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. Inhibitory modulation of synaptic plasticity is stronger in the dentate gyrus than in the CA1 region of the hippocampus.

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

Long-term potentiation (LTP) is a phenomenon that the efficacy of synaptic transmission is enhanced after high-frequency activation of the synapse. It was first discovered in the hippocampus, and it has been widely accepted as a cellular basis of certain forms of memory. In the medial perforant pathway-dentate gyrus granule cell synapse and in the CA3-CA1 pyramidal cell synapse, LTP is induced by a similar mechanism (postsynaptic N-methyl-D-aspartate receptor dependent), while several reports suggested that the modulation of LTP by γ-aminobutyric acid type A ($GABA_A$) receptor-mediated inhibitory inputs is stronger in the medial perforant pathway-dentate gyrus granule cell synapse. To explore the underlying molecular mechanism that makes the difference between the two regions, we compared LTP in the presence of the $GABA_A$ receptor antagonist picrotoxin with LTP in its absence in the CA1 region and in the dentate gyrus using acute slices of the rat hippocampus. We then compared the inhibitory monosynaptic responses with excitatory monosynaptic responses, and also compared their summation during an LTP-inducing stimulus between the two regions. Our results suggest that the stronger inhibitory modulation of LTP in the dentate gyrus may be due to the balance biased towards inhibition between the summated inhibitory and excitatory postsynaptic currents during conditioning in the dentate gyrus. Besides these examinations of synaptic inhibitory inputs, several reports suggested that continuous activation of extrasynaptic $GABA_A$ receptors by ambient GABA is different in several aspects between the two regions, which could also contribute to the finding about LTP modulation as well. For example, it is reported that continuous activation of extrasynaptic $GABA_A$ receptors is mediated by the receptor with different subunit compositions between the two regions, which may result in different properties of the inhibition. Thus, we are currently

examining whether this kind of inhibition is associated with the stronger inhibitory modulation of LTP in the dentate gyrus using the whole-cell patch-clamp technique.

2. Functional properties of the NMDA receptor in the lateral amygdala: a comparison with those in the hippocampal CA1 region.

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The amygdala is a crucial brain structure for the acquisition and expression of fear memory. The N-methyl-D-aspartate (NMDA)-type glutamate receptor channel, composed of the NR1 (GluRζ) and NR2 (GluRε) subunits, plays a key role in synaptic plasticity in the central nervous system. NR2 subunits (NR2A-NR2D) are differentially expressed, depending on developmental stages and brain regions, but their functional roles in the amygdala are still largely unknown. In this study, we have investigated the properties of synaptic NMDA receptors in the lateral nucleus of the amygdala (LA), comparing them with those in the hippocampal CA1 region. We find that the biophysical properties of NMDA receptors and the NR2A/NR2B ratio in the LA are distinct from those in the CA1 region and that the NR2B subunit contributes to synaptic transmission and LTP induction to a greater extent in the LA than in the CA1 region. Our data suggest that these properties of NMDA receptors in the LA are responsible for unique properties of amygdaloid synaptic function and plasticity.

3. GABAergic interneurons facilitate mossy fiber excitability in the developing hippocampus.

Michiko Nakamura, Yuko Sekino and Toshiya Manabe

Profound activity-dependent synaptic facilitation at hippocampal mossy fiber synapses is a unique and functionally important property. Although presynaptic ionotropic receptors, such as kainate receptors, contribute partially to the facilitation in the hippocampus, the precise mechanisms of presynaptic regulation by endogenous neurotransmitters remain unclear. In this study, we report that axonal $GABA_A$ receptors on mossy fibers are involved in the activity-dependent facilitation during development. In immature mouse hippocampal slices, short-train stimulation (5 pulses at 25 Hz) caused frequency-dependent facilitation of not only postsynaptic responses but also presynaptic fiber volleys that represent presynaptic activities. This fiber volley facilitation was inhibited by selective $GABA_A$ receptor antagonists, or by enkephalin that selectively suppresses excitability of interneurons. Furthermore, we directly demonstrated that this facilitation resulted from depolarization of mossy fibers in imaging experiments using a voltage-sensitive dye. This increased mossy fiber excitability caused by depolarizing action of GABA gradually decreased with development and eventually disappeared at around postnatal day 30. These results suggested that GABA released from interneurons acted on axonal $GABA_A$ receptors on mossy fibers and contributed at least partially to the activity- and age-dependent facilitation in the hippocampus.

