learning also can be affected. In this study, we applied these three protocols to pcp2-cre mice. Briefly, This mice had normal range of basal ocular motor performance and they are able to learn every learning protocols. Therefore, we can conclude the idea that this cre-recombinase knock-in mice does not have any defect in not only basal ocular motor performance but also learning of cerebellum-dependent eye movement.

**Key Words:** Vestibulo-ocular reflex, cerebellum, purkinje neuron

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**P07-37**

Dysregulation of metabotropic glutamate receptor 5 in periaqueductal gray perpetuate chronic neuropathic pain

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Mechanism of neuropathic pain manifestation is still not fully understood. Not all individual with nerve injury end up with intractable pain, also not all nerve injury-induced pain turn into chronic. Given that inherent capability to regulate painful sensation is diverse among individuals, involvement of endogenous pain modulatory system has been suggested. Among related brain areas, periaqueductal gray (PAG) is one of the most important area in terms of endogenous pain modulation. PAG integrates ascending and descending pain modulatory signals from numerous sites and sends signal to rostral ventromedial medulla (RVM), thus modulates pain signals coming from spinal cord. We focused on the role of metabotropic glutamate receptor 5 (mGluR5) in the PAG in that mGluR5 is involved in various pathological change of the nervous system. It is well known that mGluR5 also contributes to the diverse variety of physiological functions through modulation of neuronal activity. Given the essential role of PAG in pain modulation, it is assumable that alteration of mGluR5 activity in the PAG would result in pain modulatory dysfunction and affect manifestation of neuropathic pain. In this study, we measured brain glucose metabolism from neuropathic pain rats and control rats in vivo using fluorodeoxyglucose (FDG) – positron emission tomography (PET) to compare whole-brain activity of awake, resting state animals. Consistent with our predictions, reduced activity was observed from PAG and RVM of neuropathic pain rats, which was rescued by administration of the group I mGluR agonist into PAG. This treatment induced powerful analgesic effect as well, which was sufficient to cancel out neuropathic pain symptom. Based on the results from PET study, we further hypothesized that mGluR5 in PAG is persistently active to regulate nociception in normal state. Indeed, we could find that mGluR5 persistently regulates neuronal activity in PAG to control pain transmission, and decline of this activity is responsible for maintenance of neuropathic pain. Our findings provide previously unknown mechanism through which pain become chronic, emphasizing an important role of mGluR5 in pain modulatory function.

**Key Words:** Neuropathic pain, Periaqueductal gray, Metabotropic glutamate receptor, Brain imaging

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P07-38

Upregulation of prelimbic metabotropic glutamate receptor 5 in chronic neuropathic pain state
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In this study, we focused on the change of mGluRs in the brain following chronic neuropathic pain. Metabotropic glutamate receptor 5 (mGluR5) is widely expressed on brain regions and exerts various cellular effects related to neuronal plasticity. Considering its importance, however, change of mGluR5 in brain and its functional role in pathophysiology of chronic pain is barely known. Based on other mGluR studies about non-pain neuronal diseases, we hypothesized that there would be an expressional change of mGluR5 in pain-related brain regions under chronic neuropathic pain state. We compared expression level of mGluR5 in the brain between chronic neuropathic pain model animals and sham control in vivo using positron emission tomography (PET) with mGluR5 radiotracer [11C]-ABP688. These images showed that expression of mGluR5 in prefrontal cortex is increased in neuropathic pain rats compared to control. To identify its functional role in pain signaling, mGluR5 antagonist MPEP was injected into the prefrontal cortex of neuropathic pain rats and behavioral change was measured. We could find that blocking mGluR5 in prefrontal cortex evoked analogic effect sufficient to cancel out neuropathic pain symptoms. MPEP-treated neuropathic pain rats showed significantly increased pain threshold to mechanical stimuli, and they preferred to MPEP-conditioned chamber in conditioned place preference experiment. Throughout this process from PET imaging to behavior test, we show that mGluRs of prefrontal cortex is increased in neuropathic pain state, and this prefrontal mGluRs is strongly related to pain perception.

Key Words: Neuropathic pain, Prelimbic cortex, Metabotropic glutamate receptor 5, Brain imaging

P07-39

Changes in Field Potentials Following Transcranial Direct Current Stimulation on the Motor Cortex of Rats in Vivo
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Transcranial direct current stimulation (tDCS) is a noninvasive cortical neuromodulatory tool with therapeutic applications and cognitive enhancing. A number of electrophysiological data of human have shown that tDCS applied to the motor cortex can modulate cortical excitability. Especially, tDCS with sufficient duration and intensity of stimulation enables to induce long-term effects like plasticity. Recently, an in vitro study demonstrated that slow frequency synaptic activation during tDCS was required to induce long-lasting potentiation like plasticity. However, the mechanism how tDCS modulate cortical excitability on the cortex for a long time is still highly unclear. Here, we investigated changes of field potentials, evoked by stimulating contralateral corpus callosum, on the motor cortex of rats before and after anodal tDCS under urethane anaesthesia. Field potentials in the motor cortex were gradually increased for more than one hour after anodal tDCS with or without repeatedly low frequency synaptic activation unlike a previous in vitro study. To elicit these long-lasting effects, the sufficient duration of stimulation (more 20 minutes) was required rather than the high intensity of stimulation. We propose that anodal tDCS with the enough duration of stimulation regardless of repetitive low-frequency synaptic activation may contribute to induce long-term potentiation like plasticity in relation to learning as well as the neuromodulation of the motor cortex.

Key Words: tDCS, neuromodulation, electrophysiology, motor cortex

P07-40

Characterizing the function of Negr1, a newly-identified obesity-related gene, in the nervous system
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Neuronal growth regulator 1 (Negr1) is newly identified obesity-related gene, a member of the immunoglobulin superfamily of GPI-anchored cell adhesion molecule. This gene is recently known to affect synapse formation and dendritic process of both hippocampal and cortical neuron, and categorized as a candidate gene for obesity and psychiatric disorder. Although there are several evidences suggesting the role of Negr1 as a neuronal regulation, in vivo functions of this gene are still unknown. To elucidate the function of Negr1 in the nervous system, we have generated Negr1 knockout mice (KO) and characterized the neurological phenotype by behavioral studies such as anxiety/depression, spatial memory, and recognition. Our data showed that there was no difference in recognition function between wild type and Negr1 KO mice, however, elevated anxiety- and depression-like behavior was observed in the KO group. In electrophysiological studies, we found that hippocampal LTP was severely compromised in the Negr1 KO mice. In our effort to elucidate the underlying mechanisms, we found Lipocalin 2 (Lcn2) gene was decreased in the hippocampus of Negr1 KO mice compared to wild type control mice. In addition, hippocampal synaptic density was increased in hippocampal CA3 and dentate gyrus in Negr1 KO mice. Taken together, our data suggest that Negr1 is involved in mood regulation putatively by regulating synaptic spine density via Lcn2.

