Society Symposia

Society Symposium 1

Japan-Korea Joint Symposium - Towards FAOPS2019

「Gut to brain information flow in systemic physiology」

March 23 (Wed), 9:00 – 10:30, Room C

2S1C1-1

Gastrointestinal tract regulates energy metabolism: lesson from bariatric surgery

Cho Youn-Min

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Roux-en Y gastric bypass (RYGB) is a highly effective bariatric/metabolic surgical procedure that can induce robust weight loss and even remission of type 2 diabetes. One of the characteristic consequences of RYGB is the expedited nutrient delivery to the distal small intestine, where L-cells are abundant. To examine the role of the distal small intestine in isolation from other components of RYGB, the ileal transposition (IT) surgery has been developed. IT relocates the distal ileal segment to the upper jejunum distal to the ligament of Treitz without any other alterations in the gastrointestinal anatomy. Therefore, IT exposes the distal ileal tissue to ingested nutrients faster than normal condition. Although there is some inconsistency in the effect of IT according to different types of rat models and different types of surgical protocols, IT typically improved glucose tolerance, increased insulin sensitivity, and induced weight loss, which findings were more prominent in obese diabetic rats. Suggested mechanisms for the metabolic improvements after IT include increased L-cell secretion (e.g., glucagon-like peptides and peptide YY), altered bile acid metabolism, altered host-microbial interaction, attenuated metabolic endotoxemia, and many others. Based on the effect of IT, we can conclude that the contribution of the distal small intestine to the metabolic benefits of bariatric/metabolic surgery is quite considerable. By unveiling the mechanism of action of IT, we may revolutionize the treatment for obesity and type 2 diabetes. (COI:No)

2S1C1-2

Regulation of gut hormone release by food components and molecular mechanism

Hira Tohru、Hara Hiroshi

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Gut hormones produced in enteroendocrine cells are released mainly in response to meal ingestion. Macronutrient-derived components such as glucose, fatty acids, peptides and amino acids are potent stimuli for various gut hormone secretions. We have been studying the mechanism of dietary peptides- or amino acids-induced gut hormone secretion. By using murine enteroendocrine cell line STC-1, we firstly demonstrated that extracellular calcium-sensing receptor (CaSR) functions as a sensor for phenylalanine to induce cholecystokinin (CCK) secretion. Further studies revealed the role of CaSR for dietary peptide-induced CCK secretion. In conscious rats, oral administration of CaSR-agonist peptides reduced glycemic response under oral glucose tolerance test. The glucose-lowering effect of the peptides was mediated by intestinal CaSR, subsequent serotonin signal and reduced gastric emptying. In separated experiments, we found that a dietary peptide, zein-peptide, prepared from indigestible corn protein zein potently stimulated GLP-1 secretion in enteroendocrine cell line, and in anesthetized rat intestine. Zein peptide directly administrated into the ileum or orally administrated in rats potently stimulated GLP-1 secretion, followed by enhanced insulin secretion and reduced glycemic response under intraperitoneal glucose tolerance test. Our results revealed that 1) CaSR functions as one of nutrient sensors in enteroendocrine cells to detect luminal peptides and amino acids, and 2) activating GLP-1 secretion or CaSR by food factors are promising target for reducing postprandial glycemia through the gut hormone secretion. (COI:No)

2S1C1-3

Reduced appetite and weight after total gastrectomy are rescued by Rikkunshito: Glucagon-like peptide-1mediated intestinal-brain interplay

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Gastrectomy in gastric cancer patients reduces appetite and weight, deteriorating quality of life. Rikkunshito, a Japanese kampo medicine, reportedly increases plasma orexigenic ghrelin levels and promote appetite in animals and patients treated with anti-cancer agents. However, it remains unknown whether Rikkunshito can promote appetite after removal of the ghrelin-producing organ stomach. To address this question, we performed total gastrectomy with roux-en-Y reconstruction in rats, and examined the effect of Rikkunshito. Rikkunshito, when administered in early period after gastrectomy, increased food intake and weight in rats without affecting plasma ghrelin levels. Fasting as well as postprandial plasma glucagon-like peptide-1 (GLP-1) levels increased early after gastrectomy, and these GLP-1 elevations were suppressed by Rikkunshito. Administration of a GLP-1 receptor antagonist early after gastrectomy increased food intake and weight. Plasma GLP-1 elevations was no longer observed at late post-operative period, and late administration of Rikkunshito had no effect on food intake and weight. In a preliminary clinical study, plasma GLP-1 was significantly elevated early after gastrectomy in patients with gastric cancer. The current study demonstrates that early administration of Rikkunshito restores food intake and weight by counteracting the GLP-1 elevation after gastrectomy in rats, implying that this new strategy may be clinically useful. (COI:Properly Declared)

2S1C1-4

Gut microbes and short-chain fatty acids regulating energy metabolism

Kimura Ikuo

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Food intake regulates energy balance and its dysregulation leads to metabolic disorder, such as obesity and diabetes. During feeding, gut microbiota affects host nutrient acquisition and energy regulation and can influence the development of obesity and diabetes. Short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate, which are produced by gut microbial fermentation of dietary fiber, are recognized as essential host energy sources and act as signal transduction molecules via G-protein coupled receptors (GPR41, GPR43, OLFR78, GPR109A) and as epigenetic regulators of gene expression by the inhibition of histone deacetylase. Recent evidence suggests that dietary fiber and the gut microbial-derived SCFAs exert multiple beneficial effects on the host energy metabolism not only by improving the intestinal environment, but also by directly affecting various host peripheral tissues. We report that GPR41 regulates sympathetic activity, and GPR43 regulates adipose-insulin signaling by sensing SCFAs produced by gut microbiota. We believe that these results will provide valuable insights into therapeutic targets for treating metabolic disorder, and diabetes and the use of probiotics to control gut microbiota. (COI:No)

Society Symposium 2

Japan-China Joint Symposium - Towards FAOPS2019

Regulation of the function, structure and trafficking of ion channel complexes by accessary subunits

March 23 (Wed), 15:00 – 16:30, Room C

2S2C2-1

Mechanistic insights into modulation of voltage-gated Kv4 channel function by auxiliary KChIP proteins

Kewei Wang

(Peking University School of Pharmaceutical Sciences)

Voltage-gated potassium channels regulate membrane excitability that defines the fundamental mechanism of neuronal functions such as learning and memory. Cytosolic Kv channel-interacting proteins KChIPs that belong to neuronal calcium sensor (NCS) family of calcium binding EF-hand proteins co-assemble with Kv4 αsubunits to form a native complex that encodes major components of neuronal somatodendritic A-type K+ current, ISA, in neurons and transient outward current, ITO, in cardiac myocytes. The specific binding of auxiliary KChIPs to the Kv4 N-terminus results in modulation of gating properties, surface expression and subunit assembly of Kv4 channels. Multifunctional KChIPs1-4 subunits that share a high homology in the C-terminal core regions exhibit distinctive modulation on gating properties, surface expression and subunit assembly of pore-forming Kv4 subunits. In this presentation, I will focus on our recent findings/attempts on mechanistic insights into modulation of Kv4 channel function by auxiliary KChIP1 and KChIP4 subunits. Greater insights into molecular mechanism between KChIPs and Kv4 interaction may provide therapeutic potentials of designing compounds aimed at disrupting the protein-protein interaction for treatment of membrane excitability-related disorders. (COI:No)

2S2C2-2

Stoichiometry and function of Kv4.2/KChIP4/DPP10 complexes

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Kv4.2 channel is known to form a molecular complex with accessary subunits such as KChIP4 and DPP10. However, the number of accessary subunit molecules bound to the KV4.2 tetramer, i.e. stoichiometry, remains unknown. We approached the stoichiometry by expressing fluorescent protein tagged molecules in Xenopus oocytes and by counting the number of bound accessary subunits under single molecule imaging. We also analyzed the electrophysiological properties of molecular complexes. We observed the followings. (1) With the increase in the coexpressed amount of KChIP4, the speed of recovery from inactivation of Kv4.2/KChIP4 was gradually accelerated. This change was also confirmed by comparing the properties of tandem repeat constructs of fixed stoichiometry of 4:4 and 4:2. (2) The stoichiometry of Kv4.2/KChIP4 varied depending on the relative expression level, and the distribution followed binomial distribution well. (3) With the increase in the coexpressed amount of DPP10, the speed of recovery from inactivation of Kv4.2/DPP10 was gradually accelerated. (4) When expressed alone, 70 % of DPP10 existed as a dimer. (5) The stoichiometry of Kv4/2.DPP10 varied depending on the relative expression level with a clear preference to 4:2 stoichiometry. (6) The presence of DPP10 did not change the stoichiometry of Kv4.2/KChIP4 and vice versa. Taken together, we showed that the stoichiometry of Kv4.2/KChIP4 changes probabilistically depending on the relative expression level, and that of DPP10 is variable with a preference to 4:2. (COI:No)

2S2C2-3

Modulation of Neuronal Ca^{2+} Channels by RIM Proteins

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Fine regulation of neurotransmitter (NT) release is crucial for the plasticity of the nervous system. For voltage-dependent Ca^{2+} channels (VDCCs) to control NT release *via* Ca^{2+} influx into the presynaptic active zone (AZ), VDCCs are localized in the close proximity to the vesicular release machinery. We previously proposed that the interaction of α-RIMs (RIM1α and RIM2α) *via* their C_2B domain-containing C-terminus with VDCC-β subunits in the AZ support NT release *via* two distinct mechanisms: 1) by sustaining Ca^{2+} influx through inhibition of VDCC inactivation and 2) by anchoring NT-containing vesicles in the vicinity of VDCCs. We also revealed that γ-RIMs (RIM3γ and RIM4γ), which mainly comprises the C_2B domain, also exert prominent suppression of VDCC inactivation *via* directly binding to VDCC-β but block the localization of NT-containing vesicles in AZ. These results suggest that suppression of VDCC inactivation by RIMs is ubiquitous among neurons, whereas the extent of vesicle anchoring to VDCCs in AZ may depend on the competition of α-RIMs with γ-RIMs for VDCC-β subunits. Recently, genetic analysis has identified two mutations in RIM3γ C_2B domain from autism patients. By introducing the corresponding mutations into the C_2B domain of RIM3γ, both mutations partly canceled the suppressive RIM3γ effect on VDCC inactivation and altered RIM3γ regulation of depolarization-induced NT release. Thus, RIM-VDCC interactions may play roles in the regulation of higher brain functions.

Key Words
Voltage-dependent Ca^{2+} channels (VDCCs), RIM proteins, Neurotransmitter release, Voltage-dependent inactivation, Autism
(COI:No)

2S2C2-4

Intracellular trafficking of AMPA receptor-TARP complex

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Synaptic plasticity is thought to be the underlying mechanism for learning and memory in brain. Long-term depression (LTD) is one of the most well studied forms of synaptic plasticity. It has been clarified that the reduction of the number of cell surface AMPA type glutamate receptor (AMPA receptor) is the molecular basis for LTD induction. However, it is still unclear how the number of AMPA receptor is regulated. Recently, we clarified that TARP (transmembrane AMPA receptor regulatory protein) forms a ternary complex with adaptor proteins AP-2 and AP-3A in hippocampal neurons, depending on its phosphorylation state. Inhibiting the TARP - AP-2, 3A interaction disrupts NMDA-induced reduction of cell surface number of AMPA receptor. Similarly, the interaction between TARP and AP-2 or AP-3A is necessary for low-frequency stimulus-evoked LTD in CA1 hippocampal neurons. Therefore, TARP has a crucial role in NMDA-dependent LTD by regulating the trafficking pathways of AMPA receptors, via its binding to AP-2 and AP-3A. We also found that the TARP binds to other membrane trafficking related proteins, AP-1, sorting nexin 17, and synaptotagmin-7 in a phosphorylation dependent manner. These results suggest that the phosphorylation of TARP regulate the various pathways of AMPA receptor trafficking and contribute to various forms of synaptic plasticity. (COI:No)

Society Symposium 3

Sensory-Motor Integration for Rehabilitation

March 24 (Thu), 15:00 – 16:30, Room F

3S3F2-1

Perceptual integration of proprioceptive input induced by tendon vibration and motor imagery

Shibata Eriko
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Kinesthesia is the sense of that enables awareness of body position, weight, and movement. Afferent inputs from sensory receptors in muscle spindles and skin, and efferent signals from the central nervous system that trigger intentional movement, contribute to kinesthetic perception. For example, tendon vibration applied to biceps brachii in an appropriate pattern can evoke kinesthetic perception of elbow extension without any overt movement. Tendon vibration mainly activates Ia-type afferents from muscle spindle primary endings, and consequently, humans can experience vivid kinesthetic illusion of limb movement in the direction corresponding to the stretch of the vibrated muscle. Kinesthetic illusion might have benefits useful for rehabilitation after stroke, amputation, or cast immobilization of fractures, because it activate motor association areas without muscle contraction. On the other hand, the perceptual integration of proprioceptive input and motor imagery also contributes to kinesthetic perception. We investigated the mechanisms of perceptual integration using the psychophysical index. We are presenting on two topics at this symposium: (1) the physiological background of kinesthetic illusion induced by tendon vibration, and (2) kinesthetic perception based on perceptual integration of proprioceptive inputs from muscle spindles and motor imagery. Because perceptual integration can result in more vivid perception than is induced by proprioceptive input alone, combining proprioceptive input and motor imagery when using kinesthetic illusion is useful in rehabilitation (COI:No).

