Japan Academy Prize to:

Masayoshi Mishina
Professor, The Research Organization of Science and Technology, Ritsumeikan University
Emeritus Professor, The University of Tokyo

for “Studies on Synaptic Molecules, Learning and Memory”

Outline of the work:

Acquiring new knowledge is one of the most important functions of our brain. Brain functions are based on precise synaptic connections between nerve cells. It has been proposed that synaptic plasticity, the activity-dependent change in the efficacy of synaptic transmission, underlies learning and memory. Glutamate receptors mediate excitatory synaptic transmission in the brain and the N-methyl-D-aspartate (NMDA)-type glutamate receptor plays a key role in induction of synaptic plasticity. Prof. Masayoshi Mishina elucidated the molecular and functional diversity of the NMDA receptor by the finding of four glutamate-binding subunits. He identified a voltage-dependent Mg\(^{2+}\)-block site of the NMDA receptor that is essential for the coincidence detector function to induce long-term potentiation (LTP). Furthermore, Prof. Mishina found that NMDA receptor GluRε1 knockout mice showed a reduction of NMDA receptor currents at hippocampal synapses and increases of thresholds for both hippocampal LTP induction and contextual learning. These findings suggest that the NMDA receptor serves as a molecular basis of learning and memory.

Prof. Mishina also found a new member of the glutamate receptor family by molecular cloning, designated as GluRδ. GluRδ2 is selectively expressed in cerebellar Purkinje cells and is exclusively localized at parallel fiber synapses. He showed that GluRδ2 mutant mice exhibited impairments of long-term depression (LTD) at parallel fiber-Purkinje cell synapses and eye blink conditioning. These results suggest that GluRδ2 regulates cerebellar synaptic plasticity and motor learning. Furthermore, Prof. Mishina found that mutant mice lacking Delphilin, which interacts with GluRδ2 at the carboxyl-terminal domain, showed enhancements of both LTD induction and adaptation of optokinetic responses. Since Delphilin is selectively localized at parallel fiber-Purkinje cell synapses, these findings suggest that cerebellar synaptic plasticity regulates the adaptation of optokinetic responses, a motor learning, as a rate-limiting step.

At the same time, Prof. Mishina found that NMDA receptor GluRε2 knockout mice failed to survive after birth due to the defect of suckling response and exhibited the impairment of whisker-related barrelette formation in the trigeminal ganglion. He also showed that whisker-related barrel formation in the sensory cortex was delayed in heterozygous GluRε2 knockout mice, while it was stimulated in GluRε4 knockout mice. These observations suggest that the NMDA receptor plays a role in neuronal network formation during development. Prof. Mishina also found the appearance of numerous free spines lacking synaptic contacts in cerebellar Purkinje cells and striking decrease of parallel fiber-Purkinje cell synapses in GluRδ2 knockout mice. He further showed that the ablation of GluRδ2 in the adult brain resulted in the shrinkage of the active zone according to the decrease of GluRδ2 proteins at parallel fiber-Purkinje cell synapses and appearance of free spines in Purkinje cells. These findings suggest that GluRδ2 is essential for the formation and maintenance of parallel fiber-Purkinje cell synapses.

Prof. Mishina further found that GluRδ2 induced the axon terminal differentiation of cerebellar granule
cells through its amino-terminal domain, while the carboxyl-terminal truncation of GluRδ2 resulted in impairments of LTD induction and motor learning in mutant mice without affecting synapse formation. He thus showed that GluRδ2 regulates synaptic plasticity and learning through the carboxyl-terminal domain and synapse formation through the amino-terminal domain. These findings suggest that GluRδ2 is a molecule that bridges synapse formation and learning. Furthermore, Prof. Mishina revealed that postsynaptic GluRδ2 induces synapse formation by trans-synaptic interaction with presynaptic neurexins through secreted Cbln1.

Prof. Mishina also found that IL1-receptor accessory protein-like 1 (IL1RAPL1) responsible for intellectual disabilities induces excitatory synapse formation of cortical neurons through trans-synaptic interaction with presynaptic protein tyrosine phosphatase δ. He further showed that IL1RAPL1 knockout mice exhibited the decrease of cortical spine density and impairments of working and reference memories in several learning tests.

Finding of Prof. Mishina that molecules regulating synaptic plasticity and synapse formation underlie learning and memory is in good agreement with reports that mutations in the human genes encoding these molecules are responsible for intellectual disabilities. The achievements of Prof. Mishina in elucidation of the molecular basis of learning and memory are appreciated in the world.

List of Publications

15. Uemura, T, Kakizawa, S, Yamasaki, M, Sakimura, K, Watanabe, M, Iino, M, and Mishina, M; Regulation of long-term depression and climbing fiber territory by glutamate receptor δ2 at parallel fiber synapses through its C-terminal domain in cerebellar Purkinje cells. J. Neurosci. 27; 12096–12108, 2007.