Key Words: Negr1, Lcn2, depression, spine density

P07-41

The roles of GABA on the motivational driving force for the pain attenuation following spinal cord injury in rats
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The roles of GABA on the motivational driving force for the pain attenuation following spinal cord injury in rats GABA is the major inhibitory neurotransmitter in the central nervous system includes sensory and psychiatric pathophysiology. To investigate the roles of GABA at both sensory and psychiatric disability, the present study tested GABA-mediated neuropathic pain in reward mechanism following spinal cord injury in rats. SCI was produced by T10 clip compression injury (35 g. 1 min) in ages with 180-225 g male SD rats. To test the roles of GABA, paw withdrawal response, in vivo extracellular single cell recording, HPLC-microdialysis and immunohistochemistry were performed. Prior to injury, the baseline paw withdrawal threshold and fast EPSC was observed in the SCI group. Post injury days 40, SCI groups showed significantly decreased paw withdrawal threshold at both hindpaws and increased ultrasound vocalization compared to before injury, respectively (p<0.05). In vivo extracellular electrophysiology at the ventral segmental area (VTA), GABA neuron activity (characterized by less than 1 ms action potential duration and > 5 Hz frequency) showed increased firing rates (13.6 ± 1.7 spikes/sec) compared to sham control groups (7.3 ± 1.1 spikes/sec). In immunohistochemistry, glutamic acid decarboxylase (GAD) 67 showed increased expression compared to sham control groups (p<0.05) at the VTA. In HPLC-microdialysis at the VTA, the concentration of glutamate (608.3±0 nM) and GABA (98.8±50.5 nM) in SCI groups showed increases compared to sham controls (333±0 nM and 41±1.3 nM), respectively. In addition, the intrathecal administration of GABA receptor agonists at the spinal cord resulted in the attenuation of neuropathic pain and neuronal hyperexcitability that suggests the decreased tone of spinal GABAergic tone following SCI. Taken together, the present study suggests that chronic neuropathic pain reveals the increased activity of VTA GABA neurons that result in the suppression of dopaminergic neurons and motivational driving for the pain attenuation. This work was supported by the National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP/NRF-2015R1A5A7037508) and NRF-2014R1A4A1004179.

**Key Words:** Pain, GABA, VTA, Spinal cord injury

### P07-42

**Carvacrol inhibits mGluR1-evoked slow currents in cerebellum**

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Terpenes are organic compounds produced by plants and insects. Studies shown that many terpenes affect the central nervous system through TRP channels. Transient Receptor Potential (TRP) channels detect environmental and biological signals and changes, such as temperature, pressure, tastes and smells. Different tissues contain different types of TRP channels; TRPM7 is expressed in most tissues, TRPVs are expressed in skin and TRPCs are expressed in many brain tissues. Among TRP channel systems, TRP system in the cerebellum is well-known; mGluR1-evoked slow current is mediated by TRPC1 and TRPC3. In this paper, several terpenes have been tested for the effects on mGluR1-mediated slow EPSC in the murine cerebellum. These terpenes were known to permeate blood-brain barrier (BBB). Among terpenes tested, limonene and pinene did not affect both slow and fast EPSC, linalool and eugenol inhibited both slow and fast EPSC, and carvacrol inhibited slow EPSC selectively. Further studies will be done on how carvacrol inhibit mGluR1-mediated slow EPSC.

**Key Words:** Cerebellum, TRPC, Terpene, Carvacrol, Slow EPSC

### P07-43

**Anti-inflammatory role of cytoplasmic Ref-1 in cultured astrocytes**

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Redox factor-1 (Ref-1) is a ubiquitous protein that is a redox-sensitive regulator of multiple transcription factors as well as an apurinic/apyrimidinic endonuclease in the base excision repair pathway. In recent years, the extra-nuclear role of Ref-1 against oxidative stress has been known. Astrocytes seem to be initial and crucial part in the pathological process of the neuro-inflammation, such as in epilepsy. In the present study, we found that Ref-1 increased in hippocampal astrocytes from kainite-injected epileptic rat. To know the functional role(s) of increased Ref-1 in astrocytes, we further assessed the anti-inflammatory action of Ref-1 in cultured astrocytes. Lipopolysaccharide (LPS) treatment increased iNOS expression in the astrocytes, which was significantly decreased by adenosinergic infection of Ref-1 cDNA. Ref-1 overexpression also significantly inhibited LPS-induced tumor necrosis factor-α (TNF-α) release. In contrast Ref-1 small interference RNS (siRNA) enhanced LPS-induced iNOS expression. Down-regulation of Ref-1 increased LPS-induced TNF-α release. Nuclear localization signal (ANLS) deletion mutation in astrocytes has increased cytoplasmic Ref-1, this effect is similar with wild type. This result supports that endogenous cytoplasmic Ref-1 in astrocytes has anti-inflammatory action. But, both overexpression and knockdown of Ref-1 did not affect the expression of iNOS, iNOS degradation and phosphorylation of NF-kB in LPS-treated astrocytes Overall these data suggest that biological functions of Ref-1, endogenous astrocyte Ref-1 might serve an anti-inflammatory action in astrocytes, which would involve in inflammatory neuro-disease such as epilepsy.

**Key Words:** Redox factor-1 (Ref-1), Inflammation, astrocytes

### P07-44

**Clonidine, an alpha-2 adrenoceptor agonist relieves mechanical allodynia in oxaliplatin-induced neuropathic mice; potentiation by spinal p38 MAPK inhibition without motor dysfunction and hypotension**

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Cancer chemotherapy with platinum-based antineoplastic agents including oxaliplatin frequently results in a debilitating and painful peripheral neuropathy. We evaluated the antinociceptive effects of
the alpha-2 adrenoceptor agonist, clonidine on oxaliplatin-induced neuropathic pain. Specifically, we determined if (1) the intraperitoneal (i.p.) injection of clonidine reduces mechanical allodynia in mice with an oxaliplatin-induced neuropathy, and (2) concurrent inhibition of p38 mitogen-activated protein kinase (MAPK) activity by the p38 MAPK inhibitor SB203580 enhances clonidine’s anti-allodynic effect. Clonidine (0.01-0.1 mg kg-1 i.p.), with or without SB203580 (1-10 nmol, intrathecal) was administered two weeks after oxaliplatin injection (10 mg kg-1, i.p.) to mice. Mechanical withdrawal threshold, motor coordination and blood pressure were measured. Post-mortem expression of p38 MAPK and ERK as well as their phosphorylated forms (p-p38 and p-ERK) were quantified in the spinal cord dorsal horn of treated and control mice. Clonidine dose-dependently reduced oxaliplatin-induced mechanical allodynia and spinal p-p38 MAPK expression, but not p-ERK. At 0.1 mg kg-1, clonidine also impaired motor coordination and decreased blood pressure. A 10 nmol dose of SB203580 alone significantly reduced mechanical allodynia, while a sub-effective dose (3 nmol) potentiated the anti-allodynic effect of 0.03 mg kg-1 clonidine. Co-administration of SB203580 and 0.03 mg kg-1 clonidine decreased allodynia similar to that of 0.10 mg kg-1 clonidine, but without significant motor or vascular effects. These findings demonstrate that clonidine treatment reduces oxaliplatin-induced mechanical allodynia. The concurrent administration of SB203580 reduces the dosage requirements for clonidine, thereby alleviating allodynia without producing undesirable motor or cardiovascular effects.

