Department of Basic Medical Sciences

Division of Neuronal Network
神経ネットワーク分野

Professor	Toshiya Manabe, M.D., Ph.D.	教　授	医学博士	真　鍋　俊　也
Project Associate Professor	Naoto Matsuda, M.D., Ph.D.	特任准教授	医学博士	松　田　尚　人
Assistant Professor	Hiroyuki Katagiri, Ph.D.	助　教	医学博士	片　桐　大　之
Assistant Professor	Yuji Kiyama, Ph.D.	助　教	医学博士	城　山　優　治
Assistant Professor	Shizuka Kobayashi, Ph.D.	助　教	生命科学博士	小　林　静　香

Our major research interest is the molecular mechanisms of higher brain functions in mammals such as emotion, and learning and memory. We are especially focusing on the roles of functional molecules localized in synapses, for instance, neurotransmitter receptors, signal transduction molecules and adhesion molecules, in neuronal information processing. We are examining receptor functions, synaptic transmission and plasticity, and their roles in the whole animal with electrophysiological, biochemical, molecular genetic and behavioral approaches.

1. Point mutation in syntaxin-1A causes abnormal vesicle recycling, behaviors, and short-term plasticity

Norikazu Katayama, Yumi Watanabe[1], Tetsuya Togano[1,2], Michiko Sato[1], Kosei Takeuchi[1,3], Maya Yamazaki[4], Manabu Abe[4], Toshiya Sato[5], Kanako Oda[5], Minesuke Yokoyama[5], Kenji Sakimura[4], Michihiro Igarashi[1,3] and Toshiya Manabe: Departments of [1]Neurochemistry and Molecular Cell Biology and [2]Ophthalmology, Graduate School of Medical and Dental Sciences, [3]Transdiciplinary Research Program, Departments of [4]Cellular Neurobiology and [5]Experimental Animal Resource, Brain Research Institute, Niigata University

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is an important modulator of neural plasticity. CaMKII is a major protein component not only of postsynaptic densities but also of presynaptic terminals; therefore, CaMKII is likely to mediate presynaptic plasticity via regulation of the exocytotic machinery. Previously, we found that autophosphorylated CaMKII interacts with syntaxin-1A to regulate exocytosis and that a syntaxin missense mutation [R151G] severely attenuated exocytosis. To more precisely analyze the physiological importance of this interaction, we generated mice with a knock-in (KI) syntaxin-1A [R151G] mutation. These KI mice exhibited abnormal presynaptic short-term plasticity in electrophysiological examinations. Biochemically, these mice exhibited reduced recruitment of complexin, which is known to modulate exocytosis, to the SNARE complex via the CaMKII-syntaxin interaction. These results indicate that presynaptic CaMKII plays an important role in the expression of short-term plasticity through the interaction with syntaxin-1A, which regulates the exocytotic mechanisms directly.

2. LMTK3 deficiency causes pronounced locomotor hyperactivity and impairs endocytic trafficking

Yuji Kiyama, Shizuka Kobayashi, Takeshi Inoue[6], Naosuke Hoshina[6,7], Takanobu Nakazawa[6], Takaya Abe[8], Toshifumi Yamamoto[9], Tadashi Yamamoto[6,7] and Toshiya Manabe: [6]Division of Oncology, Institute of Medical Science, University of Tokyo, [7]Cell Signal Unit, Okinawa Institute of Science and

Technology, [8]Laboratory for Animal Resources and Genetic Engineering, RIKEN Center for Developmental Biology, [9]Laboratory of Molecular Recognition, Graduate School of Arts and Sciences, Yokohama City University

LMTK3 belongs to the LMTK family of protein kinases that are predominantly expressed in the brain. Physiological functions of LMTK3 and other members of the LMTK family in the central nervous system remain unknown. In this study, we performed a battery of behavioral analyses using *Lmtk3*$^{-/-}$ mice and showed that these mice exhibited abnormal behaviors, including pronounced locomotor hyperactivity, reduced anxiety behavior, and decreased depression-like behavior. Concurrently, the dopamine metabolite levels and dopamine turnover rate were increased in the striata of *Lmtk3*$^{-/-}$ mice compared with wild-type controls. In addition, using cultured primary neurons from *Lmtk3*$^{-/-}$ mice, we found that LMTK3 was involved in the endocytic trafficking of *N*-methyl-D-aspartate receptors, a type of ionotropic glutamate receptor. Altered membrane traffic of the receptor in *Lmtk3*$^{-/-}$ neurons may underlie behavioral abnormalities in the mutant animals. Taken together, our data suggest that LMTK3 plays an important role in regulating locomotor behavior in mice.

3. The glutamate receptor GluN2 subunit regulates synaptic trafficking of AMPA receptors in the neonatal mouse brain

Shun Hamada, Itone Ogawa, Yuji Kiyama, Ayako M. Watabe, Miwako Yamasaki[10], Hidetoshi Kassai[11,12], Kazuki Nakao[11,13], Atsu Aiba[11,12], Masahiko Watanabe[10] and Toshiya Manabe: [10]Department of Anatomy, Hokkaido University Graduate School of Medicine, [11]Laboratory of Animal Resources, Center for Disease Biology and Integrative Medicine, Faculty of Medicine, University of Tokyo, [12]Division of Molecular Genetics, Kobe University Graduate School of Medicine, [13]Laboratory for Animal Resources and Genetic Engineering, Center for Developmental Biology, RIKEN

The N-methyl-D-aspartate receptor (NMDAR) plays various physiological and pathological roles in neural development, synaptic plasticity and neuronal cell death. It is composed of two GluN1 and two GluN2 subunits, and in the neonatal hippocampus, most synaptic NMDARs are GluN2B-containing receptors, which are gradually replaced with GluN2A-containing receptors during development. Here, we examined whether GluN2A could be substituted for GluN2B in neural development and functions by analyzing knock-in (KI) mice in which GluN2B is replaced with GluN2A. The KI mutation was neonatally lethal, although GluN2A-containing receptors were transported to the postsynaptic membrane even without GluN2B and functional at synapses of acute hippocampal slices of postnatal day 0 (P0), indicating that GluN2A-containing NMDARs could not be substituted for GluN2B-containing NMDARs. Importantly, the synaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) subunit GluA1 was increased, and the transmembrane AMPAR regulatory protein (TARP) and synaptic Ras-GTPase activating protein (SynGAP), which are both involved in AMPAR synaptic trafficking, were increased and decreased, respectively, in KI mice, whereas calcium/calmodulin-dependent protein kinase IIα (CaMKIIα) was not involved in the increase of GluA1. Although the regulation of AMPARs by GluN2B has been reported in cultured neurons, we showed here that AMPAR-mediated synaptic responses were increased in acute KI slices, suggesting differential roles of GluN2A and GluN2B in AMPAR expression and trafficking *in vivo*. Taken together, our results suggest that GluN2B is essential for the survival of animals and that the GluN2B-GluN2A switching plays a critical role in synaptic integration of AMPARs through regulation of GluA1 in the whole animal.

Publications

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