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.

1. Age-dependent regulation of depression-like behaviors through modulation of adrenergic receptor α_{1A} subtype expression revealed by the analysis of IL-1Ra knockout mice

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Interleukin-1 (IL-1) plays a crucial role in stress responses and its mRNA is induced in the brain by stress load; however, the precise role of IL-1 in higher brain functions and their abnormalities is largely unknown. Here, we report that IL-1 receptor antagonist (IL-1Ra) knockout (KO) mice, which lack IL-1Ra molecules that antagonize the IL-1 receptor, displayed anti-depression-like phenotypes in the tail-suspension test (TST) and forced-swim test (FST) only at a young stage (8 weeks), whereas the phenotypes disappeared at later stages (20 and 32 weeks). These anti-depression-like phenotypes were reversed by administration of adrenergic receptor (AR) antagonists against the ARα_1, ARα_2 and ARβ subtypes. Although the contents of 5-hydroxytryptamine, norepinephrine and dopamine, which are known to be associated with major symptoms of psychiatric disorders, were not significantly different in the hippocampus or cerebral cortex between IL-1Ra KO and their wild-type littermate mice, the mRNA expression level of the ARα_{1A} subtype was significantly changed in the cerebral cortex. Interestingly, the change in expression of the ARα_{1A} subtype was correlated with an age-dependent alteration in the TST and FST in IL-1 Ra KO mice. Furthermore, mild immobilization stress loaded on C57BL/6J control mice caused similar anti-depression-like phenotypes in the TST and FST to those observed in mutant mice. These results suggest that sustained activation of IL-1 signaling induced by gene manipulation in mutant mice affects the expression of the ARα_{1A} subtype and that modification of adrenergic signaling by the IL-1 system may ultimately cause significant psychiatric abnormalities such as depression, and this mutant mouse could be

regarded as a model animal of depression that specifically appears in children and adolescents.

2. The mechanisms of the strong inhibitory modulation of long-term potentiation in the rat dentate gyrus

Fumiko Arima-Yoshida, Ayako M. Watabe and Toshiya Manabe

The hippocampus is essential for the formation of certain types of memory, and synaptic plasticity such as long-term potentiation (LTP) is widely accepted as a cellular basis of hippocampus-dependent memory. Although LTP in both perforant path-dentate gyrus (DG) granule cell and CA3-CA1 pyramidal cell synapses is similarly dependent on activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors, several reports suggest that modulation of LTP by γ-aminobutyric acid (GABA) receptor-mediated inhibitory inputs is stronger in perforant path-DG granule cell synapses. However, little is known about how different the mechanism and physiological relevance of the GABAergic modulation of LTP induction among different brain regions are. We confirmed that the action of $GABA_A$-receptor antagonists on LTP was more prominent in the DG, and explored the mechanism introducing such difference by examining two types of $GABA_A$ receptor -mediated inhibition, synaptic and tonic inhibition. As synaptic inhibition, we compared inhibitory versus excitatory monosynaptic responses and their summation during an LTP-inducing stimulus, and found that the balance of the summated postsynaptic currents was biased toward inhibition in the DG. As tonic inhibition, or sustained activation of extrasynaptic $GABA_A$ receptors by ambient GABA, we measured the change in holding currents of the postsynaptic cells induced by $GABA_A$-receptor antagonists, and found that the tonic inhibition was significantly stronger in the DG. Furthermore, we found that tonic inhibition was associated with LTP modulation. Our results suggest that both the larger tonic inhibition and the larger inhibitory/excitatory summation balance during conditioning are involved in the stronger inhibitory modulation of LTP in the DG.

3. Specific regulation of spatial memory and pattern separation by plexin-A2 through structural modification of mossy fiber projection in the CA3 region of the mouse hippocampus

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The hippocampus has been implicated in certain types of memory, including spatial memory. It has been known that the distribution of mossy fibers, axons of dentate-gyrus granule cells, is modified dynamically by spatial learning in living animals. However, the precise mechanism of the regulation of mossy fiber distribution during memory formation is not well understood. We have previously reported that plexin-A2 (PlxnA2), one of the type A plexins that mediate repulsive activities of the class 6 semaphorins, regulates the distribution of mossy fiber terminals in the CA3 region and that the mutant mice lacking PlxnA2 (*PlxnA2-/-* mice) exhibit a shift of mossy fibers from the suprapyramidal to the infra- and intrapyramidal regions. In order to test whether the difference in the distribution of mossy fiber terminals affects abilities of learning and memory, we have performed extensive behavioral analyses of *PlxnA2-/-* mice. We found that sensorimotor reflexes and emotional behaviors of *PlxnA2-/-* mice were normal, although motor learning and swimming abilities were markedly impaired presumably through aberrant distribution of cerebellar granule cells, and that contextual and auditory fear conditioning, which is at least partially dependent on the hippocampus, was also intact. In contrast, *PlxnA2-/-* mice exhibited enhanced hippocampus-dependent spatial reference memory and spatial pattern separation, which is the ability to discriminate fine differences in external environments, tested by the 8-arm radial-maze task. These results suggest that the projection of mossy fibers regulated by PlxnA2 may be a specific determinant of the ability of spatial reference memory and pattern separation.