**Key Words:** clonidine, mechanical allodynia, oxaliplatin, p38 mitogen-activated protein kinase

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### P07-45

**Role of capsaicin-sensitive primary afferents in the development of hypersensitivity in a new mouse model for nitroglycerin-induced chronic migraine**

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Despite the relatively high prevalence of migraine or headache, the pathophysiological mechanisms triggering headache, especially in relation to chronic migraine are unknown. Since nitric oxide (NO) is well known as a causative factor in the pathogenesis of migraine, we were to establish a new mouse model of chronic migraine using nitroglycerin (NTG), a donor of NO. NTG (10 mg/kg) was repetitively administrated every other day for 9 days. Repetitive administration of NTG produced acute mechanical allodynia and thermal hyperalgesia in the hind paws 2 hours after each injection from the second injection day (day 3) of NTG (Post-treatment responses). In contrast, the cold allodynia significantly occurred in the facial region with similar time course. In addition, the NTG-treated mice appeared a progressive and long-lasting decrease of basal thresholds (Basal responses). These chronic basal pain responses also persisted for 10 days after cessation of NTG administration. This NTG-induced peripheral hypersensitivity in facial region and hind paws was reduced by concomitant treatment of sumatriptan (0.6 mg/kg), a medication used for the treatment of migraine headaches. We next examined whether the depletion of capsaicin sensitive primary afferents (CSPAs) with resiniferatoxin (RTX) modified the development of peripheral hypersensitivity in migraine. Interestingly, RTX (0.02 mg/kg) pretreatment partially prevented the induction of mechanical allodynia in hind paw, whereas it did not affect the development of cold allodynia in facial region. These findings demonstrated that repetitive NTG administration resulted in acute and long-lasting pain responses in both hind paws and facial region. In addition, the NTG-induced mechanical hypersensitivity in hind paws was partially mediated by the CSPAs. Therefore, the development of peripheral hypersensitivity in migraine patients could be dependent on the site, the modality and the primary afferent types.

**Key Words:** migraine, nitroglycerin, hypersensitivity, resiniferatoxin, capsaicin-sensitive primary afferent

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### P08-01

**Altered rhythmic behaviors in Alzheimer’s disease model flies by dim light exposure at night**

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Accumulation of Amyloid β (Aβ) peptides in the brain is the hallmark for the progression of Alzheimer’s disease (AD) in humans. The AD is related during aging with aggregation of Aβ42 fibrils in the brain which may arises due to improper cleavage of Amyloid Precursor Protein (APP) by beta-secretase enzyme and other mechanisms. Disruption of circadian rhythmicity with altered sleep-wake cycle, dysregulation of locomotion and increased memory defects have been shown in AD patients. In Drosophila, we show that over-expression of Aβ42 peptide in neurons gives rise to increased locomotor defects and neurodegeneration with aging. Here we have characterized that neuronal over-expression of Aβ42 peptide showed decreased lifespan due to neuronal Aβ toxicity. The AD flies when exposed to dim light at night, shows disruption of circadian rhythmicity and sleep-wake cycle with increased locomotor defects. Hence using fly model system, we hereby report that dim light at night may have an adverse effect on circadian rhythmicity with disturbed sleep-wake behavior in wild type flies and these phenotypes are more severely pronounced in AD flies which becomes sick under dim light exposure. This work was supported by Future Environmental R&D Grant funded by the Korea Environmental Industry and Technology Institute (No. RE201206020)

**Key Words:** APP, circadian rhythmicity, neurodegeneration, Drosophila

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### P09-01

**Signals governing the trafficking of PKD1L1 and PKD2L1 to primary cilia**

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Primary cilia are solitary organelles that extend from the basal body of the apical surface into the extra cellular matrix of most eukaryotic cells. Dysfunctions of primary cilium underlie a multitude of human disorders, including autosomal dominant polycystic kidney disease (ADPKD), yet membrane targeting to the cilium remains poorly understood. Several proteins that contain targeting sequences that serve as a type of cellular zip code to direct the proteins to the cilium have previously reported. Among the aforementioned motifs, arguably the best understood
mechanistically is VxPxF motif found in polycystin 2, CNGB1b, and rhodopsin that is necessary for targeting of these proteins to renal cilia, olfactory cilia, and photoreceptor outer segments, respectively. The motif, V765TPD, is detected in PKD2L1 which are reported to play an important role in flow sensing mechanism and calcium regulation in cilia. To confirm the detected ciliary targeting sequence (CTS), hPKD2L1 was overexpressed in mLMCD-3, and localized to cilia. However, we found that V765TPD hPKD2L1 protein does not traffic into cilia, which indicates that this motif is responsible for ciliary localization. We also investigated electrophysiological characteristics of hPKD2L1 and ΔV765TPD mutant. In whole-cell patch clamp of HEK293 cells transiently transfected with hPKD2L1 and the mutant, each produced outward currents, 134.1 ± 48.7 pA/pF and 158.4 ± 27.4 pA/pF, respectively. Since patients with PKD show abnormal sensory cilia function, the aim of our current study is to search for CTS in PKD2L1 and the candidate domain responsible for ciliary localization in PKD1L1 and their unknown role in calcium regulation mechanism in cilia. Here, we try to identify a novel ciliary trafficking determinant in PKD1L1 and PKD2L1 that furthers our understanding of how proteins are selectively targeted to the cilium and their functional role in calcium regulation.

**Key Words:** PKD1L1, PKD2L1, Cilia, CTS, PKD

**P09-02**

Klotho ameliorates proteinuria through protecting podocyte injury

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Klotho is an anti-aging protein predominantly produced in the kidney, the extracellular domain of which is secreted into the systemic circulation. Klotho is known to protect organs including the kidney. Whether and how Klotho directly protects the glomerular filter remains largely elusive. Here, we report that Klotho exerts protective role against podocyte injury leading albuminuria in diabetic nephropathy and chronic kidney diseases (CKD). Klotho was expressed in podocytes of mouse and human kidney. Type II diabetic db/db mice showed typical diabetic nephropathy features such as albuminuria and disruption of podocyte slit-diaphragm whose features were rescued by administration of purified Klotho protein. Heterozygous klotho-deficient CKD mice have aggravated albuminuria compared to that in wild-type CKD mice with a similar degree of hypertension and reduced clearance function. Disrupting the integrity of glomerular filter by saline infusion-mediated extracellular fluid volume expansion increased urinary Klotho excretion. These results reveal a novel function of Klotho in protecting the glomerular filter and offer a potential new therapeutic strategy for treatment of proteinuria. [This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2010-0024789)]