3S3F2-2

Cortical activation following passive movements

Onishi Hideaki
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The detailed time courses of cortical activities and source localizations following passive finger movement were studied using whole-head magnetoencephalography (MEG). Two peaks of MEG response associated with passive finger movement were recorded from 30 to 100 ms after movement onset. The earliest component (PM1) peaked at 36.2 ms, and the second component (PM2) peaked at 86.1 ms after movement onset. The ECD localization of PM1, estimated to be in area 4 (M1). ECDs of PM2 were estimated to be not only in M1 but also in the supplementary motor area and the posterior parietal cortex. Moreover, activities in the secondary somatosensory cortex over the hemisphere contralateral and ipsilateral to the movement were detected after passive movement. In addition, we investigated corticospinal excitability after repetitive passive finger movement for 10 minutes using transcranial magnetic stimulation. Motor evoked potentials (MEPs) were recorded before passive movement (pre-intervention) and 2 and 10 minutes after passive movement (post-2 min and post-10 min, respectively). We found that the MEP amplitudes at post-2 min were significantly decreased compared with that before the passive movement. Moreover, when 2 mA anodal transcranial direct current stimulation (tDCS) applied to the motor cortex during repetitive passive movement, the MEP depression could not be observed. These results indicated that M1 activities are elicited by passive movement and repetitive passive movement depresses M1 excitability transiently, and anodal tDCS reduced post-movement MEP depression after passive movements. (COI:No)

3S3F2-3

Cerebellum and sensorimotor control

Matsugi Akiyoshi
(Shijonawate Gakuen Univ, Osaka, Japan)

Motor control based on an upcoming sensory state and feedback is important for daily living tasks such as reaching, tracking, catching, and standing. To achieve these tasks, the cerebellum contributes to [1] visual feedback control, [2] visuomotor integration, and [3] sensory weighting. [1] In visual feedback control, the cerebellum is required for adapting predictive control from one movement to the next through error-dependent learning mechanisms. This reduces errors in the feedforward command during subsequent movements, and thus removes the need for sensory feedback-dependent corrections (Bastian 2006). When movement is coordinated according to external visual cues, the cerebellar hemisphere is associated with modulation of the contralateral corticospinal excitability (Matsugi, in preparation). [2] Visuo-motor integration, which involves visual perception and eye-hand coordination, is the ability of the eyes and hands to work together in smooth (Beery 1989). Eye-hand coordination is the ability of the vision system to coordinate the information received through the eyes to control, guide, and direct the hands in daily tasks. Some studies used fMRI (Miall 2000, 2001) and TMS (Matsugi 2012, 2013) to show task-specific activities in the cerebellum during the eye-hand coordination task. [3] Sensory feedback from vision, somatic sensation, and vestibular stimuli is necessary to achieve balance while standing, and the contributions of these sensory stimuli for postural control are partially modulated by the cerebellum (Matsugi, in preparation). I will introduce some studies on the cerebellum and sensorimotor control, and discuss aspects related to rehabilitation. (COI:No)

Society Symposium 4

Symposium in Collaboration with the Japanese Association of Rehabilitation Medicine

Physiological specificity in disability persons

March 23 (Wed), 9:00 – 10:30, Room H

2S4H1-1

Oxidative stress and augmented sympathoexcitation in response to exercise in heart failure

Koba Satoshi

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Although supervised exercise training in patients with heart failure (HF) has been accepted as therapeutic treatment, sympathoexcitatory response to exercise becomes exaggerated in this disease. This exaggeration is a possible cause of exercise intolerance. Sympathoexcitation during exercise is evoked by two principle neural mechanisms, namely central command (CC) and the exercise pressor reflex (EPR). CC is a feedforward mechanism that emanates from the rostral brain and evokes parallel modifications of motor and autonomic functions during exercise. EPR, a feedback mechanism, is activated as thin fiber muscle afferents are stimulated by mechanical deformation of the afferents' receptive fields and metabolic by products during skeletal muscle contraction. Here, effects of HF on sympathoexcitation evoked by either CC or EPR are examined based on experimental data obtained from a rat HF model. Mechanisms by which CC or EPR function becomes abnormal in HF are also discussed. Oxidative stress, which is induced in HF, is considered a factor to lead to dysfunction of CC and EPR. (COI:No).

2S4H1-2

Endoperoxide 4 receptors play a role in evoking the exercise pressor reflex in rats with simulated peripheral artery disease

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Ligating the femoral artery for 72 hours in decerebrated rats exaggerates the exercise pressor reflex (EPR).The sensory arm of this reflex is comprised of group III and IV afferents, which can be either sensitized or stimulated by PGE2. We tested that blockade of EP3 and EP4 receptors attenuated the exaggerated exercise pressor reflex in rats with ligated femoral arteries. We measured the cardiovascular responses to static hindlimb contraction or tendon stretch before and after femoral arterial injection of L798106 (an EP3 antagonist) or L161982 (an EP4 antagonist). The pressor and cardioaccelerator responses to either contraction or tendon stretch were not attenuated by L798106 in either the ligated or freely perfused rats. Likewise in five rats whose hindlimb muscles were freely perfused, the pressor and cardioaccelerator responses to either contraction or tendon stretch were not attenuated by L161982. In the six ligated rats, however, the pressor response to contraction was attenuated by L161982, averaging 37mmHg before, 18mmHg afterward ($p < 0.05$). Western blotting analysis revealed that ligation of the femoral artery for 72 hours increased the EP4 receptor protein in the L4 and L5 dorsal root ganglia over their freely perfused counterparts by 24% ($p < 0.05$). We conclude that EP4 receptors, but not EP3 receptors, play an important role in the exaggerated EPR found in rats with ligated femoral arteries. (COI:No)

2S4H1-3

Thermoregulatory and cardiovascular dysfunctions in persons with spinal cord injury

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([1]Dept. of Rehab. Med., Wakayama Med. Univ.、[2]Faculty of Human Life and Envir., Nara Women's Univ.)

Persons with spinal cord injury (SCI) suffer from thermoregulatory and cardiovascular impairments, which might be at high risk of both hyperthermia and hypothermia. Sweating and cutaneous vasodilation during heat stress and cutaneous vasoconstriction during cold stress are mainly controlled by sympathetic nervous system through thermoregulatory center and also peripheral reflex via sensory nerves. Cardiac function and cerebral blood flow control are closely associated with maintaining blood pressure during both conditions. Preganglionic neurons are found within the spinal cord in segments Th1-L2; the heart for Th1-5 and blood vessels for Th1-L2. Thus sympathetic control of thermoregulatory responses are strikingly attenuated in cervical or high-thoracic SCI, and suppressed within sensory disturbance area but preserved in intact area in mid-to-low lumbar SCI. Contractile properties of cardiac ventricles remain unchanged in cervical or high-thoracic SCI during heat stress. In contrast, cutaneous vasodilation and vasoconstriction in response to local heating and cooling are observed even within sensory disturbance area of the skin in SCI regardless levels of injury. Moreover, autoregulation of cerebral blood flow are preserved even in cervical SCI when blood pressure alters during cold stress. In summary, thermoregulatory and cardiovascular responses via central nervous system are absent or impaired in SCI depend on the level of injury, but local reflex controls for thermoregulatory and cardiovascular responses are preserved. (COI:No)

2S4H1-4

Therapeutic modulation of interhemispheric inhibition using transcranial magnetic stimulation in stroke patients

Kakuda Wataru、Abo Masahiro

(Dept. of Rehabilitation Medicine, Jikei Univ, Tokyo, Japan)

In the adult human brain, there exist interhemispheric inhibitions via corpus callosum. In healthy adults, neural activity between two brain hemispheres is reciprocally balanced through the inhibitions. However, stroke occurs in the cerebral hemisphere, the balance between the hemispheres is impaired. Typically, the inhibition towards the non-lesional hemisphere is decreased and that towards the lesional hemisphere is increased. Consequently, the neural activity of the lesional hemisphere is suppressed profoundly, which interferes neurological recovery after stroke. Recently, on the other hand, transcranial magnetic stimulation (TMS) has been introduced as a therapeutic tool for neurological disorders. TMS stimulates the brain non-invasively and focally. The effect of repetitive TMS (rTMS) depends on the frequency of stimulation. High-frequency rTMS facilitates local cortical excitability, whereas low-frequency rTMS suppresses the excitability. Therefore, some researchers have therapeutically applied low-frequency rTMS over the non-lesional hemisphere for stroke patients. They expected that this application of rTMS would suppress pathologically increased inhibition towards the lesional hemisphere, and disinhibit the hemisphere. As a result, this application of rTMS proved to be beneficial for some neurological symptoms such hemiparesis and aphasia after stroke. So far, our department has introduced therapeutic rTMS for more than 2,000 stroke patients. Neuromodulation of interhemispheric inhibition with rTMS seems to be a novel therapeutic approach for such patients. (COI:No).

Society Symposium 5

JPS Symposium: How to submit your paper to good journals

March 24 (Thu), 15:00 – 16:30, Room C

3S5C2-1

JPS Symposium: How to submit your paper to good journals?

Ishikawa Yoshihiro

(CVRI, Sch Med, Yokohama City Univ, Yokohama, Japan)

As physiology scientist, it is our job to conduct scientific study. It is then our duty to publish the results of our scientific studies so that we can share the results with other scientists. Simultaneously, as an active scientist, publishing his/her scientific paper on a good journal(s) is important because such activity is essential to build up their own scientific career. For young scientist, his/her publication record may play a critical role for his/her promotion as well as for his/her tenure appointment. For senior scientist, it may be necessary to obtain research grants to support young scientists. As there is a better way to learn how to play baseball, there is a better way to publish a paper on a good journal. Such information can be obtained by asking editors who actually play a critical role in the reviewing process. In general, such editors are selected from those who have many years of experience as reviewer. We will explain to our young scientists our experience as editor as well as reviewer so that everyone can learn how to publish his/her paper on a good journal. (COI:No)

3S5C2-2

Direction of Pflugers Archiv - European Journal of Physiology

Tominaga Makoto

(Div Cell Signaling, Okazaki Inst Integrative Bioscience, Okazaki, Japan)

Pflugers Archiv European Journal of Physiology (Editor-in-Chief: Bernd Nilius) publishes the results of original research considered likely to further the physiological sciences in their broadest sense. Topics include pathophysiological or methodological issues when these can be used as a tool for further investigation of physiological mechanisms. Papers should give mechanistic insights into physiological functions at the molecular and cellular level. Priority will be given to manuscripts that provide conceptual novelty. Pflugers currently specifically aims at publishing work on ion channels, transporters, cardiac electrophysiology, and sensory physiology on a molecular and cellular level partly because they are the research themes that Dr. Nilius has been involved in. However, this direction might be changed depending on the change of Editor-in-Chief. The journal welcomes papers linking genomic and proteomic approaches to physiological functions, as well as articles describing work on the mechanistic phenotyping of transgenic animal models. (COI:No)

3S5C2-3

Issues in preparing academic papers in medical and biological engineering

Sakuma Ichiro

(Medical Device Development and Regulation Research Center, Graduate School of Engineering, The University of Tokyo)

In preparing scientific papers in biomedical engineering, both of engineering significance and medical/biological/clinical significance of obtained results should be demonstrated. Engineering significance can be divided in to two categories: Novelty in methodology, and Novelty in application. Novelty in methodology can be demonstrated as in conventional engineering papers. In case of demonstrating novelty of application, technical considerations how to implement the previously reported methods to actual problems should be clearly stated. Modification of the original methods in actual application, limitation of the method should be also discussed. In conventional engineering, various well established physical models are available such as Navier-Stokes equation that can be widely applicable to various fluid dynamics phenomena. Limited amount of quantitative dynamical models of biological systems are available at present. As a result, various statistical methods are utilized. Design of data analysis is also important. Weighting of technical significance and medical/biological/clinical significance in the paper influences required completeness of the obtained results. To show feasibility of a novel methodology, limited amount of experimental results using biological samples can be accepted. On the other hand, to show the efficacy of application of a system where previously reported technical methods are integrated for a specific purpose, certain amount of data showing validity of the proposed system are required. (COI:No)