4. Physiological and behavioral analysis of Plexin-A2 knockout mice.

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Hippocampal mossy fibers project preferentially to the stratum lucidum, the proximal-most lamina of the suprapyramidal region of the CA3 region in the hippocampus. The molecular mechanisms that govern this lamina-restricted projection are still unknown. Type A plexins can directly show repulsive activities, and all type A plexins (plexin-A1, -A2, -A3, and -A4) are expressed in the developing hippocampal system, suggesting their involvement in neuronal wiring in the hippocampus. In this study, we generated Plexin-A2-null mutant mice and found that Plexin-A2 deficiency caused a shift of mossy fibers from the suprapyramidal region to the infra- and intrapyramidal regions. However, all of the electrophysiological properties examined, including paired-pulse facilitation, sensitivity to group II mGluR agonists and LTP, were normal. In the behavioral analysis, mutant mice exhibited enhanced hippocampus-dependent spatial reference memory and spatial pattern separation tested by the 8-arm radial maze task. These results suggest that the pattern of synaptic inputs in the CA3 region determines the spatial learning ability.

5. Involvement of protein-tyrosine phosphatase PTPMEG in motor learning and cerebellar long-term depression.

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Although protein-tyrosine phosphorylation is important for hippocampus-dependent learning, its role in cerebellum-dependent learning remains unclear. We previously found that PTPMEG, a cytoplasmic protein-tyrosine phosphatase expressed in Purkinje cells (PCs), bound to the carboxyl-terminus of the glutamate receptor δ2 via the postsynaptic density-95/discs-large/ZO-1 domain of PTPMEG. In the present study, we generated PTPMEG-knockout (KO) mice, and addressed whether PTPMEG is involved in cerebellar plasticity and cerebellum-dependent learning. The structure of the cerebellum in PTPMEG-KO mice appeared grossly normal. However, we found that PTPMEG-KO mice showed severe impairment in the accelerated rotarod test. These mice also exhibited impairment in rapid acquisition of the cerebellum-dependent delay eyeblink conditioning, in which conditioned stimulus (450-ms tone) and unconditioned stimulus (100-ms periorbital electrical shock) were co-terminated. Moreover, long -term depression at parallel fiber-PC synapses was significantly attenuated in these mice. Developmental elimination of surplus climbing fibers and the physiological properties of excitatory synaptic inputs to PCs appeared normal in PTPMEG-KO mice. These results suggest that tyrosine dephosphorylation events regulated by PTPMEG are important for both motor learning and cerebellar synaptic plasticity.

6. The neuropeptide nociceptin is a synaptically released endogenous inhibitor of hippocampal long-term potentiation.

Saknan Bongsebandhu-phubhakdi and Toshiya Manabe

Hippocampal long-term potentiation (LTP) of excitatory synaptic transmission has been regarded as a cellular model of learning and memory. Its induction is regulated by many functional molecules at synapses, including the neuropeptide nociceptin identified as an endogenous ligand for the orphan opioid receptor. Mutant mice lacking the receptor exhibit enhanced LTP and hippocampus-dependent memory formation; however, the precise molecular and cellular mechanism is largely unknown. In this study, we show that LTP in the hippocampal CA1 region is inhibited by nociceptin synaptically released from interneurons by tetanic stimulation. This endogenous nociceptin downregulates the excitability of pyramidal cells by the hyperpolarization induced by the activation of K^+ channels, which are the common target shared with γ-aminobutyric acid type B ($GABA_B$) receptors although the mode of action is considerably different. Interestingly, the modulation of LTP by endogenous nociceptin is not observed when theta-burst stimulation is used in stead of tetanic stimulation, suggesting that relatively longer high-frequency synaptic activation is required for the release of endogenous nociceptin. These results indicate that, in addition to GABA, nociceptin released from interneurons by their high-frequency activation is a novel endogenous neuromodulator that negatively regulates LTP induction in the hippocampus through direct modulation of pyramidal cells.

7. Roles of the actin cytoskeleton in synaptogenesis, synaptic plasticity and adult neurogenesis.

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Excitatory synapses in the central nervous system generally have specialized postsynaptic structures called dendritic spines, and their morphological plasticity is believed to play a pivotal role in higher brain functions, such as learning and memory. The spine morphology is dynamically regulated by the actin cytoskeleton, which is highly concentrated in dendritic spines. Many studies suggest that actin remodeling is the molecular mechanism underlying activity-dependent morphological changes. Mechanical properties of actin filaments are generally regulated by their side-binding proteins. This project aims to elucidate a role of reorganization of the

actin cytoskeleton in the spine during the maturation of synaptic functions and plasticity.