**Key Words:** Klotho, podocyte, proteinuria, diabetic nephropathy (DN), chronic kidney disease (CKD)

**P09-03**

Klotho inhibits tumor progression by IGF-1 receptor activation in human clear cell renal cell carcinoma

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Klotho is an anti-aging hormone as emerging role in tumor suppressor. Growth factor receptor (GFRs) signaling regulates cell growth, proliferation, metabolism, and survival in all kind of malignancy, including clear cell renal cell carcinoma (ccRCC). Klotho is known as a regulator of IGF-1 receptor signaling, which has been implicated in the development of highly invasive metastatic ccRCC. However, the correlation of Klotho and IGF-1 receptor in ccRCC has not been examined. Here, we hypothesize that Klotho and IGF-1 receptor expression may correlate with the clinico-pathological parameters of ccRCC. Klotho expression was significantly correlated with clinical outcomes including tumor necrosis, Furman nuclear grade, cystic change, pathologic T stage, and TNM stage. IGF-1 receptor was highly expressed in tumor tissues compared to that in normal adjacent mesenchyme. Reduction of Klotho expression in tissues with high Fuhrman nuclear grade and large tumor size indicates that Klotho suppresses tumorigenesis of ccRCC. Moreover, higher expression of Klotho showed in small size of tumor, absent of cystic change and tumor necrosis, pathologic T stage 1 and TNM stage I. Functionally, Klotho blunted IGF-1-stimulated migration and proliferation in CakiI, a ccRCC cell line. In conclusion, the expression of Klotho is decreased as the grade of cancer progression, which affects clinico-pathological parameters. These results reveal that Klotho is a new prognostic marker for ccRCC and may open new avenues for the development of feasible carcinostasis substance. [This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2010-0024789)]

**Key Words:** Klotho, IGF-1, IGF-1R, renal cell carcinoma

**P09-04**

Orai1 expression is closely related with favorable prognostic factors in clear cell renal cell carcinoma

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Store-operated calcium (Ca2+ entry) (SOCE) is a major Ca2+ entry mechanism in non-excitable cells, including epithelial cells, which are the most common origin of cancer. We previously described Orai1 and STIM1 as the molecular components of SOCE that are related in cancer hallmark of clear cell renal cell carcinoma (ccRCC). However, the clinical relevance of Orai1 and STIM1 expression in ccRCC remains elusive. Here, we report the expression of Orai1 and STIM1 in ccRCC, and compare their expression with the patient’s outcome and clinico-pathological parameters. Immunohistochemical staining of Orai1 and STIM1 was...
performed with 126 formalin fixed paraffin embedded ccRCC tissues and protein expression was analyzed by western blot on available fresh tissues. The results were compared to generally well-established clinicopathologic prognostic factors in ccRCC with patient survival. Although Orai1 is plasma membrane protein, Orai1 was mainly expressed in ccRCC nuclei, while STIM1 showed the cytosol expressing pattern in staining. Furthermore, Orai1 expression level was inversely correlated with ccRCC tumor grade, whereas STIM1 expression level was not associated with tumor grade. Higher Orai1 expression was significantly associated with lower Fuhrman nuclear grade, pathologic T stage, and TNM stage with favorable prognosis. Unlike Orai1 expression, the expression level of STIM1 did not correlate with ccRCC grade and clinical outcomes. These results suggest that Orai1 is an appealing prognostic marker and therapeutic target for ccRCC. [This research was supported by Basic Science Research program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology [NRF-2010-0024789]].

**Key Words:** Orai1, STIM1, Clear cell renal cell carcinoma, Tumorigenesis, Prognosis

### P10-01

**Improved application of the electrophoretic tissue clearing technology, CLARITY, to intact solid organs**

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Mapping of tissue structure at the cellular, circuit, and organ-wide scale is important for understanding physiological and biological functions. A bio-electrochemical technique known as CLARITY used for three-dimensional anatomical and phenotypical mapping within transparent intact brain has been recently developed. In the present study, we aimed to improve the original CLARITY procedure and developed specific CLARITY protocols for various intact organs including pancreas. Adult mice were perfused transcardially with hydrogel solution with a mixture of 4% PFA, 4% acrylamide, 0.05% bisacrylamide, 0.25% VA044 in PBS. Organs were extracted and incubated in the same solution at 37°C to initiate polymerization. Hydrogel-embedded organs were placed in an electrophoretic tissue clearing (ETC) chamber. While 4% SDS solution was circulated through the chamber, 250-280 mA was applied across the organs at 42°C for 1-2 weeks. We determined the optimal conditions for reducing bubble formation, discoloration, and depositing of black particles on the surface of tissue, which allowed production of clearer organ images. We also determined the appropriate replacement cycles of clearing solution for each type of organ, and convincingly demonstrated that 250-280 mA is the ideal range of electrical current for tissue clearing. We then acquired each type of cleared organs including brain, pancreas, liver, lung, kidney, and intestine. Additionally, we determined the images of axon fibers of hippocampal region, the Purkinje layer of cerebellum, and vessels and cellular nuclei of pancreas. CLARITY is an innovative biochemical technology for the structural and molecular analysis of various types of tissue. We developed improved CLARITY methods for clearing of the brain, pancreas, lung, intestine, liver, and kidney, and identified the appropriate experimental conditions for clearing of each specific tissue type. These optimized methods will be useful for the application of CLARITY to various types of organs.

**Key Words:** CLARITY, Brain, Nervous system, Electrophoretic tissue clearing, Purkinje layer

### P10-02

**The Effect of Bio-active Materials Coated Fabric on Rat Skeletal Muscular Mitochondria**

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The bio-active materials coated fabric (BMCF) was coated with bio-active materials containing over 30 kinds of minerals. The clothing made of this fabric has layer of bio-active energy which reacts with far infrared rays from human body and it is penetration into human body. To observe the effects, the fabric (10 and 30%) was worn to old-aged rat then the oxygen consumption efficiency and copy numbers of mitochondria, and mRNA expression of apoptosis- and mitophagy-related genes were verified. By wearing the BMCF, the oxidative respiration significantly increased when using the 30% materials coated fabric. The mitochondrial DNA copy number significantly decreased and subsequently recovered in a dose-dependent manner. The respiratory control ratio to mitochondrial DNA copy number showed a dose-dependent increment. As times passed, Bax, caspase 9, PGC-1α and β-actin increased, and Bcl-2 decreased in a dose-dependent manner on mRNA expressions. However, the BMCF can be seen to have had no effect on Fas receptor. PINK1 expression did not change considerably and was inclined to decrease in control group, but the expression was down-regulated then subsequently increased with the use of the BMCF in a dose-dependent manner. Caspase 3 increased and subsequently decreased in a dose-dependent manner. These results suggest that the BMCF invigorates mitophagy and improves mitochondrial oxidative respiration in skeletal muscle, and in early stage of apoptosis induced by the BMCF is not related to extrinsic death-receptor mediated but mitochondria-mediated signaling pathway.