3S5C2-4

What do Physiology Journal Editors want? : In case of the Experimental Physiology (Physiological Society)

Ogoh Shigehiko

(Dept Biomed Eng, Toyo Univ, Saitama, Japan)

The Physiological Society members in over 60 countries have made significant contributions to the knowledge of biological systems and the treatment of disease since its foundation in 1876. The Physiological Society promotes and supports those working in the physiological research area by organizing world-class scientific meetings, offering grants for research, and by publishing the latest developments in the leading scientific journals. The Journal of Physiology was first published in 1878 by the Physiological Society and covers all areas of physiology illustrating new physiological principles or mechanisms with an emphasis on human and mammalian physiology. Experimental Physiology is a sister Journal of The Journal of Physiology and The Physiological Society established this journal in 1908 to focus on original Integrative and Translational physiological research. In addition, Experimental Physiology is interested in methodological papers reporting important new developments in physiological techniques that could lead to significant new insight, papers obtaining a significant new physiological behavior or phenomenon which has the potential to alter the understanding of that field, and papers demonstrating experimentally examination and exclusion of a number of plausible mechanisms for the important novel phenomenon. In this symposium, I would like to talk about what Journal editors want the authors in their submitted manuscript especially regarding Experimental Physiology. (COI:No)

Society Symposium 6

Japan-Australia Joint Symposium - Towards FAOPS2019

Recent advances in Hearing Research: From Channel to Behavioral Regulation

March 24 (Thu), 9:00 – 10:30, Room C

3S6C1-1

Homeostatic plasticity in central auditory circuit

Kuba Hiroshi

(Dept Cell Physiol, Grad Sch Med,Nagoya Univ, Nagoya, Japan)

Appropriate adjustment of neuronal activity is crucial for development and maintenance of neural circuits, and it is accomplished via various forms of homeostatic plasticity. Recent studies revealed that homeostatic plasticity occurs as structural and functional changes of the axon initial segment (AIS), which is a specialized axonal region involved in initiation of action potentials. This plasticity at the AIS has the most direct impact on neuronal excitability, and should be an efficient mechanism of regulating activity in a circuit. In this symposium, I will summarize our findings on this plasticity and discuss its functional relevance in auditory circuits. In avian cochlear nucleus, deprivation of auditory inputs elongates length of the AIS, which increases Na^+ conductance in the axon and augments excitability of neurons. Importantly, this elongation accompanies subtype-specific changes in expressions of voltage-gated K^+ (Kv) channels at the AIS; Kv1 decreases, while Kv7 increases, showing a complementary change in their expressions. Kv1 has low threshold and rapid kinetics for activation and strongly inhibits firing, while Kv7 has slow kinetics and contributes to set resting membrane potential, indicating that the decrease of Kv1 enhances excitability, while it is balanced with the increase of Kv7 at the rest. Indeed, auditory deprivation reduces spike threshold with little effects on resting potential. These results indicate that the structural and functional plasticities of the AIS work synergistically and maintain homeostasis of central auditory circuits after hearing loss. (COI:No)

3S6C1-2

Unique electrochemical properties in the cochlea of the inner ear: their origin, physiological roles, and pathological significance

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Cochlear endolymph of the mammalian inner ear exhibits a positive potential of +80 mV, which is called endocochlear potential (EP), and a high $[K^+]$ of 150 mM. These unique properties, which greatly sensitize sensory hair cells, are maintained by the unidirectional K^+ transport across the lateral cochlear wall. The tissue is made up of two epithelial-like layers, each of which harbors a different set of ion channels and transporters. Using a microelectrode sensitive to $[K^+]$ and potential, we previously demonstrated that the EP depends on two K^+ diffusion potentials, each of which occurs on the apical membrane of either layer. Computational model incorporating the channels and transporters expressed in the two layers revealed that functional coupling of these apparatus is necessary for the unidirectional K^+ transport across the lateral wall. This mechanism likely controls not only intra/extracellular $[K^+]$, the determinants of the K^+ diffusion potentials, but the endolymphatic high $[K^+]$. Finally, transgenic mice expressing channelrhodopsin-2 in the lateral wall showed the EP value and hearing level that can be temporally impaired by light exposure. Because the long-term exposure induced irreversible hearing loss, the mice may mimic commonly observed human diseases, in which hearing level reversibly and moderately impairs at early stage but becomes incurably and severely damaged during repetition of the episodes. (COI:No)

3S6C1-3

Cochlear amplifier sensori-motor feedback via the medial olivocochlear reflex contributes to sustained hearing adaptation

Gary Housley[1], Kristina Parley[1], Jennie Cederholm[1], Jean-Pierre Julien[2], Matthias Klugmann[1], Allen Ryan[3]

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Peripherin knockout (PrKO) mice lack innervation of the cochlear outer hair cells by the type II spiral ganglion neurons. Loud sound in one ear of PrKO mice failed to elicit medial olivocochlear (MOC) reflex - mediated contralateral suppression of hearing in the opposite ear, distortion product otoacoustic emissions (DPOAE) via the outer hair cell - based cochlear amplifier were undiminished (Froud et al. Nature Comm. 2015, 6,7115). Here we investigated MOC reflex - based hearing adaptation. White noise (4 kHz-32 kHz) was presented at 93, 101 & 108 dBSPL for one hour (open field, ketamine-xylazine-acepromazine anaesthetic). At cessation of 93 dBSPL noise, PrKO mice had significantly less temporary threshold shift in the cubic (2f1-f2) DPOAE around 16 kHz compared with wildtype (WT) littermates ($p<0.01$, t-test, n = 6 PrKO, 9 WT). However, the PrKO mice had permanent hearing loss measured by auditory brainstem response above 16 kHz with 108 dBSPL noise ($p<0.05$, t-test, n = 7 PrKO, 8 WT). This suggests that the MOC reflex has a sustained contribution to hearing adaptation that is oto-protective. Support: National Health & Medical Research Council (NHMRC) Australia (APP1052463) NIH-NIDCD DC00139, Veterans Affairs 1-01RX000977; 1-01BX001205. (COI:No)

3S6C1-4

Hearing and the Brain: Activity, Deafness, and Neural Plasticity

Ryugo David, Catherine Connelly, Kirupa Suthakar

(Garvan Institute of Medical Research)

It is estimated that just over 20% of the world's adult population suffer from hearing loss and that this number exceeds 50% for those over 65 years of age. In children, hearing loss impairs speech and language development, which in turn undermines academic achievement. In adults, it has a negative impact on employment opportunities and impairs social functioning. Moreover, hearing loss creates social isolation that can develop into depression and early onset dementia. The problems with hearing loss, however, are the symptoms: difficulty understanding speech in noise, the emergence of phantom sounds (tinnitus), and distortions in loudness perception. These symptoms are created by the brain's response to hearing loss, not by hearing loss per se. Our lab has been studying the brain changes that might underlie these symptoms.We have shown that hearing loss results in atrophic alterations of the ascending auditory pathways, abnormalities in excitatory synapses, loss and reorganization of inhibitory circuits, and pathology in the efferent and descending auditory systems. Collectively, such alterations are presumed to cause a corruption of ascending sound information and defective controls over selective listening. These brain changes need to be considered in the design of the next generation assistive hearing devices. Supported by NHMRC grant 1080652 and gifts from Alan and Lynne Rydge and the Walker Family Foundation. (COI:No)

Society Symposium 7

Next generation physiology with state-of-art techniques

Supported by Science Council of JAPAN

March 22 (Tue), 9:00 – 11:00, Room A

1S7A1-1

Visualization of ATP levels in vivo

Yamamoto Masamichi[1,2]

([1]Dept Nephrol, Grad Sch Med, Kyoto Univ, Kyoto, Japan、[2]PRESTO, JST, Japan)

Adenosine 5-triphosphate (ATP) is the major energy currency of cells and is involved in many cellular processes, such as cell motility and development. However, there is no method for real-time monitoring of ATP levels inside individual living cells. In 2009, two new methods were reported, one is a series of Forster resonance energy transfer (FRET)-based indicators for ATP, ATeam and other is a engineered fluorescent sensor of ATP and ADP, Perceval. I generated the ATP visualization mouse using modified ATeam. In my talk, I will show and discuss the dynamics of ATP metabolism in vivo. (COI:No)

1S7A1-2

Towards Organisms-level Systems Biology

Ueda Hiroki[1,2]

([1]Department of Systems Pharmacology, Graduate School of Medicine, The University of Tokyo、[2]RIKEN (QBiC))

The logic of biological networks is difficult to elucidate without (1) comprehensive identification of network structure, (2) prediction and validation based on quantitative measurement and perturbation of network behavior, and (3) design and implementation of artificial networks of identified structure and observed dynamics. Mammalian sleep/wake cycle is such a complex and dynamic system consisting of complicatedly integrated regulatory cellular and molecular networks and displaying the various dynamic behaviors such as sleep/wake homeostasis.
I will discuss the challenges and opportunities towards the organism-level systems biology. Especially, I will introduce the current update on the whole-brain and whole-body imaging with single-cell resolution as well as its biological applications.

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1S7A1-3

Non-invasive human brain stimulation methods and clinical applications

Mima Tatsuya

(Graduate School of Core Ethics and Frontier Sciences, Ristumeikan Univ, Kyoto, Japan)

From 1980s, various techniques to non-invasively stimulate the human brain have been introduced. Transcranial magnetic stimulation (TMS) is one of the most common methods for this purpose. Magnetic pulse given over the human head can induce the short electrical pulse in the brain through the scalp and skin, which causes local neural firings. Artificially-generated neural firings in the living human brain opened up a new frontiers in neuroscience, especially in the motor physiology. Moreover, since it has been reported that the repetitive TMS can produce human neural plasticity non-invasively, via LTD/LTP-like mechanism, clinical application of repetitive TMS in the field of rehabilitation is rapidly progressing. In this presentation, I will introduce recent clinical examples of stroke rehabilitation using TMS. In addition, couples of new non-invasive brain stimulation methods other than TMS, such as transcranial DC stimulation (tDCS), patterned tDCS, static magnetic field stimulation (SMS), will be briefly shown and discussed. (COI:No)

1S7A1-4

Mechanomedicine

Naruse Keiji

(Cardiovasc Physiol, Grad Sch Med, Okayama Univ, Okayama, Japan)

Our bodies maintain normal physiological functions by sensing and responding to various mechanical stresses not only from outside but also within the body. These mechanical stress sensing and response mechanisms contribute to the regulation of physiological functions on a broad space-time scale including cell division, developmental processes, and the emergence of organ-specific functions; evidence has accumulated which suggests that collapse of these mechanical stress sensing and response mechanisms is involved in various pathologies. Looking toward the goal of establishing mechanomedicine in order to devise novel therapeutic methods, we have developed a number of new research methods and systems as well as resolving issues based on the elucidation of pathology employing a vertical research approach covering mechanosensor molecules, cells, tissues, and organs, at individual levels, in combination with horizontal research on diseases affecting each organ, from the perspective of mechanobiology. This lecture provides an overview of basic medical research on mechanobiology, specifically the mechanism of mechanical stress sensing, and introduces research derived from the aforementioned research processes, specifically as applied to regenerative medicine (three-dimensional culture using self-assembling peptide + mechanical stress loading system) and assisted reproduction technologies (microfluidic sperm sorting system/stretch-induced fertilized egg culture system). (COI:Properly Declared)

Society Symposium 8

Symposium in Collaboration with the Japanese Association of Anatomists

New biological approaches based on large-scale data analyses

March 24 (Thu), 9:00 – 10:30, Room I

3S8I1-1

Systematic two-photon imaging of the motor cortex during voluntary movements

Matsuzaki Masanori

(Div Brain Circuits, Natl Inst Basic Biol, Japan)

The primary motor cortex (M1) possesses multiple layers, from layers 1 to 6. This layered structure integrates various types of signals related to motor planning and selection, motor primitives, and sensory feedback from other cortical areas and subcortical regions into the motor-output activity. Although repetitive training often improves motor performance and movement coding by M1 neuronal ensembles, it is unclear how neuronal activities in different layers are reorganized during motor task learning. First, we conducted two-photon calcium imaging in layers 2/3 and 5a in the mouse M1 during 14 training sessions of a self-initiated lever-pull task. In layer 2/3, no overall change in the accuracy of neuronal ensemble prediction of lever trajectory was detected, and a subset of individual neurons retained high prediction accuracy. By contrast, in layer 5a, ensemble prediction steadily improved and one-third of neurons including corticostriatal neurons, evolved to contribute to ensemble prediction in the late stage of learning. At present, we can scan three-dimensional regions to detect the activity of more than hundreds of M1 neurons from layers 2/3 to 6, and the activity of the axons projecting to layer 1 in M1. In addition, we have started to image M1 neuronal activity in the adult common marmoset (Callithrix jacchus), a small New World primate. I'd like to discuss the big data acquired by systematic two-photon imaging of multiple cortical neurons. (COI:No)

3S8I1-2

Systematic isolation of deletion mutants for phenotype analyses in the nematode *C. elegans*.