Drebrin, one of the actin side-binding proteins, is highly enriched in dendritic spines of the mature brain. By immunoelectron microscopy using a newly-developed antibody against drebrin A, a neuron-specific isoform of drebrin, we have shown that drebrin A localizes in sites of prospective excitatory synapses in the immature brain, and suggested that the drebrin content in a dendritic spine might be closely related to its synaptic function. Interestingly, some recent studies on neurological disorders accompanied by cognitive deficits suggested that the loss of drebrin in dendritic spines is a common pathognomonic feature of synaptic dysfunction. We have also found that the translocation of drebrin from the dendritic spines is induced by glutamate, which might be related to morphological plasticity. We are now investigating the ATPase-dependent mechanism of the drebrin translocation.

Down-regulation of the drebrin-A isoform caused by antisense oligonucleotides in developing cultured hippocampal neurons prevents spine formation and PSD-95 accumulation in dendritic spines. Filopodia, which are thin and headless protrusions, are thought to be precursors of dendritic spines. Drebrin is responsible for recruiting F-actin and PSD-95 into filopodia, and is suggested to govern spine morphogenesis. We are now interested in a role of drebrin in trafficking of glutamate receptors during synaptogenesis.

"Synaptic scaling" has been reported as scaling up of AMPA receptor (AMPAR)-mediated miniature excitatory postsynaptic currents (mEPSCs) induced by blockade of action potentials or AMPARs. In this study, we showed a novel type of synaptic scaling induced by the N-methyl-D-aspartate receptor (NMDAR) blockade. We analyzed AMPAR-mediated mEPSCs in hippocampal neurons (16 days in vitro) treated with the NMDAR antagonist D-(-)-2-amino-5-phosphonopentanoic acid (AP5) for 48 h in low-density cultures, using a whole-cell patch-clamp technique. The mEPSC amplitudes recorded from neurons chronically treated with AP5 were significantly larger than those from control neurons, whereas the frequency of mEPSCs was not changed. Immunocytochemistry showed that the number of synapsin I clusters of AP5-treated neurons was not different from that of control neurons, suggesting that the number of synapses was unchanged. Cumulative amplitude histograms revealed that the amplitude of mEPSCs was scaled multiplicatively after the AP 5 treatment. We are currently examining whether knockdown of drebrin expression by RNAi affects the synaptic scaling observed in developing neurons induced by NMDA receptor blockade.

Migrating neuroblasts in the adult brain form the rostral migratory stream (RMS) from the lateral ventricle to the olfactory bulb (OB) and then differentiate in the OB. In this study, we immunohistochemically analyzed drebrin expression in the RMS of the adult rat brain. Although drebrin is concentrated in dendritic spines of mature neurons , drebrin-immunopositive (DIP) cell bodies were observed in the RMS. The polysialated form of a neural cell adhesion molecule (PSA-NCAM) was detected in DIP cells. Ki-67, a marker of proliferating cells, was also detected in a subset of DIP cells; however, neither glial fibrillary acidic protein, nestin nor vimentin was detected in DIP cells. These results indicate that DIP cells in the RMS are migrating neuroblasts. An image subtraction method with anti-pan-drebrin and anti-drebrin A antibodies demonstrated that DIP migrating neuroblasts are immunopositive for drebrin E but not for drebrin A (E+A-). Furthermore, olfactory bulbectomy increased the number of cells with drebrin E+A- signals in the RMS, indicating that these cells migrate along the RMS. Drebrin E+A- cells were also found in the subgranular layer of the dentate gyrus and in the piriform cortex. Thus, the detection of drebrin E+A- signals can be used for identifying migrating neuroblasts in the adult brain. In the OB, drebrin E+A- signals were observed in the cell bodies of migrating neuroblasts in the core region; however, only fibrous and punctate drebrin E+A- signals were observed in postmigratory neuroblasts in the outer layers. These data demonstrate that the disappearance of drebrin E+A- signals from the cell body coincides with the cessation of neuronal migration. Thus, the disappearance of drebrin E from the cell body may be a molecular switch for the cessation of migration in newly generated neuroblasts.

8. Physiological roles of adenosine A_1 receptors in modulation of neuronal activity.

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ment of Physiology and Pharmacology, Karolinska Institute, Sweden.