**Key Words:** Apoptosis, Bio-active materials coated fabric, Mitochondria, Mitophagy, Oxidative respiration

### P10-03

**Identification of Primo-Vascular System in Abdominal Subcutaneous Tissue Layer of Rats**

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The primo-vascular system (PVS) is a novel vascular network that was first reported in the 1960s by Kim, who claimed that the tissue corresponded with the acupuncture meridians. The PVS tissue has been identified in various sites, such as internal organs, brain ventricles, and blood and lymphatic vessels in several animal species. However, the PVS in subcutaneous tissue has not been well identified. In this study, we examined the putative PVS on the surface of abdominal subcutaneous tissue in rats. Hemacolor staining was conducted for the identification of the subcutaneous PVS (sc-PVS). Hemacolor solution 1 (methyl alchol) was first applied to the hypodermis region of interest for 5 s, and then Solutions 2 (eosin) and 3 (methylene blue) were applied to the same region one by one. Then, Solution 3 had been applied for 5 s the region was washed out with a 0.9% saline solution and further examined under a stereomicroscope, scanning electron microscope (SEM), and transmission electron microscope (TEM). Hemacolor staining
P10-04

Toll-like Receptor 2 is Dispensable for an Immediate-early Microglial Reaction to Two-photon Laser-induced Cortical Injury In vivo

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Microglia, the resident macrophages in the central nervous system, can rapidly respond to pathological insults. Toll-like receptor 2 (TLR2) is a pattern recognition receptor that plays a fundamental role in pathogen recognition and activation of innate immunity. Although many previous studies have suggested that TLR2 contributes to microglial activation and subsequent pathogenesis following brain tissue injury, it is still unclear whether TLR2 has a role in microglia dynamics in the resting state or in immediate-early reaction to the injury in vivo. By using in vivo two-photon microscopy imaging and Cx3cR1GFP/+ mouse line, we first monitored the motility of microglial processes (i.e. the rate of extension and retraction) in the somatosensory cortex of living TLR2-KO and WT mice. Microglial processes in TLR2-KO mice show the similar motility to that of WT mice. We further found that microglia rapidly extend their processes to the site of local tissue injury induced by a two-photon laser ablation and that such microglial response to the brain injury was similar between WT and TLR2-KO mice. These results indicate that there are no differences in the behavior of microglial processes between TLR2-KO mice and WT mice when microglia is in the resting state or encounters local injury. Thus, TLR2 might not be essential for immediate-early microglial response to brain tissue injury in vivo.

Key Words: Brain injury, In vivo two-photon microscopy imaging, Microglia, Toll-like receptor 2

P10-05

MLN4924 can promote U373MG cell migration via src dependent phosphorylation of caveolin-1

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MLN4924, recently arising as a promising anticancer agent, is a blocker of NEDD8-activating enzyme, which has significantly been reported to suppress proliferation by inducing DNA damage response, cell cycle arrest, autophagy, apoptosis, and senescence and also migration, and motility of cancer cells. Here, we report that MLN4924 can unexpectedly promote migration in U373MG cells by augmenting the level of Cav1 phosphorylation on Y14, depending on Src activity.

Key Words: caveolin, cell migration, MLN4924

P10-06

Study investigated the effects of Oligonol supplementation on sudomotor activity during heat load in human subjects

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Oligonol is a low-molecular weight polyphenol that possesses antioxidant and anti-inflammatory properties. However, nothing is known regarding the impact of Oligonol on sudomotor activity. This study investigated the effect of Oligonol supplementation on sweating response under heat stress in human subjects. Initially, we conducted a placebo-controlled, cross-over trial where participants took a daily dose of Oligonol 200 mg or placebo for one week. After a 4 week washout period, the subjects were switched to the other study arm. As a heat load, half-body immersion into hot water (42 ± 0.5°C for 30 min) was performed in an automated climate chamber. Fibroblast growth factor 21 (FGF-21), orexin, irisin tympanic and skin temperatures were measured. Sudomotor activity, including onset time, sweat rate (SR) and volume (SV), active sweat gland density (ASGD), and sweat gland output (SGO) was tested in four or eight areas of skin. When compared with placebo, Oligonol attenuated increases in tympanic and skin temperatures after the heat load. There was an increasing trend in local sweat onset time, but there was a decrease in FGF-21, orexin, irisin, local SR, SV, ASGD, and SGO for Oligonol compared to placebo. The mean ASGD was significantly higher in the Oligonol group than in the placebo group for 10, 20, and 30 min. This study demonstrates that Oligonol appears to be worthy of consideration as a natural supplement to support more economical use of body fluids against heat stress

Key Words: Oligonol, sudomotor activity, heat load

P10-07

PSA-NCAM-Negative Neural Crest Cells Emerging During Neural Induction of Pluripotent Stem Cells Cause Mesodermal Tumors and Unwanted Grafts

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The stem cell population derived from the mouse embryonic stem cells, which express both PSA and NCAM antigens, was further cultured using 3D matrices and traditional liquid culture techniques for 6 weeks. The cultured cell population was observed to form neural crest-derived cells and neural crest-derived cells were identified using putative markers: NCAM, PSA, and S100. After the 6th week, a large number of NCAM-negative neural crest cells emerged during neural induction of the pluripotent stem cells. Interestingly, these NCAM-negative neural crest cells formed mesodermal tumors and caused unwanted grafts in the animals. Moreover, the NCAM-negative neural crest cells caused unexpected tumor-like structures in the tumors of the animals. These findings suggest that NCAM-negative neural crest cells may play a crucial role in the formation of mesodermal tumors and unwanted grafts in the animals.

Key Words: Neural crest cells, Neural induction, Pluripotent stem cells, Mesodermal tumors, Unwanted grafts
**P10-08**

**The role of TRPM7 in the progression of human renal cell carcinoma (RCC)**

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**Purpose:** Transient receptor potential melastatin 7 (TRPM7) is a non-selective cationic channel containing a functional kinase domain. In normal tissues, it is distributed widely. Recent studies have shown that TRPM7 is involved in the regulation of cellular growth, proliferation, differentiation, and migration in various human cancers. However, the role of TRPM7 in pathogenesis of human RCC remains uncertain. Thus, the present study examined the effects of silencing of TRPM7 on the proliferation, migration, and invasion of human RCC cells.

**Materials & Methods:** ACHN cells were transfected with 100 nM TRPM7 siRNA using Lipofectamine RNAiMAX. Transfected RCC cells were cultured in Eagle’s minimum essential media supplemented with 10% fetal bovine serum. The effect of TRPM7 siRNA on cell viability was determined by WST-1 assay. Cell motility and invasiveness were analyzed using in-vitro wound healing assay and trans-well assay, respectively. All measurements were performed in triplicate at 24 hours after TRPM7 knockdown. Additionally, the protein levels of MMP2, MMP9, TIMP1, and TIMP2 were measured by western blot analysis to verify the influence of TRPM7 siRNAs on the expression of matrix metalloproteinases (MMP) and their inhibitors (TIMP). **Results:** Suppression of TRPM7 had no effects on proliferation of RCC cells compared with negative control. Cell movement was decreased about 50% by silencing RNA targeting TRPM7. Invasion of RCC cells were also suppressed markedly by TRPM7 RNA interference. Silencing of TRPM7 induced upregulation of MMP2 and MMP9 protein expressions. In contrast, the protein levels of TIMP1 and TIMP2 were decreased by silencing RNA of TRPM7.