Mitani Shohei

(Dept Physiol, Tokyo Women's Medical Univ.)

Complex biological processes such as behavior and development of animals are being extensively studied. To understand better, we should reveal the hierarchic relations among molecules, cells, tissues and organisms. The nematode *C. elegans* is a model organism suitable for such analyses; the cell lineage, electron microscopic morphologies including all the synaptic connections have been well documented. The short life cycle is advantageous for genetic analyses. In addition, *C. elegans* is the first animal whose whole genome sequence was completed. To perform the analyses, it is desirable to obtain gene knockout strains as many as possible to understand the roles of those genes. We have been trying to isolate deletion mutants using the genome sequence of the animal. The numbers of the protein coding genes in the nematode are estimated as about 20,500, and 7,663 genes were predicted to be orthologous to human genes. We developed a PCR protocol which detects small amounts of short (deleted) fragments mixed with large amounts of wild-type fragments. We isolated about 6,000 mutants using the method. Recently we developed a new method; we sequence the whole genome of the mutagenized clonal animals and efficiently find deletion mutants. We isolated about 1,000 mutants using the method. As an application of these mutants, many of the phenotypes of these mutants are being analyzed and published by many laboratories in the *C. elegans* research community. We are using by ourselves for screening for mutants with behavioral phenotypes and other anlyses. (COI:No)

3S8I1-3

Three dimensional ultrastructural analyses of cells and tissues by a novel scanning electron microscopy

Nakamura Kei-ichiro[1]、Kanazawa Tomonoshin[1]、Rikimaru Yukiko[1]、Hirashima Shingo[1]、Miyazono Yoshihiro[1]、Okayama Satoko[1]、Higashi Ryuhei[2]、Ohta Keisuke[1]

([1]Dept.Anat, Kurume Univ Sch Med, Kurume, Japan、[2]Electron Microscope Unit, Kurume University School of Medicine)

Narayan & Subramaniam have mentioned " A quiet revolution is under way in technologies used for nanoscale cellular imaging" in the recent review article of Nature Methods. Their core message is the focused ion beam/scanning electron microscopy, FIB/SEM, previously restricted to the materials sciences fields, is becoming a powerful tool for ultrastructural imaging of biological specimens. This novel EM technique enables material contrast observations of broad flat cut surface of resin embedded specimens at ultrastructural resolution, and also enables three-dimensional ultrastructural analyses that referred to as FIB/SEM tomography by reconstructing huge number of serial sections to visualize cell and tissue architectures. Similar methods are now becoming available and improving quickly; Dik-SEM, array tomography and so on. These techniques reveal new biological structures that no one could even imagine from single sections. By FIB/SEM, a thousand or more images of sections could be obtained over night. Such large-scale images potentially possess so big morphological information, however, objective handling and analyses of those comprehensive data is sometimes difficult. Thus, demands for novel strategy emerge for analyzing large-scale morphological data in them. In the present study, we will show some examples of large-scale morphological data and some trial to analyze them. (COI:No)

3S8I1-4

Processing of terabyte scale images derived from cryo-electron microscope.

Kikkawa Masahide

(Dept. Cell Biol., Grad. Sch Med, The Univ. of Tokyo, Tokyo, Japan)

Cryo-electron microscopy (cryo-EM) has been used to visualize three-dimensional structures of biological structures by embedding unstained samples in vitreous ice. Because of the radiation damage caused by high-energy electron used for imaging, the electron dose for cryo-EM imaging is limited to 10~60 electron per squire Angstrom. As a result, individual cryo-EM images are noisy and it is necessary to collect thousands to millions of images to obtain one three-dimensional structure.

We have been studying eukaryotic cilia/flagella, which works as a propeller and antenna of cell. To elucidate the mechanism of complex molecular mechanism, we have developed a novel method for identifying the 3D locations of proteins using biotin-streptavidin labeling and cryo-electron tomography. This methods prove to be very specific and powerful as we have determined the 3D locations of more than 30 proteins in cilia/flagella. During this process, our lab expanded the computational resources including CPUs, GPUs, faster and larger storages, and archiving tapes to keep up with the image processing (~0.1 TB / day). In addition, our university recently installed a new electron microscope equipped with a direct electron detector, which outputs a few TB / day.

In this symposium, we would like share our experience and discuss about the future potentials of terabyte scale processing of cryo-EM images. (COI:No)

3S8I1-5

Mathematics and Informatics for Exploring Information in Quantitative Data

Kobayashi Tetsuya[1]

([1]IIS, Univ. Tokyo, Tokyo Japan、[2]JST PRESTO, Saitama, Japan)

Recent advancement of imaging and sequencing technologies enables us to obtain a variety of quantitative data on the phenotypic and genotypic heterogeneity and dynamics of different organisms. Extracting relevant information from such quantitative data is a technical challenge in quantitative biology, which may also contribute to medical science.In this work, we are going to review the technologies of mathematics and informatics to explore various quantitative data such as 4D time-lapse imaging data and single-cell sequence data.We may also discuss possible applications of these technologies for future medical problems. (COI:No)

Society Symposium 9

Symposium in Collaboration with the Japan Society of Neurovegetative

Eye and autonomic nerves

March 23 (Wed), 16:30 – 18:00, Room H

2S9H2-1

Evaluation of mental stress with the pupillary response

Hara Naoto[1]、Mukuno Kazuo[2]

([1]Department of Orthoptics and Visual Science, International University of Health and Welfare, Tochigi, Japan、[2]Department of Ophthalmology, Yokohama Dental and Medical Clinic, Kanagawa Dental University)

The pupil dilates due to human emotions such as anger, anxiety, fear, and arousal and in response to sensory stimuli. Conversely, the pupil constricts due to fatigue, sleepiness, and aging. The pupil thus responds to subtle psychological and mental sensations. Moreover, pupillary oscillations in which subtle fluctuations in pupil size occur even in the dark, known as "fatigue waves", are already being used as an objective indicator of fatigue in Germany. The pupil has thus been studied as a biometric indicator in the fields of psychology, biomedical engineering, and medicine. At this academic conference, we will present various applications of the pupillary response as an indicator of stress response. First, we describe the pupillary response following treatment of malocclusion, followed by a discussion of the significance and origin of pupillary oscillations based on simultaneous analysis rate variability and pupillary oscillations. Finally, we describe the potential application of the pupillary response as an objective diagnostic indicator of depression by analyzing the relationship between the pupillary response and a mental health questionnaire (the General Health Questionnaire-28; GHQ-28) in visual display terminals (VDTs) workers. Based on the above, we wish to clarify the significance of the pupillary response as a stress indicator. (COI:No)

2S9H2-2

Influence of mouth guards on autonomic nervous system activities: A quantitative study of pupillary flash responses

Ishida Jun-ichi

(Dept Oral Maxillofac Surg, Hattori Memorial Hosp, Nara Japan)

Recently, it has been reported that mouth guards (MGs), which reduce the incidence and severity of traumatic oral injuries in contact sports, may actually affect sports performance. We have observed that a majority of subjects showed improved dynamic visual acuity during head rotation when using a MG, but subjects who were unwilling to use a MG showed the opposite effect. Thus, we hypothesized that unpleasant sensations due to MGs may decrease sports performance. In this study, we measured autonomic nervous system activity to evaluate unpleasant sensations objectively and quantitatively by measuring the pupillary flash response (PFR) and heart rate variability (HRV), before, during, and after wearing 3- and 5-mm-thick custom-made MGs in 10 healthy subjects.It was found that the 5-mm MG had a higher incidence of unpleasant sensations (50% of subjects) than did the 3-mm MG (10%). PFR (not HRV) analysis showed that both sympathetic and parasympathetic nervous system activities increased in subjects with unpleasant sensations.We suggest that the unpleasant sensation induced this unusual autonomic nervous system response, which could not be detected by traditional methods such as HRV analysis. By using PFR analysis, it is possible to make MGs without unpleasant sensations for better sports performance.Reference: Ishida, J. et al. Influence of mouth guards on autonomic nervous system activities: A quantitative study of pupillary flash responses. Oral sci. int. 2012;9:38-42. (COI:No)

2S9H2-3

Autonomic control of ocular function by somatic afferent stimulation

Uchida Sae

(Dept Auton Neurosci, Tokyo Metropol Inst Gerontol, Tokyo, Japan)

Ocular functions, such as pupil diameter, ocular accommodation, ocular blood flow, and intraocular pressure, are regulated by autonomic nerves. Here, we present a study of autonomic neural mechanisms underlying reflex responses of ocular blood flow and pupil diameter in response to somatic afferent stimulation in anesthetized rats.
1. Ocular blood flow
Eye has two types of blood vessels: retinal and choroidal. The autonomic vasoactive nerves innervate the choroid but not to the retinal vessels.In anesthetized rats, noxious mechanical stimulation of a forepaw produced an increase in choroidal blood flow with pressor response. When pressor response was eliminated, the choroidal blood flow initially increased, followed by a decrease in response to the forepaw stimulation.The somatically induced vasodilative response was caused by the release of nitric oxide from the parasympathetic nerves, and the vasoconstrictive response was because of the release of noradrenaline from the sympathetic nerves.
2. Pupil diameter
Pupil diameter is controlled by two muscles: sphincter and dilator pupillae of the iris. Both these muscles are innervated by autonomic nerves.In anesthetized rats under stable light circumstances, electro-acupuncture stimulation of a hindpaw induced pupil dilation. Severing the cervical sympathetic trunks had no effect on the response; however, the response was eliminated by severing the 3rd cranial parasympathetic nerve. When parasympathetic activity to the pupil sphincter muscle was high under light circumstances, somatic inputs induced pupil dilation because of the inhibition of high tonic parasympathetic activity.
(COI: No)

2S9H2-4

The role of autonomic nerve system in the regulation of retinal blood flow regulation during acute increase in systemic blood pressure

Nagaoka Taiji、Yoshida Akitoshi

(Department of Ophthalmology, Asahikawa Medical University)

Systemic hypertension is one of the risk factor for many ocular diseases. However, it remains unclear how retinal blood flow is regulated during systemic hypertension. We evaluated the change in retinal blood flow in response to acute increase in systemic blood pressure in both healthy humans and anesthetized cats. In healthy human subjects, we found an inverse correlation between the changes in retinal arteriolar diameter and a mild (i.e., 15%) increase in MABP in healthy humans, suggesting the important role of myogenic vasoconstriction in maintaining retinal blood flow constant during pressure elevation. In addition, the peak change in vessel diameter significantly correlates with the peak increase in MABP, suggesting that constriction of the retinal arterioles plays an important role in the maintenance of RBF in response to an acute increase in systemic BP.In anesthetized cats, the major findings of this study are as follows: 1) The change of retinal arteriolar diameter upon severe systemic BP elevation does not correlate with the change in OPP; 2) L-NAME and indomethacin enhance retinal arteriolar constriction and attenuate increased flow in response to severe BP elevation; 3) BQ-123 and fasudil potentiate the increase in retinal arteriolar velocity and flow upon BP elevation. Because it is generally accepted that sympathetic nerves system is nonfunctional in the retinal vascular bed, our findings suggest that retinal blood flow is regulated by both myogenic and flow-regulated mechanism during acute increase in systemic blood pressure. (COI:No)

Society Symposium 10

Symposium in Collaboration with the Japan Society of Acupuncture and Moxibustion

Symptoms improved by Acupuncture: therapeutic effect and its mechanism

March 24 (Thu), 9:00 – 10:30, Room J

3S10J1-1

Effectiveness and mechanism of a gentle skin stimulation for nocturia due to overactive bladder

Hotta Harumi
(Dept Auton Neurosci, Tokyo Metropol Inst Gerontol)

