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. Plexin-A2 regulates spatial memory and pattern separation 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 (DG) 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 (PLA2), one of the type A plexins that show repulsive activities to the class 6 semaphorins, regulates the distribution of mossy fiber terminals in the CA3 region and that the mutant mice lacking PLA2 (PLA2$^{-/-}$ 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 PLA2$^{-/-}$ mice. We found that sensorimotor functions and emotional behaviors of PLA2$^{-/-}$ mice were normal, although motor learning was 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, PLA2$^{-/-}$ 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 PLA2 may be a specific determinant of the ability of spatial reference memory and pattern separation.

2. Tyrosine phosphorylation of the GluN2B subunit of NMDA receptors regulates anxiety-like behavior and CRF expression in the amygdala

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Anxiety disorders are a highly prevalent and disabling class of psychiatric disorders. There is growing evidence implicating the glutamate system in the pathophysiology and treatment of anxiety disorders, though the molecular mechanism by which the glutamate system regulates anxiety-like behavior remains unclear. In this study, we provide evidence suggesting that tyrosine phosphorylation of the NMDA receptor, an ionotropic glutamate receptor, contributes to anxiety-like behavior. The GluN2B subunit of the NMDA receptor is tyrosine-phosphorylated: Tyr-1472 is the major phosphorylation site. Homozygous knock-in mice that express a Tyr-1472 -Phe mutant of GluN2B, which prevents phosphorylation of this site, show enhanced anxiety-like behavior in the elevated plus-maze test. Expression of corticotropin-releasing factor (CRF), which is important for the regulation of anxiety-like behavior, is increased in the amygdala of the knock-in mice. Furthermore, injection of CRF-receptor antagonists attenuates the enhanced anxiety-like behavior of the knock-in mice. We also show that elevated plus-maze exposure simultaneously induces dephosphorylation of Tyr-1472 and increased CRF expression. These data suggest that Tyr-1472 phosphorylation on GluN2B is important for anxiety-like behavior by negative regulation of CRF expression in the amygdala.

3. Age-dependent regulation of depression-like behavior by interleukin-1 through modification of adrenergic signaling

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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 the administration of adrenergic receptor (AR) antagonists against the $AR\alpha_1$, $AR\alpha_2$, 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 $AR\alpha_{1A}$ subtype was significantly changed in the cerebral cortex. Interestingly, the change in the expression of the $AR\alpha_{1A}$ subtype was correlated with an age-dependent alteration in the TST and FST in IL-1 Ra KO mice. These results suggest that sustained activation of the IL-1 signaling induced by gene manipulation in mutant mice affects the expression of the $AR\alpha_{1A}$ subtype and that modification of the 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.

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

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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 mecha-

nism 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.

5. Functional coupling of the metabotropic glutamate receptor 5, IP_3 receptor and L-type calcium channel: A role in regulation of calcium dynamics and synaptic plasticity.

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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, voltage-dependent calcium channels (VDCCs) are the major source of calcium influx, but their modulation by synaptic activity has still been under debate. While metabotropic glutamate receptors (mGluRs) are supposed to modulate L-type VDCCs (L-VDCCs), their reported effects include both facilitation and suppression, probably reflecting the uncertainty of both the molecular targets of the agonists and the source of the recorded calcium signals in those previous reports. In this study, using subtype-specific knockout mice, we have clearly shown the mGluR 5-induced facilitation of the depolarization-evoked calcium currents. This facilitation was not accompanied by the change in the single-channel properties of VDCC itself; instead, it was caused by the activation of calcium-induced calcium release that is triggered by VDCC opening. This effect was blocked by the inhibitors of both L-VDCCs and IP_3 receptors (IP_3Rs), suggesting the specific functional coupling between the mGluR5, IP_3R and L-VDCC. Furthermore, we have shown the mGluR5-mediated enhancement of VDCC-dependent long-term potentiation of excitatory synaptic transmission. Our data identify a novel mechanism of the interaction between the mGluR and calcium signaling, and suggest a possible contribution of mGluR5 in synaptic plasticity.

Publications

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