**Conclusion:** TRPM7 knockdown inhibits RCC cell migration and invasion. In addition, it induces expressve imbalance of MMPs/TIMPs. These results suggest that TRPM7 may have a role in the RCC progression.

**Key Words:** TRPM7, siRNA, RCC, MMP, TIMP

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**P10-09**

**A novel function of JHDM in Hepatic steatosis**

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Histone modification is one of major type of epigenetic regulation that possesses a big part of modulating biological event. JHDM, a Jmjc histone demethylase is known as demethylase of the Histone H3K9 while it binds to H3K4me3 with PHD domain. JHDM also reported that working with some of metabolism-related transcription factors. In this study, we identified the role of JHDM in the progression of non-alcoholic hepatic steatosis. Overexpression of JHDM attenuated hepatic steatosis and insulin resistance in mice fed with high fat diet. The expression of lipogenic genes were decreased in TG mice liver. In contrast, treatment of LXR agonist in JHDM knock down HepG2 cell line showed that further induction of adipogenic genes. In addition, we found that JHDM physically interact with SREBP1c. We suggest that this interaction interrupts the demethylase activity of JHDM, this causes the inhibition of lipogenic event in Liver.

**Key Words:** Epigenetic regulation, JHDM, hepatic steatosis

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**P10-10**

**KSP inhibitor SB743921 induces death of multiple myeloma cells via inhibition of the NF-kB signaling pathway**

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SB743921 is a potent inhibitor of the spindle protein kinesin and is being investigated in ongoing clinical trials for the treatment of myeloma. However, little is known about the molecular events underlying the induction of cell death by SB743921 alone or in combination treatment, in multiple myeloma (MM). Here, we report that SB743921 induces mitochondria-mediated cell death via inhibition of the NF-kB signaling pathway, but does not cause cell cycle arrest in KMS20 MM cells. SB743921-mediated inhibition of the NF-κB pathway results in reduced expression of SOD2 and Mcl-1, leading to mitochondrial dysfunction. Moreover, we found that combination treatment with SB743921 and bortezomib induces death in bortezomib-resistant KMS20 cells. Taken together, these data suggest that treatment with SB743921 alone or in combination with bortezomib offers excellent translational potential and promises to be a novel MM therapy.

**Key Words:** SB743921, NF-kB, multiple Myeloma, combination therapy, superoxide dismutase 2, Mcl-1
P10-11
The Effect of Low-Intensity Ultrasound in Resolution of Synovitis
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Background: Low-intensity ultrasound (LIUS) can be a feasible therapy for arthritic joints with reducing pain and functional improvement. Neutrophils are first line actors in host defense that recruit macrophages. Dead neutrophils are removed during resolution of inflammation. Delayed neutrophil clearance can lead to extended inflammation or even chronic autoimmune disease.

Neutrophil extracellular traps (NETs) in arthritic tissue are involved in the pathogenesis of arthritis; however, the functional role of NETs has not been clarified. Objectives: The aims of this study were to investigate the effect of LIUS on synovial inflammation and its resolution via neutrophil clearance.

Methods: Synovitis was induced by intra-articular injection of complete Freund’s adjuvant (CFA) into the left knee joint of male Sprague-Dawley rats. LIUS (1 MHz, 200 mW/cm²) was applied for 10 minutes daily. The neutrophil clearance was assessed with the expression of myeloperoxidase (MPO). In addition, the TUNEL staining and NETs formation in the synovium were observed. In neutrophils and macrophages cultures from peripheral blood, the effect of NETs and NETs formation in the synovium were observed. In neutrophils and macrophages, that might be an underlying factor for therapeutic result in neutrophil clearance by enhancing the phagocytosis of NETs act in inflammatory synovitis, and LIUS enhanced the NETs and macrophages, that might be an underlying factor for therapeutic LIUS revealed reduced synovial hyperplasia and earlier MPO clearance. Neutrophils in the core of the inflamed synovium exhibited NET formation, which increased by LIUS. LIUS also induced NETs in peripheral polymorphonuclear cells in an intensity-dependent manner and potentiated phorbol myristate acetate (PMA)-induced NETosis. PMA-induced NETs were cleared by macrophages; the clearance was enhanced by LIUS.

Conclusion: NETs act in inflammatory synovitis, and LIUS enhanced the NETs and resulted in neutrophil clearance by enhancing the phagocytosis of macrophages, that might be an underlying factor for therapeutic effect of LIUS in arthritic synovium. Acknowledgements This study was supported by a Korea Research Foundation (KRF) grant from the Korean government (MEST) (2009-0076242); a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (2012R1A2A2A01011417); the Chronic Inflammatory Disease Research Center (NRF-2012R1A5A204183); and a grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Korea (A091120).

Key Words: arthritis, low-intensity ultrasound, neutrophil clearance, neutrophil extracellular trap

P10-12
Role of CXCR2 in Acetylated Pro-Gly-Pro(Ac-PGP)-induced Vascular Regeneration in Murine Hind limb Ischemia Model
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Many therapeutic approaches to treat ischemic diseases using endothelial progenitor cells (EPCs) have been developed. EPCs can integrate into blood vessels and stimulate neovascularization of the ischemic limbs and hearts. Therefore, mobilization and recruitment of bone marrow-derived endothelial progenitor cells are critical for ischemia-induced neovascularization. The exact signaling, however, involved in the homing of EPCs to sites of endothelial injury remains to be understood. Chemokine receptor 2 (CXCR2), a receptor of interleukin 8 (IL-8), mediates neutrophil migration to the site of inflammation. The angiogenic effects of IL-8 in intestinal vascular endothelial cells are mediated by this receptor. Our hypothesis is that CXCR2 is involved in the regulating growth and survival of endothelial cell and EPCs through the mechanism similar to IL-8-regulated angiogenesis. We explored the role of CXCR2 in angiogenesis and tissue regeneration by using Acetylated Pro-Gly-Pro (Ac-PGP), which is the endogenous degradation product of extracellular collagen and binds to CXCR2. Ac-PGP stimulated chemotactic migration, tube formation ability of human EPCs in vitro. The blockade of CXCR2 abrogated Ac-PGP-induced migration and tube formation of EPCs. Intramuscular injection of Ac-PGP into the ischemic hindlimb resulted in the attenuation of the severe limb loss and the stimulation of blood perfusion and angiogenesis in the ischemic limb. CXCR2 knockout mice showed the attenuation in Ac-PGP-induced in vivo neovascularization and ischemic limb salvage. These results suggest that Ac-PGP has therapeutic effects by stimulating neovascularization through CXCR2-dependent mechanism.