Somatic afferent nerve stimuli are used for treating an overactive bladder (OAB), a major cause of nocturia in the elderly, but clinical evidence for such treatment is insufficient. Our studies on anesthetized rats show gentle stimuli applied to perineal skin with a roller could inhibit micturition contractions depending on its surface material. To examine the efficacy of gentle skin stimuli for treating nocturia, we conducted a cross-over, placebo-controlled, double-blind randomized clinical study using two rollers with different effects on micturition contractions. Participants were elderly women with nocturia. Active (elastomer roller) or placebo (polystyrene roller) stimuli were applied to perineal skin by participants for 1 min at bedtime during 3-day stimulation period. In participants with OAB, mean frequency of urination per night during the active treatment was significantly lower than that of placebo treatment (-0.6 times). This results suggest that gentle perineal stimulation with an elastomer roller is effective for treating OAB-associated nocturia in the elderly. We then examined effect of gentle perineal stimulation on micturition contractions in aged rats. There were age-related changes in time course of inhibitory effect. Contributions of skin afferent fibers in early and late phases of inhibition were examined by stimulation of and recording from the different groups of skin afferent nerve fibers. We conclude that this gentle stimulation is beneficial to evoke appropriate extent of discharge of mechanoreceptive fibers to inhibit micturition reflex. (COI:No)

3S10J1-2

irritable bowel syndrome

Noguchi Eitaro
(Grad Sch, Tsukuba Univ of Technology, Tsukuba, Japan)

Irritable bowel syndrome (IBS) has recently been recognized as a common disease in Japan, and clinical practice guidelines for IBS were developed by the Japanese Society of Gastroenterology. The guidelines have indicated that the effectiveness of acupuncture treatment does not exceed the placebo effect, so acupuncture treatment is not recommended. This paper introduces the possibility of IBS clinical treatment by acupuncture stimulation based on findings from basic medical research. In Japan, there is a long history of basic research on acupuncture and moxibustion stimulation and its effect on digestive tract functions. Research in acupuncture treatment continued to make progress and in 1993, Sato et al. reported that when adding acupuncture stimulation to the abdomen, gastric motility was controlled by spinal reflex through the sympathetic nerves. Further, the acupuncture stimulation of extremities have proved to the increased response of gastric motility by excitement of the vagus nerve via supraspinal reflex. By the stimulation to the extremities, the mechanism of increased response due to excitement of vague nerves through an upper spinal reflex. Also, Noguchi et al. confirmed that the same response occurred in the duodenum by electroacupuncture stimulation. Moreover, IWA et al. reported that needle stimulation to the lower extremities causes an increase in motility of the large bowel via Barrington nucleus of the lower extremities. (COI:No)

3S10J1-3

The effect and mechanisms of the acupuncture for the cervicobrachial syndrome

Kimura Kenichi
(Dept Health Sci, Kansai Univ Health Sci, Osaka, Japan)

The cervicobrachial syndrome(CS)is a syndrome with chief complaints of pain and numbness across the neck, shoulder, and upper limb. A narrow definition of the CS is excluded organic diseases such as cervical disc herniation. The term is often used to indicate a condition with chronic muscle tension in the neck, shoulder, and upper limb, such as from computer overuse, as well as muscle fatigue and malaise. Although many patients in acupuncture clinics complain cervicobrachial pain, it remains unclear about the effects and mechanisms of acupuncture. In the case with chronic pain, sympathetic and motor nerves reflexively tense and, as a result of decreased muscle blood flow and increased muscle tension, metabolic products accumulate and algesic substances are produced (the negative spiral of pain). The CS has been suggested to be based on this negative spiral of pain. Acupuncture is known to interrupt this negative spiral of pain by improving local blood flow and facilitating the elimination of metabolic products and algesic substances. Clinically, patients often feel that the stiffness of muscle loosens after treatment. Electromyograms have also been demonstrated to show decreases in muscle rigidity (Ohta et al, 2015). This is an interesting report showing the relief of the muscle tension with acupuncture stimulation. As mentioned above, various symptoms including muscle fatigue and malaise are seen in the CS. Acupuncture may help to relieve these symptoms of the CS by improvement of local blood flow and muscle tension. (COI:No)

3S10J1-4

Remedial mechanism of the electroacupuncture stimulation for paclitaxel-induced peripheral neuropathy

Ishikawa Shintaro
(Dept Physiol, Sch Med, Showa Univ, Tokyo, Japan)

Chemotherapy, particularly for breast cancer and ovarian cancer, is one of the indispensable treatments for a malignant tumor. Paclitaxel (PTX) is a mitotic inhibitor used in cancer chemotherapy, but it causes chemotherapy-induced peripheral neuropathy (CIPN). The acupuncture stimulation (ACU) has been used for a treatment of dysesthesia and paresthesia. Therefore, we tested the influence of electro-ACU with PTX-CIPN model rats.The SD rats were randomly divided into 4 groups: PTX group, ACU of PTX pre-treatment (ACU-prePTX; ACU started on day 0), ACU of PTX post-treatment (ACU-postPTX; ACU started on day 14), and control group. All rats were injected intraperitoneally on 4 alternate days (days 1, 3, 5, and 7) with vehicle (saline) or 2.0 mg/kg PTX. Electro-ACU, which caused slight muscle twitch, was applied to ZuSanli acupoint (ST36) in the limbs on every other day (right side, 1Hz, 20 min., 3-5V). Behavioral assays were carried out by mechanical allodynia von Frey hair test in the feet, which is the sciatic nerve territory. All rats were sacrificed on day 35, and the lumbosacral spinal cord was collected for microscopy examination. PTX and ACU-postPTX group produced significant mechanical allodynia in the feet, but ACU-prePTX group did not show any decrease in the mechanical threshold. In the PTX and ACU-postPTX, activity of microglia was recognized. In conclusion, our study indicates that applying ACU before PTX administration relieves PTX-CIPN by suppressing of the satellite cell in the dorsal horn of spinal cord. Therefore, ACU is effective in preventing PTX-CIPN. (COI:No)

Society Symposium 11

Symposium in Collaboration with the Japanese Society of Neurology

Thermal biology: critical interaction between temperature and life

March 24 (Thu), 9:00 – 10:30, Room D

3S11D1-1

Physiological functions of thermosensitive TRP channels

Tominaga Makoto
(Div Cell Signaling, Okazaki Inst Integrative Bioscience, Okazaki, Japan)

TRP (transient receptor potential) channels were first described in Drosophila in 1989, and they comprise six related protein families in mammals (TRPC, TRPV, TRPM, TRPA, TRPML, TRPP). One subunit of the TRP channel is composed of six transmembrane domains and a putative pore region with both amino and carboxyl termini on the cytosolic side. The subunits form functional channels as homo- or hetero-tetramers, and most of the TRP channels work as nonselective cation channels. TRP channels are best recognized for their contributions to sensory transduction, responding to temperature, nociceptive stimuli, touch, osmolarity, pheromones and other stimuli from both within and outside the cell. Among the huge TRP super family of ion channels, some have been proven to be involved in thermosensation detecting ambient temperatures from cold to hot. There are now nine thermosensitive TRP channels (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM3, TRPM4, TRPM5, TRPM8 and TRPA1) with distinct temperature thresholds for their activation. Thermosensitive TRP channels work as multimodal receptors which respond to various chemical and physical stimuli. Although the structures of TRPV1 and TRPA1 were clarified as a atomic level through single particle analysis with cryoEM, it is still not known how temperature opens the channels. I would like to talk about the physiological significance of some of the thermosensitive TRP channels (TRPV1, TRPA1, TRPV4 and TRPM2). In addition, how structure and functions of thermosensitive TRP channels were changed dynamically in the process of evolution will also be discussed. (COI:No)

3S11D1-2

Lipid-mediated control of energy metabolism and thermoregulatory behavior in *Drosophila melanogaster*

Umeda Masato、Murakami Akira、Juni Naoto、Nagao Kohjiro、Hara Yuji
(Dept Synth.Chem.Biol.Chem. Grad Sch Engin. Kyoto Univ. Japan)

Lipid-mediated control of energy metabolism and thermoregulatory behavior in *Drosophila melanogaster*
Masato Umeda, Akira Murakami, Naoto Juni, Kohjiro Nagao, Yuji Hara
Dept Synth.Chem.Biol.Chem., Grad Sch Eng., Kyoto Univ.
Although most ectothermic animals do not use metabolically produced heat to regulate body temperature, we demonstrated that thermoregulatory behavior of *Drosophila* is highly dependent on the level of energy metabolism; the increase in mitochondrial oxidative phosphorylation induced the low-temperature preference, while the suppression of energy metabolism by inhibiting insulin signaling caused a warm-seeking thermoregulatory behavior.
During the course of identifying molecules involved in the control of thermoregulatory behavior, we found that delta-9 fatty acid desaturase (DESAT1) expressed in the fat body played a pivotal role in the control of energy metabolism as well as thermoregulatory behavior. Defective expression of DESAT1 suppressed oxidative phosphorylation, causing a significant decrease in body size and warm-seeking phenotype. We also demonstrated that the expression of DESAT1 was precisely controlled by the changes in environmental temperature as well as fatty acid composition of the membrane. These observations raise the intriguing possibility that the temperature and membrane fluidity-dependent regulation of DESAT1 expression coordinately regulate energy metabolism and thermoregulatory behavior of *Drosophila*. Molecular mechanisms underlying the control of DESAT1 expression will also be discussed. (COI:No)

3S11D1-3

Medullary circuit for neuropeptide Y-driven metabolic inhibition: a hunger response to survive starvation

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([1]Dept Integrative Physiol, Nagoya Univ Grad Sch Med, Nagoya, Japan、[2]PRESTO, JST, Japan)

Peripheral hunger signals, such as ghrelin secreted from an empty stomach, stimulates neuropeptide Y (NPY)-containing neurons in the arcuate nucleus of the hypothalamus, which then release NPY from their nerve endings in the paraventricular hypothalamic nucleus (PVH) to inhibit metabolic activities including brown adipose tissue (BAT) thermogenesis. However, the neural circuit mechanism by which the NPY-triggered signaling from the PVH inhibits BAT thermogenesis remains unknown. In this study, we found that NPY injection into the PVH in rats inhibits BAT thermogenesis through GABAergic inhibitory inputs to BAT-controlling sympathetic premotor neurons in the rostral medullary raphe (rMR). Our anterograde and retrograde tract tracing revealed that GABAergic neurons in the intermediate and parvicellular reticular nuclei (IRt/PCRt) of the medulla oblongata directly innervate sympathetic premotor neurons in the rMR. In vivo stimulation of neurons in the IRt/PCRt with a nanoinjection of bicuculline, a $GABA_A$ receptor antagonist, strongly inhibited either skin cooling-evoked or pyrogenic mediator-evoked BAT thermogenesis. Furthermore, inactivation of IRt/PCRt neurons with bilateral nanoinjections of muscimol, a $GABA_A$ receptor agonist, reversed the inhibition of BAT thermogenesis by hypothalamic NPY. These data indicate that the hunger-driven hypothalamic NPY signaling inhibits BAT thermogenesis through the GABAergic innervation from IRt/PCRt neurons to sympathetic premotor neurons in the rMR. (COI:No)

3S11D1-4

The role of habenula complex in regulation of autonomic physiological function

Ootsuka Youichirou
(Cnt Neurosci, Dept Human Physiol, Sch Med, Flinders Uni)

For successful survival and reproduction, animals must respond appropriately to external threats and modify behaviours that lead to adverse outcomes. Corrective behavioural responses are integrated with changes in physiological-autonomic function. Body temperature increases via brown adipose tissue (BAT) thermogenesis, and thermoregulatory cutaneous blood flow decreases, when animals encounter salient, potentially threatening environmental events. We refer to the resultant increase in body temperature as emotional hyperthermia (1). Recent research in animals and humans has established that the habenula complex, an evolutionarily-ancient nucleus in the dorsal diencephalon, is activated by adverse environments, substantially contributing to modification of adverse-outcome. So far there is no information as to whether the habenula complex also regulates the physiological-autonomic responses associated with behaviour modification. Recently we discovered that activation of neurons in the habenula complex in rats increases body temperature by activating thermogenesis and decreases by selectively constricting the tail artery (2). We also showed that these responses are mediated by the medullary raphé, which is the main medullary thermoregulatory centre. These results will provide a new clue as to the actual neural circuitry linking cognitive-emotional functions and autonomic physiological function. 1. Mohammed at al AJP Physiol (2013). 2. Ootsuka and Mohammed Physiol Rep (2015). (COI:No)

Society Symposium 12

Symposium in Collaboration with the Japanese Society of Physical Fitness and Sports Medicine

Exercise + milk product intake as a countermeasure for age-associated diseases

March 23 (Wed), 15:00 – 16:30, Room H

2S12H2-1

Milk-derived proteins in combination with exercise to prevent sarcopenia

Fujita Satoshi
(Dept Ex Sports Sci,Ritsumeikan Univ,Shiga,Japan)

The age-associated loss of skeletal muscle mass and strength (sarcopenia) has been shown to increase the risk of injury due to falls and incidence of metabolic complications including insulin resistance and diabetes, which subsequently becomes a significant factor to disability among the elderly population. Nutrient intake, specifically essential amino acids and meal-induced insulin, both independently stimulates muscle protein synthesis. However, age-specific changes in muscle anabolic responses to an essential amino acid leucine becomes apparent when sub-maximal amounts of amino acids are administered in older subjects. Furthermore, insulin resistance of muscle protein metabolism with aging has been demonstrated in healthy non-diabetic older subjects. Resistance exercise is another anabolic stimuli which increases myofibrillar muscle protein synthesis in both young and older individuals. The increased muscle anabolism is apparent within 2-3 hr after a single bout of heavy resistance exercise and remain elevated up to 2 days following the exercise. Finally, recent evidence on the cumulative effect of resistance exercise in combination with milk-derived proteins on muscle protein metabolism will be discussed to propose a possible preventative measure against sarcopenia. (COI:No)

2S12H2-2

Coingestion of milk affects blood glucose and insulin responses to glucose load.

