Award Presentations

AP1 – AP2	Promotion Award of the Physiological Society of Japan for Young Scientists
AP3 – AP6	Hiroshi and Aya Irisawa Memorial Promotion Award for Young Physiologists
AP7	Hiroshi and Aya Irisawa Memorial Award for Excellent Papers in The Journal of Physiological Sciences
AP8	Hiroshi and Aya Irisawa Memorial Award for Excellent Papers on Research in Circulation in The Journal of Physiological Sciences
AP9	Aya Irisawa Memorial Promotion Award for Excellence by Women Physiologists

AP1 (1S15I2-4)

Cerebral cortex circuits for perceptual memory consolidation during sleep

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During tactile perception, long-range intracortical top-down axonal projections are essential for processing sensory information. Whether these projections regulate sleep-dependent long-term memory consolidation is unknown. We combined in vivo optogenetics and electrophysiology (Miyamoto & Murayama, Neurosci Res, 2016) to alter top-down inputs from higher order cortex to sensory cortex during sleep for examining the consolidation of memories acquired earlier during waking texture perception (Miyamoto et al., Science, 2016). Mice learned novel textures and consolidated them during sleep. Within the first hour of non-rapid eye movement (NREM) sleep, optogenetic inhibition of top-down projecting axons from secondary motor cortex (M2) to primary somatosensory cortex (S1) impaired memory reactivation of S1 neurons, and memory consolidation. In NREM sleep and sleep-deprived states, closed-loop asynchronous or synchronous M2-S1 co-activation, respectively, reduced or prolonged memory retention. Top-down cortical information flow in NREM sleep is thus required for perceptual memory consolidation. (COI:No)

AP2 (1S02B1-1)

A new strategy for imaging protein localization and dynamics in the mammalian brain

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A scalable and high-throughput method to identify precise subcellular localization of endogenous proteins is essential for integrative understanding of a cell. We have recently developed a simple and generalizable technique to image endogenous proteins with high specificity, resolution and contrast in single cells in mammalian brain tissue (Mikuni et al., *Cell* 2016). The technique, termed SLENDR (single-cell labeling of endogenous proteins by CRISPR-Cas9-mediated homology-directed repair), is based on *in vivo* genome editing to insert a sequence encoding an epitope tag or a fluorescent protein to a gene of interest by CRISPR-Cas9-mediated homology-directed repair. We demonstrate that a tag sequence can be rapidly and precisely inserted into an endogenous gene of interest *in vivo*. This method is scalable to many species of proteins in diverse cell types, and permits high-resolution protein imaging with light and electron microscopy both in fixed and live tissue. Thus, SLENDR allows researchers to rapidly and precisely determine the localization and dynamics of endogenous proteins with the resolution of micro- to nanometers in various cell types, regions and ages, providing a new level of understanding of cellular and molecular function of the brain. (COI:No)

AP3 (1S11D2-6)

In vivo cardiac nano-imaging high-resolution analysis of excitation-contraction coupling in the heart

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Cardiac pump function is a result of a rise in $[Ca^{2+}]i$ and the ensuing sarcomeric contractions (i.e., EC coupling) in myocytes in various locations of the heart. However, because of a lack of technological developments for *in vivo* analyses, our knowledge on the sub-cellular mechanisms of the physiology of the living heart remains limited. In the present study, we developed a high-speed (100 fps) high-resolution (20 nm) imaging system for myocardial sarcomeres in living mice. Using this system, we conducted three-dimensional analysis of sarcomere dynamics in left ventricular myocytes during the cardiac cycle, simultaneous with electrocardiogram and left ventricular pressure measurements. We found that (1) the working range of sarcomere length existed on the shorter resting distribution side, and (2) the left ventricular developed pressure was positively correlated with the sarcomere length change between diastole and systole ($P<0.05$). Next, we performed an analysis of $[Ca^{2+}]i$ in myocytes of isolated perfused mouse heart. We found that Ca^{2+} waves occurred in cardiomyocytes in an independent manner without electric stimulation, demonstrating that Ca^{2+}-induced Ca^{2+}-release (CICR) occurs in an independent and autonomous fashion in cardiomyocytes in the whole heart. The initial velocity of the CICR expansion was ~120 μm/s on the confocal *X-Y* plane in the myocyte, and afterwards, the Ca^{2+} wave propagated at a faster velocity in the longitudinal direction in the myocyte (~170μm/s). Based on these findings, we discuss how cardiac EC coupling is organized *in vivo*. (COI:No)

AP4 (3PS14C1-4)

Physiological and pathophysiological modeling studies of excitation conduction in the heart: prediction from changes in the subcellular Na^+ channel distribution

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The contractile function in the heart results from the accurate propagation of action potentials (APs) in cardiomyocytes. The voltage-gated sodium (Na^+) channels, playing key roles in AP initiation and propagation, alter the distribution within a myocyte in congenital and acquired heart diseases. We hypothesize that an alteration in subcellular Na^+ channel distribution may lead to the development of lethal arrhythmias. To test this hypothesis, we have proposed physiologically relevant *in silico* ventricular myofiber models where myocytes were electrically connected by both gap junctions and an electric field mechanism, the latter of which involves an interference effect between intercalated discs (IDs), in which the electrical communication between myocytes is mediated by the extracellular potential changes elicited in the intercellular cleft space facing the IDs. We have investigated the relationship between the altered subcellular Na^+ channel distribution and arrhythmogenicity through a computer simulation of AP propagation in the myofibers. In this symposium, we will present our recent simulation results and would like to discuss the proarrhythmic effects of alteration in the subcellular Na^+ channel distributions. (COI:No)