Key Words: Ac-PGP, CXCR2, EPC, neovascularization, ischemia

P10-13
Wnt signaling pathway augments Endothelial Progenitor Cells commitment and its angiogenic potential through SDF1-CXCR4 axis
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Endothelial progenitor cell (EPC) has considered as a potential therapeutic strategy for vascular regeneration in ischemic tissue. However, use of EPCs for cell-based therapy is hindered due to attenuated cellular yield and biological activity. In this study, we investigated the role of Wnt pathway that is a powerful regulator of cell proliferation and differentiation. In EPC colony forming assays, we found that proliferation, migration and invasion capacity of EPCs were attenuated in KDR and Flk-1 double negative (EPC) cells by using Wnt inhibitor, CHIR99021. We then examined the role of Wnt pathway that is a powerful regulator of cell proliferation and differentiation. In EPC colony forming assays, we found that proliferation, migration and invasion capacity of EPCs were attenuated in KDR and Flk-1 double negative (EPC) cells by using Wnt inhibitor, CHIR99021.

Key Words: Wnt pathway, SDF1-CXCR4 axis

P10-14(O-9)
The Sulfated Polysaccharide Fucoidan Rescues Senescence of Endothelial Colony Forming Cells for Ischemic Repair
P10-15

Novel angiogenic peptide stimulates mouse hindlimb ischemia repair

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Ischemia is a major disease which can plague modern living. We searched for peptide drugs to treat ischemia and identified SR-0379 as a potential candidate. In previous studies, SR-0379 significantly stimulated wound healing in rats and had angiogenic property and anti-microbial ability. In our study, we first observed that migration and tube-forming ability of EPCs were enhanced by SR-0379 treatment in vitro. However, SR-0379 did not affect cell survival significantly. To determine whether SR-0379 can promote the recovery from hindlimb ischemia and increase repair, we injected SR-0379 into the muscle of ischemia-induced hindlimb of mice. Repair in ischemia injury mouse model was significantly enhanced in peptide injected hindlimb compared to sham-injected hindlimb. In addition, we confirmed the increased expression of CD31 and SMA-α by immunostaining in SR-0379-injected ischemic hindlimb. These results suggest that SR-0379 can be a novel drug candidate for treating ischemic disease.

Key Words: Hindlimb ischemia, SR-0379, Angiogenic peptide, EPC

P10-16

Caffeine links dopamine, serotonin and prolactin release during thermal stress in human

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The aim of this study was to investigate the serum serotonin (5-HT), prolactin (PRL) and plasma dopamine (DA) levels in humans with and without caffeine ingestion during and after thermal stress (half immersion in 42°C hot water). Eleven male volunteers participated in the randomized experiment (CON, n=15, 200 mL of tap water vs. CAFF, n=15, 3 mg·kg⁻¹ and 200 mL tap water). After 60 min, thermal stress was conducted for 30 min. Blood samples were collected and assessed for 5-HT, DA and PRL with and without caffeine during and after thermal stress. 5-HT was significantly lower in the CAFF group compared to the CON group after thermal stress for 30 min (p < 0.05) and also after 60 min of resting (p < 0.01). DA and PRL were significantly higher in the CAFF group than in the CDN group at the Post time point (p < 0.001). In conclusion, 3 mg·kg⁻¹ of caffeine ingestion prior to thermal stress can alter central serotonergic and dopaminergic activity, which may contribute to reduced central fatigue and subsequently, to reduced general fatigue. PRL responses during thermal stress were also significantly related to caffeine ingestion in this study. However, the inhibitory effects of DA on PRL by caffeine remain to be elucidated.

Key Words: Caffeine, Dopamine, Prolactin, Serotonin, thermal stress

P10-17

Improved sweat gland function during active heating in physically trained human

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Relative few studies on the peripheral sweating mechanisms of in physically trained human have been conducted. The purpose of this study was to compare the sweating capacities of physically trained human against untrained subjects (controls). Thirty-five healthy male volunteers participated; 15 untrained subjects and 20 physically trained human. Active heat generation was performed for 30 min (running at 60% VO₂max) in a climate chamber (temperature, 25 ± 0.5°C; relative humidity, 60±3%, termed active heating). Sweating data (local sweat onset time, local sweat volume, activated sweat glands, sweat output per gland, whole body sweat loss volume) were measured by the capacitance hygrometer-ventilated capsule method and starch-iodide paper. Mean body temperature was calculated from tympanic and skin temperatures. Local sweat onset time was shorter for tennis athletes (p < 0.001). Local sweat volume, activated sweat glands of the torso and limbs, sweat output per gland and whole body sweat loss volume were
significantly higher for physically trained human than control subjects after active heating (p < 0.001). Tympanic and mean body temperatures were lower among physically trained human than controls (p < 0.05). These results indicate that physically trained human had increased regulatory capacity of their sweat gland function. Physically trained human, Sweating function, Sweat onset time, Sweat output

Key Words: Active heating, Activated sweat glands, Physically trained human, Sweating function, Sweat onset time, Sweat output

P10-18

Assessment of eye irritation potential of hair dye chemicals using human conjunctival keratinocytes

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The harmful effects of hair dyes on human health have been widely studied in the field of dermatology and hemato-oncology. Hair dye-induced toxic conjunctivitis is frequently encountered in the Ophthalmology Clinic, but researches on the hazardous potential to eye are lacking. We investigated the irritation potential of hair dye chemicals to primary cultured human conjunctival epithelial cells. Five common ingredients in hair dyes were selected based on the priority chemicals listed on the labels of 10 commercially available hair dyes. Human conjunctival epithelial cells were primarily cultured using the explant techniques from the conjunctival tissues obtained during conjunctivochalasis surgery.

Key Words: Human conjunctival keratinocytes, Hair dye, Para-phenylenediamine, Cytotoxicity, Toxic conjunctivitis