Terada Shin
(The University of Tokyo, Tokyo, Japan)

Epidemiological studies have suggested that dietary intakes of milk and dairy products are associated with the reduced risk of diabetes, although the physiological and biochemical mechanisms have not been fully elucidated. Recently, we examined the effects of coingestion of milk on blood glucose and insulin responses to glucose load in mice and humans. Consequently, we found that milk ingestion in combination with glucose augmented insulin secretion and attenuated the rise in blood glucose level compared with glucose alone. Plasma concentration of glucose-dependent insulinotropic polypeptide (GIP), which is a gut-derived incretin hormone, was significantly higher in the mice coadministered glucose and milk compared with the mice fed glucose alone and the significant relationship between plasma GIP and insulin concentrations was observed. It is therefore likely that milk ingestion potentiates glucose-induced insulin secretion via gut-derived GIP and, thereby, enhances glucose disposal after glucose load. We also found that coadministration of emulsified fat with glucose potentiated GIP and insulin secretion and reduced glycemic response in mice, suggesting that milk fat seems to be involved in the milk-induced increases in GIP and insulin secretion. In addition, coingestion of milk or emulsified fat with glucose after an acute bout of exercise was able to enhance glycogen resynthesis in mice skeletal muscle and liver. These results indicate that coingestion of milk or fat may be an effective strategy for post-exercise energy recovery in athletes as well as glycemic control in diabetic patients. (COI:No)

2S12H2-3

Effect of different types or forms of milk protein on muscle protein synthesis ~ basic and applied research at a food company~

Kanda Atsushi
(R&D Labs., Meiji Co., Ltd., Kanagawa, Japan)

Bovine milk protein is among the highest quality proteins, containing a complete profile of essential amino acids, and having distinct traits thought to be advantageous for stimulating muscle protein synthesis (MPS). Whey has been characterized as "fast" protein and casein as "slow" protein because of their digestion and absorption rates. These characteristics may affect the time course for stimulating MPS. We hypothesized that co-ingestion of milk proteins (whey and casein) is effective at prolonging the MPS response. Therefore, we compared the effect of ingestion of milk protein on MPS to both whey and casein alone.We produced whey protein hydrolysates (WPH) to develop more efficient whey protein material. We previously showed that WPH were more rapidly absorbed than intact whey protein. However, it has not been convincingly demonstrated that WPH are superior to undenatured proteins for stimulating MPS. Therefore, we compared the effects of WPH on MPS with intact whey protein for the purpose of evaluating the functionality of WPH.Furthermore, we recently developed new type of acidic milk (AM). Bovine milk coagulates under acidic conditions due to the properties of casein. However, AM maintains solubility under acidic conditions and therefore its proteins are absorbed faster than those of skim milk. We hypothesized that the faster absorption rate of AM may affect MPS after ingestion, and therefore compared the effects of ingestion of AM and skim milk on MPS.In this presentation, we will discuss our recent results and discuss future prospects. (COI:No)

2S12H2-4

Effects of interval walking training + milk product intake on thigh muscle strength and methylation of NFκB genes in older women

Masuki Shizue[1,2]、Nose Hiroshi[1,2]
([1]Dept Sports Med Sci, Shinshu Univ Grad Sch Med、[2]IBS, Shinshu Univ, Matsumoto, Japan)

Muscle atrophy with aging is the fundamental causes for lifestyle-related diseases. As for the mechanisms, muscle atrophy may induce release of cytokines from the muscle or other organs, causing chronic inflammation. In the present study, we assessed whether post-exercise milk product intake (PEMPI) during 5-month interval walking training (IWT) enhanced the increase in thigh muscle strength and ameliorated the susceptibility to inflammation in older women. Subjects (n=37, 66±5(SD) yr) were randomly divided into 3 groups: IWT alone (CNT, n=12), IWT + PEMPI of low dose (LD, n=12; 4g protein, 3g carbohydrate, and 3g fat) or 3 times higher dose (HD, n=13). They were instructed to repeat >5 sets of fast and slow walking for 3 min each at >70% and 40% peak aerobic capacity for walking, respectively, per day >4 days/wk. After IWT, thigh muscle strength increased in HD (8±2%) more than in CNT (-2±3%, P=0.022) despite similar IWT achievement between groups (P>0.5). Moreover, the genome-wide microarray analysis showed that NFκB signaling, a well-known transcriptional regulator of inflammation, was altered by IWT + PEMPI. Further, the pyrosequencing analysis showed that methylation of NFKB1 and NFKB2 genes after IWT was enhanced in HD (28±6% and 43±9%, respectively) more than in CNT (-23±8% and -10±9%, respectively; both, P<0.001), suggesting greater suppression of pro-inflammatory cytokines in HD. Thus, PEMPI enhanced the increases in thigh muscle strength and methylation of NFKB1 and NFKB2 genes by IWT in older women. (COI:No)

Society Symposium 13

Symposium in Collaboration with the Biophysical Society of Japan

Cutting-edge muscle physiology studies

March 24 (Thu), 9:00 – 10:30, Room G

3S13G1-1

CryoEM structure of muscle thin filament with the tropomyosin and troponin complex

Fujii Takashi

(Frontier Bioscience, Osaka Univ, Osaka, Japan)

Muscle contraction is driven by cyclic interactions of myosin in the thick filament with thin filament composed of actin, tropomyosin (Tm) and troponin (TnC, TnI, TnT). It is thought that the binding of Ca2+ released from sarcoplasmic reticulum to TnC causes a conformational change of Tm on the actin filament to allow actin-myosin interaction. To understand this regulatory mechanism, it is indispensable to elucidate the structure of thin filament at high resolution. We established a method to purify intact, Ca2+-free and Ca2+-bound thin filaments from skeletal muscle of a crab, Portunus trituberculatus, at high yield. We developed a novel image analysis approach for 3D reconstruction of thin filament. A cryoEM density map of thin filament in the absence of Ca2+ shows interesting features of actin-Tm-Tn interactions never seen before. (COI:No)

3S13G1-2

Molecular mechanism of cooperative force generations between skeletal myosins revealing efficient muscle contractions

Kaya Motoshi[1]、Washio Takumi[2]、Hisada Toshiaki[2]、Higuchi Hideo[1]

([1]Dept Phys, Grad Sch Sci, Univ Tokyo, Tokyo, Japan、[2]Grad Sch Front Sci, Univ Tokyo, Tokyo, Japan)

To understand the molecular mechanism of cooperative force generation between skeletal myosin molecules, we measured forces generated by synthetic myosin-rod cofilaments, in which approximately 17 myosin molecules interact with single actins at the mixing ratio used in this study. Optical tweezers were used to measure forces generated by myosins, showing experimental results that infer forces are generated by synchronous actions of active myosin motors. Combined with results from the computational model, three factors are important for synchronization of power strokes between myosin motors. First, strain-dependent kinetics are necessary to couple mechanochemical cycles between myosins. Second, multiple power stroke states further enhance a chance of power stroke synchronization. Finally, the physiological ATP concentration is another important factor to enhance a chance of power stroke synchronization, since the strain-dependent transitions accompanied by the first or second power stroke are the rate limiting steps at higher ATP concentrations. Consequently, our computational model predicts that most of steps were generated by synchronous execution of power strokes between several myosin motors at 1 mM ATP, while they are generated primarily by single myosin at 10 μM. Thus, ensemble average curves of steps obtained from our simulation model were distinctively different between 1 mM and 10 μM ATP and show in good agreement with those from experimental data, supporting our conclusions. (COI:No)

3S13G1-3

Self-organization of contractile actomyosin rings inside a cell-sized confined space *in vitro*

Miyazaki Makito[1]、Ishiwata Shin'ichi[1,2]

([1]Dept Physics, Waseda Univ, Tokyo, Japan、[2]WABIOS, Waseda Univ, Singapore, Singapore)

During cell division, many animal cells transform into a spherical shape and assemble a contractile ring composed of actin filaments and myosin motors at the equator to separate the cell body into two. Although actomyosin regulatory proteins are spatio-temporally controlled during cytokinesis, the direct contribution of cell shape and actomyosin activity on the contractile ring assembly remains unclear. Here, we demonstrated *in vitro* that actin polymerization inside cell-sized spherical droplets (water-in-oil droplets surrounded by phospholipids, 1 to 20 μm in diameter) induced the spontaneous formation of single ring-shaped actin bundles in the presence of bundling factors such as α-actinin or methylcellulose (Miyazaki, Chiba, Eguchi, Ohki, Ishiwata, *Nature Cell Biol.* **17**, 480-489 (2015)). Despite a lack of spatial regulatory signals, the rings always assembled at the equator to minimize the bending elastic energy of the bundles. Myosin promoted ring formation through the dynamic remodeling of actin networks, and an increase in the effective concentration of myosin triggered ring contraction. The ring contraction rate was nearly proportional to the initial ring diameter, which recapitulates the common feature of cytokinetic rings in animal cells. These results will help us understand how animal cells coordinate cell shape and actomyosin activities to self-organize contractile units that are essential for cell division, motility and muscle contraction. (COI:No)

3S13G1-4

In vivo nano-imaging and a thermal manipulation of myocardial contractions

Oyama Kotaro[1]、Kobirumaki Fuyu[1]、Shimozawa Togo[2]、Fukuda Norio[1]

([1]Dept Cell Physiol, Jikei Univ, Tokyo, Japan、[2]Dept Life Sci Med Biosci, Sch Adv Sci Eng, Waseda Univ, Tokyo, Japan)

Changes in myocardial sarcomere lengths of merely ~100 nm dramatically change the heart's pump functions. Therefore, high-performance nano-imaging of cardiac sarcomeres in vivo is paramount to fully understand the contributions of SL dynamics to cardiac pump functions. In the present study, we developed a high-speed (100 fps), high-resolution (20 nm) nano-imaging system for myocardial sarcomeres in living mice. We expressed α-actinin-AcGFP to visualize the Z-disks in cardiomyocytes of the left ventricle in vivo. The length of a single sarcomere was determined by the peak-to-peak distance of the α-actinin-AcGFP fluorescence profile. Using this system, we conducted three-dimensional analyses of sarcomere dynamics during the cardiac cycle, simultaneously with electrocardiogram and left ventricular pressure measurements. These results provided the first direct evidence for the tight coupling of sarcomere dynamics and ventricular pump functions. Likewise, we developed a thermal stimulation system with infrared laser to modulate myocardial contractions. Accordingly, we found that microscopic heat pulses reproducibly induced contractions with no changes in intracellular calcium dynamics. This technique is likely to have a potential in systematically understanding the mechano-thermal coupling in cardiac as well as skeletal muscles. At the meeting, we will discuss the recent advances in cardiac nano-physiology as revealed by using cutting-edge optical technologies. (COI:No)

3S13G1-5

In vitro construction of 3D muscle tissues

Morimoto Yuya[1]

([1]IIS, Univ. Tokyo, Tokyo, Japan、[2]Takeuchi Biohybrid Innovation project, ERATO, JST, Tokyo, Japan)