AP5

LRRC8 family is involved in volume-sensitive outwardly rectifying anion channel (VSOR) activity but not in acid-sensitive outwardly rectifying anion channel (ASOR) activity

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Volume- and acid-sensitive outwardly rectifying anion channels (VSOR and ASOR) activated by cell swelling and acidification exhibit voltage-dependent inactivation and activation time courses, respectively. Recently, LRRC8 family was shown to be essentially involved in the activity and inactivation kinetics of VSOR currents in human colonic HCT116 cells. In the present study, single and multiple gene-silencing in human cervical HeLa cells indicated that combinatory expression of LRRC8A with LRRC8D and LRRC8C is essential for VSOR activity, whereas any LRRC8 member is not involved in ASOR activity. Voltage-dependent inactivation of VSOR currents was found to become accelerated by single LRRC8A knockdown but never decelerated by single knockdown of any LRRC8 member. On the other hand, the activation kinetics of ASOR currents was affected by neither single nor multiple knockdown of any LRRC8 family member. These data suggest that LRRC8A is associated not only with VSOR activity but also with the deceleration mechanism of VSOR inactivation, whereas none of LRRC8 members is related to ASOR activity or its voltage-dependent activation mechanism. (COI:No)

AP6

Computational model harvests a crucial involvement of ion transport system of the cells exhibiting a unique electrical property in homeostatic machinery of the mammalian cochlea

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Cochlear endolymph constantly exhibits +80 mV. This endocochlear potential (EP) is essential for hearing and results from sum of four membrane potentials in lateral cochlear wall, an epithelial-like tissue comprising the outer and inner layers. Our computational model integrating ion channels and transporters identified in the two layers previously described that these ion transport mechanisms drive a unidirectional K^+ flow throughout the cochlea and this circulation current maintains the EP by regulating the membrane potentials. Recent experiments demonstrated that the basolateral surface of the outer layer exhibits an unusually positive resting membrane potential due to being more permeable to Na^+ than other ions. In the new model, we incorporated Na^+,K^+-ATPases, Na^+ conductance, and leak conductance into the basolateral surface of the outer layer. Blocking Na^+,K^+-ATPases reproduced the experimentally observed electrochemical changes in the cochlea. Therefore, the system underlying correlation of the three ion transport mechanisms plays key roles in establishing the circulation current that maintains homeostasis of the cochlear environment. (COI:No)

AP7

Reciprocal effects of capsaicin and menthol on thermo-sensation through regulated activities of TRPV1 and TRPM8

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TRPV1 antagonists such as capsazepine, BCTC and CTPC were reported to have an inhibitory effect on TRPM8. In addition, ethanol has opposite effects on TRPV1 and TRPM8: it inhibits TRPM8 whereas potentiating the activity of TRPV1. These reports suggest that the effect of chemicals on TRPV1 and TRPM8 channels are intricately related each other. We examined the effects of menthol on human TRPV1 (hTRPV1) and the effects of capsaicin on hTRPM8 using Ca^{2+}-imaging and patch-clamp methods. The hTRPV1 currents induced by capsaicin were inhibited by menthol in a dose-dependent manner. In addition, an in vivo sensory irritation test showed that menthol conferred an analgesic effect on the sensory irritation produced by VBE (vanillyl butyl ether), a TRPV1 agonist. Furthermore, we found that Y511, S512 and T550 of hTRPV1, which are binding sites of capsaicin, were little involved in the inhibitory effects by menthol. On the other hand, hTRPM8 currents induced by menthol were inhibited by capsaicin in a dose-dependent manner. Moreover, we found that Y745, which is a binding site of menthol, was slightly involved in the inhibitory effects by capsaicin. Our findings suggest that capsaicin/VBE and menthol interact with both TRPV1 and TRPM8, resepctively. The anti-nociceptive effects of menthol could be partially explained by this phenomenon. (COI: No)

AP8

Partial cavopulmonary assist from the inferior vena cava to the pulmonary artery improves hemodynamics in failing Fontan circulation: A theoretical analysis

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The effectiveness of right-sided circulatory support in patients with Fontan circulation has still been controversial. A small pump, which can be implanted within extracardiac conduit of total cavopulmonary connection, will be available owing to recent development of ventricular assist devices. In this study, we investigated the effect of cavopulmonary assist (CPA) from the inferior vena cava (IVC) to the pulmonary artery for failing Fontan circulation using a computational model. Our model consisted of time-varying elastance chamber and modified three-element Windkessel vascular models. A pump inserted between divided extracardiac conduits was described as a non-linear function of a pressure head between IVC and PA and rotational frequency. This mode of CPA was able to maintain cardiac index against the increased pulmonary vascular resistance (2.1 to 5.9 Wood Units m2). This mode reduced IVC pressure most effectively, but caused an unfavorable elevation in superior vena cava pressure. This study suggests that partial CPA from the IVC to PA may restore high IVC pressure to the lowest level and improve hemodynamics in failing Fontan circulation. (COI:No)

AP9

Biosimulation for integrative understanding of physiological functions of the body — a case study using a capillary model

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Biosimulation has become an indispensable tool for scientific research in physiology. By performing simulation experiments using mathematical models, expressed as a set of ordinary differential equations, we can observe various physiological reactions in a quantitative and explicit manner. In addition, even when those mathematical models are complicated, it may be possible to clarify the underlying mechanisms of the reactions by applying adequate mathematical analyses to them. In this presentation, we will introduce our capillary model as a case study for understanding physiological functions of the capillaries. The capillary model calculates exchange of fluids and solutes between plasma in capillary and interstitial fluids in the organ tissue, using the Starling and diffusion equations. Through this presentation, we would like to demonstrate how the use of biosimulation could facilitate integrative and intuitive understanding of dynamic physiological functions of a living system. (COI:No)