P10-19

Effect of Samultang on HO-1 Mediated Vascular protection in HUVECs

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Samultang (四物湯, SMT) is a well known herbal prescription treating overall haematological disorders defined as blood deficiency, blood stasis and blood loss in traditional Korean medicine. SMT is recorded in several formularies including 'Treasured Mirror of Eastern Medicine' (東醫寶鑑, Donguibogam) and consists of 4 herbs: Angelicae Radix, Cnidii Rhizmoa, Rhemanniae Radix Preparata and Paeonia Radix. Major cause of atherosclerosis and other vascular diseases is inflammation and vascular endothelium is emphasized as central spot of vascular inflammatory process. Thus, we investigated the effects of SMT water extracts on vascular inflammation in HUVECs (Human Umbilical Vein Endothelial Cells). Expression of CAMs (cell adhesion molecules) such as VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intracellular adhesion molecule-1), E-selectin (endothelial-selectin) and HL-60 monocyte adhesion were induced by TNF-α stimulation. However, SMT pretreatment (10-50 μg/ml) inhibited CAMs expression and monocyte adhesion significantly. TNF-α stimulation led HUVECs to produce ROS (reactive oxygen species) and translocate NF-κB (nuclear factor-kB) into nucleus, but SMT suppressed ROS production and NF-κB nuclear localization significantly. Furthermore, activation of NF-κB was also suppressed by SMT in dose dependent manner. HO-1 (heme oxygenase-1) protein level was significantly upregulated by SMT treatment (10-50 μg/ml) as HO-1 inducer CoPP (cobalt protoporphyrin) did. Besides, nuclear translocation of Nrf-2 (nuclear factor erythroid 2-related factor 2), which transcripts antioxidative genes including HO-1, was increased by SMT dose dependently. Intracellular NO (nitric oxide) and nitrite products were also increased by SMT treatment. Taken together, these results suggest that SMT might exerts vascular protective effects by suppressing vascular inflammatory process triggered from damaging stimulus including TNF-α and by promoting synthesis of beneficial bioactive substances including HO-1.

Key Words: Samultang (SMT), vascular inflammation, cell adhesion molecules (CAMs), heme oxygenase-1 (HO-1), nitric oxide (NO)

P10-20

Inhibitory Mechanism of Samchuleum on Renal Fibrosis

Jung Joo Yoon¹,², Yun Jung Lee¹,², Byung Hyuk Han¹,², Seung Namgung¹,³, Min Chol Kho¹,³, Ji Hun Park¹,², Dae Gill Kang¹,²,³,⁴, Ho Sub Lee¹,²,³,⁴

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Samchuleum (SCE), originally recorded in an ancient Korea medicinal book named "Donguibogam" (東醫寶鑑) is a well-known blended traditional herbal formula. SCE is composed of nine dried herbs: Rehmannia glutinosa, Paeonia japonica, Cnidium officinale Makino, Angelica gigas, Panax ginseng, Atractylodes japonica, Pinellia ternate, Citrus Aurantium, Glycyrrhiza uralensis. Diabetic nephropathy (DN) is associated with morbidity and mortality of diabetic patients. Mesangial cell proliferation is known as the major pathologic features such as glomerulosclerosis and renal fibrosis. Thus, this study investigated the inhibitory effect of SCE (1-50 μg/ml) on high glucose (HG)-stimulated rat mesangial cells (RMC) proliferation and fibrosis. Thymidine incorporation under HG was significantly accelerated, which was inhibited by SCE in a dose dependent manner. Pre-treatment of SCE induced down-regulation of cyclins/CDKs and up-regulation of CDK inhibitor, p21waf1/cip1 and p27kip1 expression. In addition, SCE significantly suppressed the HG-induced ROS production. Thus, SCE consequently inhibited HG-induced mesangial cell proliferation through the inhibition of ROS signaling pathway. HG enhanced expression of fibrosis biomarkers such as collagen IV and CTGF, which was markedly attenuated by SCE. Moreover, SCE inhibits HG-induced fibronectin mRNA expression. SCE decreased TGF-β and p-Smad2/Smad4 expression, whereas increased Smad7 expression under HG. Thus, SCE promoted ECM degradation through disturbing TGF-β–SMAD signaling. In conclusion, these results suggested that SCE has a protective effect on renal proliferation and fibrosis. These results suggest that SCE might be effective in the treatment of renal dysfunction leading to DN.

Key Words: Samchuleum (SCE), Mesangial cell, High glucose (HG), CDKs, Collagen IV, TGF-β
Inhibitory Effect of Hwangryunhaedoktang on TNF-α-induced vascular inflammation in human umbilical vein endothelial cells

Byung Hyuk Han1,2,3, Yun Jung Lee1,2, Eun Sik Choi1,2, Seung Namgung1,2,3, Xian Jun Jin1,2, Ho Sub Lee1,2,3,4, Dae Gill Kang1,2,3,4

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Hwangryunhaedoktang (HHT) originally recorded in an ancient Korea medicinal book named “Donguibogam” and has been used for the treatment of inflammatory hemorrhage relevance to vascular inflammation which can cause an atherosclerosis. This study was designed to demonstrate whether HHT has an inhibitory effect on vascular inflammation induced by TNF-α in human umbilical vein endothelial cells (HUVECs). Pretreatment with HHT decreased the adhesion of HL-60 cells to TNF-α-induced HUVEC. HHT suppressed TNF-α-induced expression level of cell adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial cell selectin (E-selectin), as well as dose dependently inhibited TNF-α-induced intracellular reactive oxygen species (ROS) production. Western blot and immunofluorescence analysis showed that HHT inhibited the translocation of p65 NF-κB to the nucleus. Phosphorylation of IκB-α also was inhibited in cytoplasm by pre-incubating with HHT, on the other hand increased expression of IκB-α. In addition, HO-1 expression in HUVECs was enhanced by HHT dose-dependently. In that case of co-treated with SnPP, HO-1 inhibitor, and CoPP, HO-1 inducer, protein expression of HO-1 was reduced and increased at each case. These data showed that pretreatment with HHT regulated the ROS/NF-κB signaling pathway. Furthermore HO-1 induction was increased by single processing of HHT in dose-dependent manner. Therefore a traditional herbal formulation HHT might be potential therapeutic agent of atherosclerosis.

Key Words: Hwangryunhaedoktang (HHT), HUVEC, TNF-α, Vascular inflammation, HO-1

Study on the mechanism of vascular relaxation by mantidis ootheca

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The aim of the present study was to define the effects of aqueous extract of mantis ootheca (AMO) on the vascular tension and its responsible mechanisms in rat thoracic aortic rings. The eggs of a mantis are enclosed in a foamy pouch. The extracts of AMO induced dose-dependent relaxation of phenylephrine-precontracted aorta, which was abolished by removal of functional endothelium. Endothelium-denudation abolished the AMO-induced vasorelaxation. Pretreatment of the endothelium-intact aortic rings with NG-nitro-L-arginine methylester (L-NAME) and 1H-[1,2,4]-oxadiazolo-[4,3-alpha]-quinoxalin-1-one (ODQ) inhibited the AMO-induced vasorelaxation. Similarly, wortmannin and LY-294002, an inhibitors of the phosphatidylinositol 3-kinase (PI3K), an upstream signaling molecule of eNOS, attenuated the AMO-induced vasorelaxation. Furthermore, K+ channel inhibition with tetraethylammonium, 4-aminopyridine and glibenclamide had inhibitory effects on the AMO-induced vasorelaxation. AMO-induced vascular relaxations were also markedly attenuated by addition of inhibitory muscarinic receptor, atropine and methoctramine. Taken together, the present study suggests that AMO relaxes vascular smooth muscle via endothelium-dependent activation of NO-cGMP signaling through the PI3K/Akt-, possible involvement of K+ channel.

Key Words: mantidis ootheca, vasorelaxation, thoracic aorta, NO-cGMP signaling
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