Department of Basic Medical Sciences

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

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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. We are also trying to elucidate fundamental aspects of psychiatrical and neurological disorders using model animals.

1. The role of active zone protein CAST in the regulation of synaptic vesicle recycling and quantal size in the mouse hippocampus

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Synaptic efficacy is determined by various factors, including the quantal size, which is dependent on the amount of neurotransmitters in synaptic vesicles at the presynaptic terminal. It is essential for stable synaptic transmission that the quantal size is kept within a constant range and that synaptic efficacy during and after repetitive synaptic activation is maintained by replenishing release sites with synaptic vesicles. However, the mechanisms for these fundamental properties have still been undetermined. We found that the active zone protein CAST (cytomatrix at the active zone structural protein) played pivotal roles in both presynaptic regulation of quantal size and recycling of endocytosed synaptic vesicles. In the CA1 region of hippocampal slices of the CAST knockout mice, miniature excitatory synaptic responses were increased in size and synaptic depression after prolonged synaptic activation was larger, which was attributable to selective impairment of synaptic vesicle trafficking via the endosome in the presynaptic terminal likely mediated by Rab6. Therefore, CAST serves as a key molecule that regulates dynamics and neurotransmitter contents of synaptic vesicles in the excitatory presynaptic terminal in the central nervous system.

2. The role of IL-1Ra in the regulation of anxiety-like behavior by aging in mice

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Interleukin 1 (IL-1) plays a critical role in stress responses, and its mRNA is induced in the brain by restraint stress. Previously, we reported that IL-1 receptor antagonist (IL-1Ra) knockout (KO) mice, which lacked IL-1Ra molecules that antagonize the IL-1 receptor, showed anti-depression-like behavior via adrenergic modulation at the age of 8 weeks. We have found that IL-1Ra KO mice display an anxiety-like phenotype that is induced spontaneously by aging in the elevated plus-maze test. This anxiety-like phenotype was improved by the administration of diazepam. The expression of the anxiety-related molecule glucocorticoid receptor was significantly reduced in 20-week-old but not in 11-week-old IL-1Ra KO mice compared to WT littermates. The expression of the mineralocorticoid receptor was not different between IL-1Ra KO mice and their WT littermates at either 11 or 20 weeks old. Analysis of monoamine concentration in the hippocampus revealed that tryptophan, the serotonin metabolite 5-hydroxyindole acetic acid and the dopamine metabolite homovanillic acid were significantly increased in 20-week-old IL-1Ra KO mice compared to their littermate WT mice. These findings strongly suggest that the anxiety-like behavior observed in older mice was caused by the complicated alteration of monoamine metabolism and/or glucocorticoid-receptor expression in the hippocampus.

3. The roles of ARHGAP33 in intracellular trafficking of TrkB and pathophysiology of neuropsychiatric disorders

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Intracellular trafficking of receptor proteins is essential for neurons to detect various extracellular factors during the formation and refinement of neural circuits. However, the precise mechanisms underlying the trafficking of neurotrophin receptors to synapses remain elusive. We have found that a brain-enriched sorting nexin, ARHGAP33, is a new type of the regulator for the intracellular trafficking of TrkB, a high-affinity receptor for brain-derived neurotrophic factor. ARHGAP33 KO mice exhibit reduced expression of synaptic TrkB, impaired spine development and neuropsychiatric disorder-related behavioral abnormalities. These deficits are rescued by specific pharmacological enhancement of TrkB signaling in ARHGAP33 KO mice. Mechanistically, ARHGAP33 interacts with SORT1 to cooperatively regulate TrkB trafficking. Human ARHGAP33 is associated with brain phenotypes and reduced SORT1 expression is found in patients with schizophrenia. We propose that ARHGAP33/SORT 1-mediated TrkB trafficking is essential for synapse development and that the dysfunction of this mechanism may be a new molecular pathology of neuropsychiatric disorders.

4. Autism-like disorders observed in Jacobsen syndrome may be caused by impaired $GABA_A$-receptor trafficking regulated by PX-RICS

Fumiko Arima-Yoshida, Tsutomu Nakamura[19], Fumika Sakaue[19], Yukiko Nasu-Nishimura[19], Yasuko Takeda[19], Ken Matsuura[19], Natacha Akshoomoff[20], Sarah N. Mattson[21], Paul D. Grossfeld[22], Tetsu Akiyama[19] and Toshiya Manabe: [19]Laboratory of Molecular and Genetic Information, Institute of Molecular and Cellular Biosciences, University of Tokyo, [20]Department of Psychiatry, School of Medicine, University of California, San Diego, USA, [21]Department of Psychology, San Diego State University, USA, [22]Department of Pediatrics, School of Medicine, University of California, San Diego, USA.

Jacobsen syndrome (JBS) is a rare congenital disorder caused by a terminal deletion of the long arm of chromosome 11. A subset of patients exhibit social behavioral problems that meet the diagnostic criteria for autism spectrum disorder (ASD); however, the underlying molecular pathogenesis remains poorly understood. *PX-RICS* is located in the chromosomal region commonly deleted in JBS patients with autism-like behavior. We have found that *PX-RICS*-deficient mice exhibit ASD-like social behaviors and ASD-related comorbidities. *PX-RICS*-deficient neurons show reduced surface γ-aminobutyric acid type A receptor ($GABA_AR$) levels and impaired $GABA_AR$-mediated synaptic transmission. PX-RICS, GABARAP and 14-3-3ζ/θ form an adaptor complex that interconnects $GABA_AR$ and dynein/dynactin, thereby facilitating $GABA_AR$ surface expression. ASD-like behavioral abnormalities in *PX-RICS*-deficient mice are ameliorated by enhancing inhibitory synaptic transmission with a $GABA_AR$ agonist. Our findings demonstrate a critical role of PX-RICS in cognition and suggest a causal link between *PX-RICS* deletion and ASD-like behavior in JBS patients.

Publications

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