4. Functional coupling of the metabotropic glutamate receptor, inositol triphosphate receptor and L-type Ca^{2+} channel in mouse CA1 pyramidal cells

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Activity-dependent regulation of calcium dynamics in neuronal cells can play significant roles in the modulation of many cellular processes such as intracellular signaling, neuronal

activity and synaptic plasticity. Among many calcium influx pathways into neurons, the voltage-dependent calcium channel (VDCC) is the major source of calcium influx, but its modulation by synaptic activity has still been under debate. While the metabotropic glutamate receptor (mGluR) is supposed to modulate L-type VDCCs (L-VDCCs), its reported actions include both facilitation and suppression, probably reflecting the uncertainty of both the molecular targets of the mGluR agonists and the source of the recorded calcium signal in previous reports. In this study, using subtype-specific knockout mice, we have shown that mGluR5 induces facilitation of the depolarization-evoked calcium current. This facilitation was not accompanied by the change in single-channel properties of the VDCC itself; instead, it required the activation of calcium-induced calcium release (CICR) that was triggered by VDCC opening, suggesting that the opening of CICR-coupled cation channels was essential for the facilitation. This facilitation was blocked or reduced by the inhibitors of both L-VDCCs and inositol triphosphate receptors (IP3Rs). Furthermore, L-VDCCs and mGluR5 were shown to form a complex by coimmunoprecipitation, suggesting that the specific functional coupling between mGluR5, IP3Rs and L-VDCCs played a pivotal role in the calcium-current facilitation. Finally, we showed that mGluR5 enhanced VDCC-dependent long-term potentiation (LTP) of synaptic transmission. Our study has identified a novel mechanism of the interaction between the mGluR and calcium signaling, and suggested contribution of mGluR5 to synaptic plasticity.

5. Dynamic development of the first synapse impinging on adult-born neurons in the olfactory bulb circuit

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The olfactory bulb (OB) receives and integrates newborn interneurons throughout life. This process is important for the proper functioning of the OB circuit and consequently, for the sense of smell. Although we know how these new interneurons are produced, the way in which they integrate into the pre-existing ongoing circuits remains poorly documented. Bearing in mind that glutamatergic inputs onto local OB interneurons are crucial for adjusting the level of bulbar inhibition, it is important to characterize when and how these inputs from excitatory synapses develop on newborn OB interneurons. We studied early synaptic events that lead to the formation and maturation of the first glutamatergic synapses on adult-born granule cells (GCs), the most abundant subtype of OB interneuron. Patch-clamp recordings and electron microscopy (EM) analysis were performed on adult-born interneurons shortly after their arrival in the adult OB circuits. We found that both the ratio of N-methyl-D-aspartate receptor (NMDAR) to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and the number of functional release sites at proximal inputs reached a maximum during the critical period for the sensory-dependent survival of newborn cells, well before the completion of dendritic arborization. EM analysis showed an accompanying change in postsynaptic density shape during the same period of time. Interestingly, the latter morphological changes disappeared in more mature newly-formed neurons, when the NMDAR to AMPAR ratio had decreased and functional presynaptic terminals expressed only single release sites. Together, these findings show that the first glutamatergic inputs to adult-generated OB interneurons undergo a unique sequence of maturation stages.

6. Dysfunction of the RAR/RXR signaling pathway in the forebrain impairs hippocampal memory and synaptic plasticity.

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Retinoid signaling pathways mediated by retinoic acid receptor (RAR)/retinoid X receptor (RXR)-mediated transcription play critical roles in hippocampal synaptic plasticity. Furthermore, recent studies have shown that treatment with retinoic acid alleviates age-related deficits in hippocampal long-term potentiation (LTP) and memory performance and, furthermore, memory deficits in a transgenic mouse model of Alzheimer's disease. However, the roles of the RAR/RXR signaling pathway in learning and memory at the behavioral level have still not

been well characterized in the adult brain. We here show essential roles for RAR/RXR in hippocampus-dependent learning and memory. In the current study, we generated transgenic mice in which the expression of dominant-negative RAR (dnRAR) could be induced in the mature brain using a tetracycline-dependent transcription factor and examined the effects of RAR/RXR loss. The expression of dnRAR in the forebrain down-regulated the expression of RARβ, a target gene of RAR/RXR, indicating that dnRAR mice exhibit dysfunction of the RAR/RXR signaling pathway. Similar with previous findings, dnRAR mice displayed impaired LTP and AMPA receptor-mediated synaptic transmission in the hippocampus. More importantly, these mutant mice displayed impaired hippocampus-dependent social recognition and spatial memory. However, these deficits of LTP and memory performance were rescued by stronger conditioning stimulation and spaced training, respectively. Finally, we found that pharmacological blockade of RARα in the hippocampus impairs social recognition memory. From these observations, we concluded that the RAR/RXR signaling pathway greatly contributes to learning and memory, and LTP in the hippocampus in the adult brain.

Publications

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