Symposium 9: Interplay of multiple types of plasticity in the cerebellar network
(Fri July 30, 9-11AM JST)
Chair: Sang Jeong Kim (Seoul National University College of Medicine, Korea)

9:00-9:30 Sang Jeong Kim (Seoul National University College of Medicine, Korea)
Synaptic and intrinsic plasticity coordinate the spike output in cerebellar Purkinje cells

9:30-10:00 Gen Ohtsuki (Dept Drug Discov Med, Kyoto Univ Grad Sch Med, Japan)
Intrinsic plasticity of the Purkinje-cell dendrites and immune stress

10:00-10:30 Keiko Tanaka-Yamamoto (Korea Institute of Science and Technology)
Chronic stress-induced activity alteration in VTA-projecting cerebellar neurons mediates depressive symptoms

10:30-11:00 Ying Shen (Zhejiang University, China)
MeCP2 deficiency in cerebellar Purkinje cells causes Rett syndrome phenotypes

Symposium 9 Speaker 1

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Synaptic and intrinsic plasticity coordinate the spike output in cerebellar Purkinje cells

Learning rule has been thought to be implemented by activity-dependent modifications of synaptic weight and intrinsic excitability. Here, we highlighted how long-term depression at parallel fiber to Purkinje cell synapses (PF-PC LTD) and intrinsic plasticity of PCs coordinate the postsynaptic spike output from C57BL/6 male mice. Intrinsic plasticity of PCs in flocculus matched to timing rules and shared intracellular signaling for PF-PC LTD in a conditioned branch-specific manner. In addition, neither PF-PC LTD nor intrinsic plasticity alone was not insufficiently to prominently affects to postsynaptic spike output, indicating that the synergistic modulation of spike output is supralinear manner. In conclusion, synergies between synaptic and intrinsic plasticity may achieve the optimal ranges of signal transduction into PC-targeted neurons corresponding to neuronal plasticity of the cerebellar PCs.

Symposium 9 Speaker 2:
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Intrinsic plasticity of the Purkinje-cell dendrites and immune stress

Intrinsic plasticity is the long-term modulation of intrinsic membrane excitability and possibly governs the higher brain functions. In the cerebellar Purkinje cells, three forms of intrinsic plasticity are identified: an increase and a decrease in the firing frequency of soma (Belmeguenai et al., 2010; Shim et al., 2017), and an increase in the excitability of dendrites (Ohtsuki et al., 2012). The association of non-synaptic (i.e., intrinsic plasticity) and synaptic plasticity are considered as a neurophysiological foundation of learning in the cerebellum. For instance, transgenic animals lacking in PP2B or SK2 channels show the failure of both forms of plasticity, and the impairment of motor coordination and its learning (Schonewille et al., 2010; Grasselli et al., 2020). Modulation of excitability is independently induced in the Purkinje-cell dendrites, and the branch-specific changes in the excitability segregate the transduction of synaptic current and determine whether the event goes to the soma or not. This mechanism could be a noble learning rule of the dendrites (Ohtsuki, 2020). Further, it is also revealed that intrinsic plasticity is induced by immune cells, such as microglia, in the cerebellum. Animals with acute immune activation in the cerebellar anterior vermis show depression-like behaviors and disruption of the cerebella-frontal cortical functional overconnectivity (Yamamoto et al., 2019). In contrast, both our psychiatric disease model of autism spectrum disorders and a large-scale analysis of human patients of a Japanese cohort suggested the brain-wide decreases in the functional connectivity between the cerebellum, midbrain, and frontal cortex. In this talk, I will introduce the induction of the plasticity of intrinsic excitability, mainly on the dendrites, and its involvement in the higher-order animal behaviors of psychiatric diseases.

Symposium 9 Speaker 3

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Chronic stress-induced activity alteration in VTA-projecting cerebellar neurons mediates depressive symptoms

Whereas cerebellar alterations have been implicated in stress responses and stress-associated disorders, it is not yet clear what is altered in the cerebellum upon the stressful events and how exactly the cerebellar alteration contributes to stress responses or depressive symptoms. In the present study, we demonstrated the crucial role of activity alterations in cerebellar neurons projecting to the ventral tegmental area (VTA) for the development of depressive symptoms. Our immunohistochemical analysis of c-Fos expression showed the activity increase in cerebellar neurons of the dentate nucleus (DN) by chronic stressor application that triggered depression-like behavior. We then found that chemogenetically-induced chronic activation of crus I Purkinje cells during stressor application suppressed both c-Fos expression in the DN and depression-like behavior. The combination of adeno-associated virus-based circuit mapping and electrophysiological recording identified network connections from crus I to the VTA via the DN. Furthermore, chemogenetic inhibition of activity specifically in VTA-projecting cerebellar neurons prevented stressed mice from being depressed. Interestingly, chronic excitation of these neurons alone triggered depressive symptoms without stress application. Our results indicate that chronic stress application resulted in the activation of the VTA-projecting cerebellar neurons, and such activation proactively leads to the development of depressive symptoms, raising the possibility that cerebellum may be an effective target for the prevention of depressive disorders.

Symposium 9 Speaker 4:

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MeCP2 deficiency in cerebellar Purkinje cells causes Rett syndrome phenotypes

Loss-of-function mutations of X-linked MeCP2 (methyl-CpG binding protein 2) cause the pervasive Rett syndrome (RTT). RTT patients show progressive loss of motor and cognitive functions, impaired social interactions, anxiety, and seizure at young ages. While studies using mouse models of RTT have demonstrated that loss of MeCP2 causes impaired circuit development and neuronal dysfunction in the hippocampus and cortex, the roles of MeCP2 and the sequelae of MeCP2 dysfunction in the cerebellum have not been investigated. Here we show that loss-of-function mutations of MeCP2 led to cerebellar dysfunction and autistic-like behavior. The typical RTT mouse model, MeCP2308/Y mice, displayed abnormal motor performance, showing defects in footprint and rotarod test as early as two month after birth. These mutant mice also showed impaired synaptic transmission and plasticity at parallel fiber-Purkinje cell (PC) synapses. More interestingly, homozygous loss of MeCP2 in PCs results in autistic-like behaviors, including abnormal social interaction and repetitive behavior, in addition to changed PC excitability, synaptic transmission and plasticity. Our findings demonstrate new roles for MeCP2 in PC function and define a molecular basis for a cerebellar contribution to RTT.