Recently, constructed skeletal muscle is gathering attentions because the skeletal muscle is applicable to various field such as medical treatment, drug development and biomimetic robots. Since skeletal muscle is one of organ in our body, the constructed muscle is a useful tool as a graft for medical treatment and a screening model for drug development. Furthermore, skeletal muscle is applicable to biomimetic robots as driving elements. Among the various applications, we want to use constructed skeletal muscles as driving elements for artificial arms or legs in future. If we succeed in construction of artificial arms using skeletal muscles, recipients will be able to control motions of the artificial arms without extra equipment; transmissions of neural signals to constructed skeletal muscle control the motions. To achieve the artificial arms, at first, motion control by neural signals, barrier covering skeletal muscle to drive in air, and biomimetic structure with multiple skeletal muscles to achieve complex motions are necessary as basic technology. In this symposium, we show our methods based on microengineering techniques to achieve the basic technologies. We introduce our fabrication method of skeletal muscle *in vitro*. In addition, We explain our approach to achieve fundamental techniques for biomimetic artificial arm; 1st topic is control of skeletal muscle contraction using neural signals, 2nd topic is covering skeletal muscle with collagen layer as barrier to allow skeletal muscle actuator drive in air, and 3rd topic is antagonistic skeletal muscle actuator to allow complex motions. (COI:No)

Society Symposium 14

Symposium in Collaboration with the Japanese Society of Orofacial Pain

Frontier in pain researches targeting on trigeminal system

March 24 (Thu), 9:00 – 10:30, Room K

3S14K1-1

Possible peripheral mechanisms of burning mouth syndrome

Shinoda Masamichi
(Dept Physiol, Nihon Univ Sch Dent, Tokyo, Japan)

Burning mouth syndrome (BMS) is characterized by altered sensory qualities, namely tongue pain hypersensitivity which is mainly characterized by oral burning or painful sensations, develops without any apparent pathological changes such as nerve injury or inflammation in the tongue. The exact mechanism of such tongue pain remains unclear, though it is reported that small-fiber neuropathy may be involved in sensitization of trigeminal ganglion (TG) neurons innervating the oral mucosa. We found that Artemin (Artn) mRNA expression in the tongue mucosa was significantly increased in BMS patients, and we have developed a mouse model of BMS by 2,4,6-trinitrobenzene sulfonic acid (TNBS) application to the tongue. TNBS treatment induced a significant increase in Artn expression and heat hyperalgesia in the tongue mucosa. The successive administration of transient receptor potential vanilloid 1 (TRPV1) antagonist or neutralizing anti-Artn antibody inhibited the heat hyperalgesia. The increased number of glial cell line-derived neurotrophic factor family receptor α-3 [Artn receptor]-IR and TRPV1-IR TG neurons innervating the tongue was significantly reduced by neutralizing anti-Artn antibody administration in the tongue mucosa. The enhanced capsaicin-induced current and afterdischarge in TG neurons innervating the tongue was inhibited by neutralizing anti-Artn antibody. These findings suggest that the overexpression of Artn in the TNBS-treated tongue causes heat hyper-responses in TG neurons via the enhancement of TRPV1 expression, resulting in tongue heat hyperalgesia. (COI:No)

3S14K1-2

Bright light activates trigeminal pathways

Okamoto Keiichiro[1,2]、Tashiro Akimasa[3]、Kurose Masayuki[1]、Yamamura Kensuke[1]、Bereiter David[2]
([1]Division Oral Physiology, Faculty of Dentistry, Niigata Univ, Niigata, Japan.、[2]University of Minnesota School of Dentistry、[3]National Defense Medical College)

Abnormal sensitivity to bright light causes discomfort and pain, and evokes protective reflexes such as lacrimation and blinking. Although the trigeminal nerve is probably involved, the mechanism linking luminance to sensory nerve activity remains uncertain. This study showed reflex circuits necessary for light to excite nociceptive neurons in trigeminal caudalis (VcC1) region where ocular sensory afferents are terminated. Ocular responsive VcC1 neurons encoded light intensity with increases in blood flow in the eye. Blockade of trigeminal root ganglion and intraocular region with lidocaine prevented VcC1 activity by light, suggesting that VcC1 activity by light required trigeminal nerve activity. Furthermore, inhibition of local vasomotor activity by intraocular injection of vasoconstrictive agents, norepinephrine, blocked light-evoked neural activity in VcC1 with decreases in blood flow, suggesting that noradrenergic mechanisms, possibly vascular reaction in the eye had critical roles for light response in VcC1. We also determined roles of superior salivatory nucleus (SSN) on light response to know possible contributions of autonomic function to VcC1 activity. Blockade of SSN activity inhibited light-evoked VcC1 activity and lacrimation. These results support the hypothesis that bright light activates trigeminal nerve pathways through intraocular mechanisms driven by a luminance-responsive circuit and increased parasympathetic outflow from SSN to the eye. (COI:No)

3S14K1-3

Orofacial stimulation-induced excitation of noradrenergic neurons in the locus coeruleus and its control of nociceptive transmission

Furue Hidemasa
(Dept Info Physiol, Nat Inst Physiol, Sci, Okazaki, Japan)

Locus coeruleus (LC) neurons in the brain stem send noradrenergic projections throughout the neuroaxis and are implicated in the control of many homeostatic functions such as arousal, focused attention and cardio-respiratory control. In addition, the LC is also a major noradrenergic nucleus to inhibit nociceptive information. We have examined how LC neurons are excited by cutaneous sensory stimuli and control nociceptive responses. LC neurons in vivo under general anesthesia elicited spontaneous action potentials. High mechanical pressure stimulation applied to the orofacial region of skin increased the firing frequency. LC neurons were more sensitive to orofacial stimulation than other region of the body such as the hind paw. Optoactivation of the LC neurons expressing ChR2 suppressed nociceptive information conveyed from the periphery by activating GABAergic interneurons. On the contrary, LC activation excited neuronal activities in the anterior cingulate cortex, which also plays an important role on a variety of functions relating to pain as well as emotional aspect of pain and pain perception. These results suggest that LC neurons in the brain stem are highly sensitive to orofacial sensory stimulation than stimulation to other body regions, and LC activation may suppress nociceptive responses coming from the periphery but enhance higher brain functions of pain. (COI:No)

3S14K1-4

Generalized sensitization and lateralized amygdala potentiation in the unilateral orofacial inflammatory pain of rats

Kato Fusao[1]、Miyazawa Yuta[1]、Sugimoto Mariko[1]、Watabe Ayako[1]、Takahashi Yukari[1]
([1]Dept Neurosci, Jikei Univ Sch Med, Tokyo, Japan、[2]Center for Neuroscience of Pain, Jikei Univ, Tokyo, Japan)

To understand the dynamic processes underlying transition from peripheral acute nociception to chronic pain, inflammatory pain model with orofacial formalin injection is useful in the following two aspects. First, unlike the intraplantar injection, the facial inflammation would not directly affect the spontaneous behaviors that depend on limb/trunk sensations. This enables various behavioral tests without direct consequences of the inflammation itself. Second, projections from the spinal trigeminal nucleus (Sp5c) are, unlike those from the spinal cord dorsal horns (DH), of bilateral nature, particularly those to the pontine lateral parabrachial nuclei (LPB), a major target of the ascending projections from both DH and Sp5c. This enables analysis of the laterality in the pain-related brain activation. We analyzed the behavior and brain activities following orofacial formalin injection after the complete fade-out of the initial acute "rubbing" behaviors and found 1) increased Fos protein expression in the bilateral LPB and in the right central amygdala (CeA) at 3 h post-injection, 2) LPB-CeA synaptic potentiation only in the right CeA at 6 h, 3) robust hypersensitivity in the bilateral hindlimb between 90 min to 72 hours and 4) changes in the spontaneous thermal preference after 90 min. Orofacial inflammation would trigger (mal)adaptive plastic changes in various regions of the brain leading to various emotional, behavioral and nociceptive consequences. (COI:No).

Society Symposium 15

Symposium in Collaboration with the Japanese Pharmacological Society

Development of novel therapeutic strategies based on the integrative physiology of metabolic regulation

March 24 (Thu), 9:00 – 10:30, Room E

3S15E1-1

Molecular mechanisms in regulating lipid storage in the liver

Adachi-Akahane Satomi、Ito Masanori、Tomida Taichiro
(Dept Physiol, Fac Med, Toho Univ, Tokyo, Japan)

Our knowledge on the intracellular and systemic mechanisms of metabolic control has been rapidly expanding. The aim of this symposium is to review late-breaking topics related to the development of novel therapeutic strategies based on the integrative physiology of metabolic regulation. Lipid droplets (LDs) regulate the storage and hydrolysis of neutral lipids, such as triacylglycerol and cholesterol esters, and thus play pivotal roles in regulating lipid metabolism. Recent progress in the studies on LD proteins and their functions has revealed that the regulation of LD metabolism and physiology is extremely dynamic, and that alterations in regulating LD function give rise to metabolic diseases such as hepatosteatosis and diabetes. In the liver, the size and number of LDs are regulated via multiple mechanisms including transport and sequestration of lipids, coalescence and expansion of LD membranes, and transfer of lipids between LDs. Specifically, phosphatidylcholine (PC), a predominant membrane phospholipid of LD, gives great influence on the coalescence and expansion of LD membranes. Therefore, local regulation of PC content may have a large impact on LD function. We have recently shown that one of PC transfer proteins, STARD10, is involved in regulating the size and number of LDs as well as lipid content in the liver. The disruption of the gene in mice prevented the development of fatty liver when fed a high-fat diet or a choline-deficient diet that is known to induce non-alcoholic steatohepatitis. We will discuss the molecular mechanisms in regulating lipid storage through lipid trafficking in the liver. (COI:No)

3S15E1-2

Neuronal network from the liver regulates systemic lipid metabolism

Uno Kenji、Katagiri Hideki
(Tohoku Univ Grad Sch Med, Sendai, Japan)

Metabolism in different tissues/organs is coordinately regulated by neuronal and humoral factors. Hepatic lipid accumulation modulates energy metabolism by enhancing energy expenditure and lipolysis in adipose tissue via neuronal network from the liver (Science 2006). However, under sustained energy excess, this endogenous system causes obesity-related hypertension (Eur Heart J 2012). Herein, we focused on the roles of hepatic amino acid (AA) signaling in the whole body metabolism. Circulating AAs are elevated in obesity and activate the mTOR/S6K pathway in the liver. Hepatic expression of an AA transporter, SNAT2, activated hepatic AA/mTOR/S6K pathway and markedly elevated serum triglycerides (TGs) in postprandial states. The hypertriglyceridemia is due to decreased TG-hydrolysis with the down-regulation of adipose LPL expression. Hepatic expression of Rheb, an mTOR signaling activator, also induced postprandial hypertriglyceridemia, and hepatic expression of DN-S6K inhibited hypertriglyceridemia in SNAT2-mice, indicating hepatic mTOR/S6K involvement. Furthermore, blockade of hepatic vagus and β-adrenergic nerves inhibited the postprandial hypertriglyceridemia and suppressed adipose LPL down-regulation in Rheb-mice. Therefore, this novel mechanism is mediated by a neuronal relay originating from the hepatic AA/mTOR/S6K signaling and is responsible for the regulation of systemic lipid metabolism. Furthermore, this inter-tissue neuronal mechanism produces inter-nutrient coordination at the whole-body level and makes an important contribution to the development of obesity-related hypertriglyceridemia (Nat Commun 2015). (COI:No)

3S15E1-3

Central insulin-mediated regulation of hepatic glucose production through vagus and Kupffer cells

Inoue Hiroshi
(InFIniti, Kanazawa Univ, Kanazawa, Japan)

Glucose intolerance in type 2 diabetes correlates with enhanced hepatic glucose production (HGP), thus understanding of the control mechanism of HGP is indispensable for the development of the treatment of type 2 diabetes. Insulin, which is the main regulatory factor of HGP, controls HGP through the direct action of hepatic insulin receptors, as well as the indirect action of insulin receptors in the hypothalamus. We have been investigating the mechanism of how central action regulates HGP and revealed that the central insulin action results in hepatic STAT3 activation, which decreases hepatic gene expression of gluconeogenic enzymes, resulting in the HGP suppression. Central insulin action suppresses the vagus nerve activity, alleviating the vagal suppression of Kupffer cells IL-6 increase and hepatic STAT3 activation.Obesity and insulin-resistance is known to impair hypothalamic insulin action, followed by the inhibition of central-insulin mediated suppression of the vagus nerve activity, which may induce persistent hepatic inflammation. Further, we have been reported that in obese mice, the low-grade proinflammatory state results in the mild increase of basal activation of Kupffer cells and blunting of acute activation response of hepatic STAT3 by IL-6. Indeed, we have revealed that STAT3-dependent suppression of hepatic gluconeogenic gene expression is depressed by hepatic ER-stress in obese mice. The impediment of central-mediated regulation of the vagus nerve may be related to both HGP increase and hepatic persistent inflammation in obesity. (COI:No)

