Invited Lectures

2SL07D1 March 17, 11:05–12:05, Room D1

Channel Function Reconstitution and Re-animation: Single-Channel Studies in the Post-Crystal Age

Oiki, Shigetoshi(*Department of Molecular Physiology and Biophysics, Faculty of Medical Sciences, University of Fukui*)

The most essential channel properties for the physiologically relevant function are the selective ion permeation and the gating. Electrophysiological methods combined with the site-directed mutagenesis have revealed the relevant functional domains, and underlying mechanisms of these molecular features. The strategy of ion channel study was dramatically changed after crystal structure of the potassium channel was resolved in 1998. In the post-crystal age, functional features of channel proteins have been discussed with the structural terms, and one imagines the active channel by breathing life into the "frozen" crystal (re-animation). In this context, experimental methods to detect motions of channel proteins are crucially important, and here we present single-molecule measurement methods applied to the KcsA potassium channel. The diffracted X-ray tracking method revealed that the channel undergoes the twisting conformational change around the channel axis, thus, allowing for on and off of the channel current. Using atomic force microscopy, we captured the structure of membrane-embedded channels, in which open gate was resolved exclusively in the activated condition. Molecular dynamics simulation demonstrated permeating ions and vigorous fluctuations of the open gate. Recently, we found that the KcsA channel undergoes clustering and dispersion on the membrane with concurrent gating conformational changes. These results serve an integrated picture of the active channel, and provide insights into processes underlying the physiological function of the channel on the cell membrane. No COI.

2SL08E March 17, 11:05–12:05, Room E

Role of Cerebellum in Acquisition and Storage of Motor Memory

Nagao, Soichi(*RIKEN Brain Science Institute*)

The cerebellum is not a small brain. Actually, a half number of neurons of the whole brain are contained in the cerebellum. The cerebellum receives inputs from wide areas of the brain through mossy fibers, and project to all areas of the brain via cerebellar or vestibular nuclei. As a principle of cerebellar function, Marr (1969), Albus (1971) and Ito (1970) independently proposed their hypothesis that the cerebellum controls motor system through learning using the error signals mediated through climbing fibers. The long-term depression (LTD) of parallel fiber-Purkinje cell synapses (Ito et al., 1982) is the basic synaptic mechanism for cerebellar motor learning control. Based on the Marr-Albus-Ito hypothesis, I will overview the role of the cerebellum in acquisition and storage of motor memory revealed by the study of adaptation of ocular reflexes, referring to multiple distributions of motor memories in the cerebellar cortico-nuclear circuitry. I will also address how the cerebellum contributes to voluntary movement and cognitive functions through cerebro-cerebellar network loops. No COI.

3SL10B March 18, 11:05–12:05, Room B

Systems Neurophysiology of the Control of Eye and Head Movements—Functional Synergies and Common Coordinates—

Shinoda, Yoshikazu(*Tokyo Medical and Dental University*)

Here I will review neural mechanisms underlying voluntary and vestibular control of eye and head movements based on neurophysiological and anatomical circuit analysis in higher mammals. Eye movements are hierarchically controlled by the frontal eye field (FEF), superior colliculus (SC) and brainstem saccade generators. Inhibition plays an important role at each level; saccade dynamics determined by inhibitory burst neurons, their suppression by inhibitory omnipause neurons and commissural inhibition between the SCs. The FEF is involved in a switching from saccade initiation to suppression via the SC and these neurons. Both SC and vestibular systems control similar functional synergies of eye or neck muscles and use the common coordinate system (semicircular canal coordinates). These CNS circuits provide a basis to reduce redundant degrees of freedom of the eye-head control system and control both eye and head movements (gaze) simultaneously. Studying on brain functions without understanding the underlying neural circuits is like building a castle on sand. However, since introduction of molecular biology into neuroscience, neurophysiologists engaged in unraveling of neural circuits in higher mammals have been on the verge of extinction. Although newly-developed approaches such as optogenetics and imaging are powerful and promising, it is essential to electrophysiologically identify input-output connections of the neurons recorded or manipulated for our understanding the brain functions. Until the pendulum swings back again, we, systems neurophysiologists will have to manage to survive the difficult status quo. No COI.

3SL14F March 18, 9:00–10:00, Room F

Voltage gated calcium channels as therapeutic targets for pain

Zamponi, Gerald W.(*University of Calgary*)

Voltage gated calcium channels are important mediators of depolarization inducted calcium entry into neurons, thereby triggering many important physiological functions such as neurotransmitter release and the shaping of neuronal firing properties. This is particularly evident in the afferent pain pathway where N-type and T-type calcium channels contribute to synaptic transmission in dorsal horn synapses, with T-type channels also regulating afferent fiber excitability. Under chronic pain conditions, T-type and N-type channels are upregulated in primary afferent neurons, thereby contributing to pain. Conversely, block of T-type or N-type channels via pharmacological means, or via activation of opioid receptors mediates analgesia. In my presentation, I will discuss how N-type channels can be used as pharmacological targets in chronic pain, both via direct inhibition and via activation of G protein coupled receptors. I will present evidence that association of N-type channels with certain receptors contributes to morphine tolerance. I will then describe mechanism underlying the aberrant upregulation of T-type calcium channels in chronic neuropathic and inflammatory pain, and present means by which these mechanisms can be exploited towards the development of novel therapeutic strategies. No COI.

3SL15H1 March 18, 9:00–10:00, Room H1

The unit glomerular response. Protein sensors of membrane potential

Cohen, Lawrence B.[1]; Braubach, Oliver[1]; Choi, Yunsook[2]; Storace, Doug[2]; Sung, Uhna[2]; Tombaz, Tuce[1] ([1]*Yale Univerisity,* [2]*Korea Institute of Science and Technology, Seoul*)

Understanding the roles of different neuron types requires fluorescent protein indicators that report activity with high spatio-temporal resolution. The FP voltage ArcLight consists of the voltage sensing domain of the Ciona intestinalis voltage-sensitive phosphatase and super ecliptic pHluorin A227D. The fluorescence of ArcLight decreases by 35% in response to a 100mV depolarization; about five times larger than previously reported signals. ArcLight reports odor-evoked electrical activity in the in vivo mammalian olfactory bulb using both 2-photon and wide-field imaging. When the signals from ArcLight were compared to those from the calcium sensor GCaMP3, ArcLight, but not GCaMP3, had sufficiently fast kinetics to clearly distinguish activity elicited by individual inspirations. It is difficult to selectively activate a single glomerulus using odor stimulation. We studied transgenic mice in which channelrhodopsin-2 is selectively expressed in sensory neurons which project their axons to a single glomerulus. Laser pulses reliably activated the target glomerulus and evoked calcium responses in 120-250 juxtaglomerular neurons. Most neurons (~95%) responded with increased intracellular calcium; these ON cells clustered near the target glomerulus. Other cells (~5%) responded with decreased intracellular calcium; these INHIBITED cells were more wide-spread. Supported by NIH DC005259 and the World Class Institute program of the National Research Foundation of Korea. No COI.