3S15E1-4

Approaches to diabetes therapy via modulation of bile acid metabolism

Miki Takashi[1]、Lee Eun-young[1]、Sakurai Kenichi[2]、Minokoshi Yasuhiko[3]
([1]Dept Med Physiol, Grad Sch Med, Chiba Univ, Chiba,Japan、[2]Cnt Preventive Med Sci, Chiba Univ, Chiba, Japan、[3]Dpt Develop Physiol, NIPs, Okazaki, Japan)

High-fat diet (HFD) feeding triggers insulin resistance and diabetes mellitus, but its underlining mechanisms remain mostly unknown. We found that insulin receptor mutant (*Insr*$^{P1195L/+}$) mice developed overt hyperglycemia when exposed to HFD and examined the pathophysiological mechanisms. In *Insr*$^{P1195L/+}$/HFD mice, lipolysis in white adipose tissues, gluconeogenesis from glycerol, and glucose-6-phospatase (*G6pc*) expression in liver were increased. We also found that mRNA expressions of several genes involved in bile acid (BA) metabolism were altered in *Insr*$^{P1195L/+}$/HFD liver. Especially, the expression of cholesterol-7-alpha-hydroxylase (*Cyp7a1*), the rate-limiting enzyme of BA synthesis, was markedly decreased. The expression of *Cyp7a1* in liver was suppressed by glycerol administration in wild-type mice. Oral glucose loading increased *Cyp7a1* in wild-type mice but much less in much less in *Kir6.2*$^{-/-}$ mice that lacks glucose-stmulated insulin secretion, suggesting the importance of insulin on postprandial *Cyp7a1* transactivation. Supplementation of cholic acid, a primary BA, ameliorated hyperglycemia and restored *G6pc* over-expression in *Insr*$^{P1195L/+}$/HFD liver. These findings suggest that intervention to BA physiology could be a novel approach to treat diabetes mellitus. (COI:No)

Society Symposium 21

Joint Symposium with the French Society for Neuroscience

Molecular neurobiology of glutamate synapse in health and diseases

March 23 (Wed), 9:00 – 10:30, Room A

2S21A1-1

Trafficking and function of kainate receptors in physiological and epileptic conditions

Christophe Mulle

（CNRS, University of Bordeaux, Bordeaux, France.）

Although kainate receptors (KARs) display close structural homology with AMPA receptors, they serve quite distinct functions in the regulation of the activity of hippocampal synaptic circuits. In pyramidal cells of the hippocampal CA3 region, KARs show a strictly confined expression; KARs are only present at mossy fiber CA3 synapses, but not at other glutamatergic inputs to CA3. In pathophysiological conditions of temporal lobe epilepsy, mossy fiber axons form abnormal excitatory synapses onto other dentate granule cells that operate via KARs. We have explored the pathophysiological implications of these aberrant KARs in generating recurrent seizures in chronic epilepsy. In models of TLE, using a pharmacological approach and mutant mice for KAR subunits, we have found that GluK2-containing KARs play a major role in the chronic seizures that characterize TLE. We propose that KARs are recruited at these pathological synapses by similar mechanisms to those at play in physiological conditions in CA3 pyramidal cells. To address the molecular mechanisms governing the recruitment and the strict compartmentalization of KARs in CA3 cells, we have combined a quantitative gene replacement approach in hippocampal slice cultures with focal glutamate uncaging and electrophysiology. We provide evidence that multiple mechanisms cooperate to control the compartmentalization of KARs at mossy fiber-CA3 synapses, including a stringent control of the amount of GluK2 subunit in CA3 PCs, a limited number of synaptic slots for KARs, and the recruitment/stabilization of KARs by N-Cadherins through the C-terminal domain of GluK2.
(COI:No)

2S21A1-2

Postsynaptic mechanisms underlying activity-dependent adaptation of glutamate synapses

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Deciphering the intricate and interactive relationship between the information encoded in the genome and the ongoing synaptic activity is critical for understanding long-term memory formation. We found that an activity-dependent signaling cascade CaMKK-CaMKIV-pCREB and nuclear translocation of CRTC1, a CREB coactivator, critically activated a plethora of adaptive transcriptional responses within an active neuronal circuit. Through an "inverse" synaptic tagging mechanism, one of CREB's target gene, Arc, acted as a brake that helped weaken the non-potentiated synapses during the maintenance phase of synaptic plasticity. Based on the biochemistry of CaMKK activation and Arc transcription, we recently designed R-CaMP2, a new genetically encoded Ca^{2+} indicator with enhanced signal linearity and kinetics, while also creating a synthetic activity-dependent promoter E-SARE to label and manipulate active neuronal ensembles. These efforts collectively start to illuminate key molecular and cellular postsynaptic events at glutamatergic synapses that are essential in information processing in active neuronal circuits. (COI:No)

2S21A1-3

Feed-forward modulation of hippocampal mossy fiber-CA3 synaptic functions by C1q proteins

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C1q is the target recognition protein of the complement pathway in the innate immune system. Recently, many proteins that belong to the C1q family have been reported to mediate various intracellular signaling. We have shown previously that a C1q family member Cbln1 is secreted from cerebellar granule cells and plays essential roles in synapse formation and maintenance by binding to its postsynaptic receptor the delta2 glutamate receptor (GluD2) on dendritic spines of Purkinje cells. Similarly, we have shown that C1q-like 1 (C1qL1), another C1q family member, is secreted from climbing fibers (CFs) and serves as a crucial feed-forward signal to determine and maintain the single CF innervation onto cerebellar Purkinje cells by specifically binding to the brain-specific angiogenesis inhibitor 3 (Bai3), a member of the cell-adhesion G-protein-coupled receptors, expressed on postsynaptic Purkinje cells. Here, we report that C1qL2 and C1qL3, related C1q family members, are secreted from mossy fibers of dentate gyrus granule cells in the hippocampus. C1ql2/3 were localized at synaptic junctions between mossy fibers and CA3 pyramidal neurons and modulated the function of these synapses. These findings indicate that C1q family proteins serve as general feed-forward synaptic regulators in multiple neuronal circuits. (COI:No)

2S21A1-4

Excitability tuning of hippocampal mossy fiber by kainate receptor

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Kainate receptors are unique class of ionotropic glutamate receptors which localize at certain synapses in limited brain areas including hippocampal CA3 region. They are also unique in that their presynaptic actions have been suggested in the previous electrophysiological studies. These include activity-dependent modulation of transmitter release and regulation of the excitability of the axons. Since hippocampal mossy fibers are the unmyelinated axons with multiple *en passant* boutons, their excitability are expected to be affected by subtle changes in local microenvironment around the axons. Enhanced excitability of mossy fibers by activation of kainate receptors could be important mechanisms for heterosynaptic or heteroaxonal interactions as well as generation of ectopic spikes at distal axons during some pathological conditions. To identify the exact site of action of kainite receotors, we carried out a series of focal application experiments as well as uncaging experiments of caged kainate. All the results are in consistent with the notion that activation of kainate receptors enhances the excitability of distal axons in the CA3 region, although it still remains unclear whether the presynaptic actions of kainate are mediated either by direct activation of the presynaptic receptors, or by indirect actions by activation of the postsynaptic receptors or the glial receptors. It will be also shown about our recent attempts to explore the the exact mechanisms and the consequence of activation of kainate receptors using direct recordings from the single mossy fiber boutons. (COI:No)

Society Symposium 22

Symposium in Collaboration with the Japanese Society of Physical Therapy

How Can Physiology Contribute to Rehabilitation?

March 22 (Tue), 16:00 – 17:30, Room H

1S22H2-1

Changes of brain function and structure induced by motor training after brain damage

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We investigated neural plasticity that underlies the recovery of motor function after brain damage, focusing on changes that occur during the course of rehabilitative training. Our previous study in macaque monkeys showed that motor training after a lesion of the primary motor cortex (M1) plays a key role in the recovery of dexterous hand movements (Murata et al., 2008). In addition, our brain activation study using positron emission tomography (PET) revealed that the activity of the ventral premotor cortex (PMv) during dexterous hand movements increases when hand movements were restored by motor training after M1 lesion (Murata et al., 2015a). The causal role of PMv in motor recovery was confirmed by means of pharmacological inactivation by muscimol; the inactivation of PMv impaired the recovered hand movements. We also investigated structural changes of neurons that occur during the training-induced motor recovery. Gene expression of growth-associated protein-43 (GAP-43), a plasticity-related molecule whose expression is related to axonal sprouting, was increased in PMv during recovery period (Murata et al., 2015b), suggesting that structural changes occurred in axonal projections from PMv. In addition, an anatomical tracer experiment showed that the projections from PMv to subcortical structures, such as the red nucleus, were more abundant in the M1-lesioned monkeys than those in the intact monkeys. These findings suggest that both functional and structural plastic changes in PMv neurons are induced by motor training after brain damage, and the changes result in the establishment of compensatory motor pathways from PMv. (COI:No)

1S22H2-2

Activation of the cardiorespiratory system by motor imagery

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It is known that motor imagery accompanies with activation of central neurons responsible for motor preparation and programming and can be utilized for improvement of motor function. Nevertheless, the effect of motor imagery on the cardiorespiratory system has not been understood well. Since the cardiorespiratory system is activated by a central feedforward mechanism in association with voluntary exercise, mental imagery of exercise may simulate the cardiorespiratory activation in the similar way. We have investigated the influences of motor imagery on the cardiorespiratory variables and regional muscle blood flow. Motor imagery of one-legged cycling increased heart rate, blood flow of bilateral vastus lateralis muscles, and minute ventilation without changing arterial blood pressure. Although the hyperventilation resulted in a decrease of end-tidal CO2, the rise in muscle blood flow was mediated by activation of sympathetic cholinergic nerves rather than the hypocapnia. The muscle vasodilatation during motor imagery appeared to diminish in elderly subjects. These findings suggest that motor imagery stimulates the motor- and cardiorespiratory-related central circuits, leading to cardiac acceleration, muscle vasodilatation, and hyperventilation without motor execution. It is likely that aging results in attenuation of the centrally-induced cardiorespiratory activation, which may be prevented by training of motor imagery (COI:No).

1S22H2-3

Understanding distinct motor learning mechanisms with non-invasive brain stimulations

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Humans learn new motor behaviors using multiple learning mechanisms; error-based, use-dependent, reinforcement and strategic learning. These mechanisms seem to depend on different neural substrates and all of them are likely to contribute to learn new behaviors, even though some might be more weighted than others. An approach to test this framework is to determine whether neurophysiological markers of one brain region are present during learning of behaviors. In a series of experiments involving motor tasks and non-invasive brain stimulations such as transcranial magnetic stimulation and direct current stimulation, we show that long-term potentiation (LTP)-like plasticity in primary motor cortex and cerebellar excitability changes are associated with reinforcement and error-based learning mechanisms, respectively. Our findings indicate that these neurophysiological markers are useful to investigate weighted learning mechanisms underling learning motor behaviors. Furthermore, those findings provide an idea that modulating neuronal excitability in specific brain regions would enhance each learning mechanism, which could reduce the time needed to train patients with neurological conditions and speed up rehabilitation. (COI:No)

1S22H2-4

Progress of physiological studies on kinesthetic illusion induced by visual stimulus, and the clinical relevance

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A clinical prospective study was commenced to prove the effectiveness of the novel intervention on sensory-motor functional reproduction in a patient with stroke. The novel intervention is called "kinesthetic illusion induced by visual stimulus" (KiNVIS). KiNVIS is used to produce a vivid kinesthetic feeling in a healthy subject and in a patient with stroke, although the body is actually at rest. Vivid subjective kinesthesia is normally experienced in the first person during KiNVIS. Although the clinical research is in the early-stages, a positive effect has been observed on sensory-motor functioning after exercise with KiNVIS in several cases. For clinical application of this novel procedure in a patient, several physiological studies have already been reported prior to clinical studies. The first evidence of the physiological effect of KiNVIS on motor function was reported in 2007, where the enhancement of the corticospinal tract (CoST) excitation was achieved using transcranial magnetic stimulation (TMS). TMS is one of main techniques used to investigate the physiological effect of a novel maneuver on the CoST. The movement direction and body dependency on the KiNVIS effect were examined during TMS experiments. Cerebral network activity during KiNVIS was analyzed in a study that employed functional magnetic resonance imaging. The fronto-parietal network including motor association areas and other network activation were indicated. In this presentation, we will report on the physiological studies associated with KiNVIS and their clinical relevance. (COI:No)