Adenosine promotes cytoprotection under conditions of infection, ischemic preconditioning and oxidative stress. Our previous studies indicate that the expression of the adenosine A_1 receptor (A_1AR) is induced by oxidative stress via activation of nuclear factor NF-κB. To determine the role of NF-κB in the regulation of the A_1AR in vivo, we compared the A_1AR RNA and protein levels in the brains of mice lacking the p50 subunit of NF-κB (p50-/- mice) and age-matched B6129PF2/J (F2) controls. Radioligand binding assays in the cortex revealed a significantly lower number of A_1AR in the cortex of p 50-/- mice than in the F2, but no change in the equilibrium dissociation constant. Similar reductions in A_1AR were detected in the hippocampus, brain stem and hypothalamus and in peripheral tissues, such as the adrenal gland, kidney and spleen. Estimation of the A_1AR following purification by antibody affinity columns also indicated reduced A_1AR in the p50-/- mice cortex, as compared with the F2 mice. A_1AR immunocytochemistry indicated distinct neuronal labeling in the F2 cortex, which was substantially reduced in similar sections obtained from p50-/- mice. The p50-/- mice expressed lower levels of A_1AR mRNA than F2 mice, as determined by real time PCR. Quantification of the A_1AR-transducing G proteins by Western blotting showed significantly less $G_{\alpha i3}$, no change in $G_{\alpha i1}$, but higher levels of $G_{\alpha o}$ and G_{β} in the cortices of p50-/-, as compared with F2 mice. Administration of bacterial lipopolysaccharide (LPS), an activator of NF-κB, increased A_1AR expression in the cortices of F2 mice but not p50-/- mice. Cortical neuron cultures prepared from p 50-/- mice showed a greater degree of apoptosis, compared with neurons from F2 mice. Activation of the A_1AR reduced apoptosis with greater efficacy in cultures from F2 than p50-/- mice. Taken together, these data support a role for NF-κB in determining both the basal and LPS-stimulated A_1AR expression in vivo, which could contribute to neuronal survival.

We also explored the possibility of intimate functional interplay between $G_{i/o}$ protein-coupled A_1AR and type-1 mGluR (mGluR1) naturally occurring in cerebellar Purkinje cells. Using a perforated-patch voltage-clamp technique, we found that both synthetic and endogenous agonists for A_1AR induced continuous depression of a mGluR1-coupled inward current. A_1AR agonists also depressed mGluR1-coupled intracellular Ca^{2+} mobilization monitored by fluorometry. A_1AR indeed mediated this depression because genetic depletion of A_1AR abolished it. Surprisingly, A_1AR agonist-induced depression persisted after blockade of $G_{i/o}$ protein. The depression appeared to involve neither the cAMP-protein kinase A cascade downstream of the a subunits of $G_{i/o}$ and G_s proteins, nor cytoplasmic Ca^{2+} that is suggested to be regulated by the β-γ subunit complex of $G_{i/o}$ protein. Moreover, A_1AR did not appear to affect G_q protein that mediates the mGluR1-coupled responses. These findings suggest that A_1AR modulates the mGluR1 signaling without the aid of the major G proteins. In this respect, the A_1AR-mediated depression of the mGluR1 signaling shown here is clearly distinguished from the A_1AR-mediated neuronal responses described so far. These findings demonstrate a novel neuromodulatory action of adenosine in central neurons.

9. Tonic enhancement of endocannabinoid-mediated retrograde suppression of inhibition by cholinergic interneuron activity in the striatum.

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Tonically active cholinergic interneurons in the striatum modulate activities of striatal outputs from medium spiny (MS) neurons and significantly influence overall functions of the basal ganglia. Cellular mechanisms of this modulation are not fully understood. In this study, we show that ambient acetylcholine (ACh) derived from tonically active cholinergic interneurons constitutively upregulates depolarization-induced release of endocannabinoids from MS neurons. The released endocannabinoids cause transient suppression of inhibitory synaptic inputs to MS neurons through acting retrogradely onto presynaptic CB_1 cannabinoid receptors. The effects were mediated by postsynaptic M_1 subtype of muscarinic ACh receptors, because the action of a muscarinic agonist to release endocannabinoids and the enhancement of depolarization-induced endocannabinoid release by ambient ACh were both deficient in M_1 knock-out mice and were blocked by postsynaptic infusion of guanosine-5′-O-(2-thiodiphosphate). Suppression of spontaneous firings of cholinergic interneurons by inhibiting I_h current reduced the depolarization-induced release of endocannabinoids. Conversely, elevation of ambient ACh concentration by inhibiting choline esterase significantly enhanced the endocannabinoid release. Paired recording from a cholinergic interneuron and an MS neuron revealed that the

activity of single cholinergic neuron could influence endocannabinoid-mediated signaling in neighboring MS neurons. These results clearly indicate that striatal endocannabinoid-mediated modulation is under the control of cholinergic interneuron activity. By immunofluorescent and immunoelectron microscopic examinations, we demonstrated that M_1 receptor was densely distributed in perikarya and dendrites of dopamine D_1 or D_2 receptor-positive MS neurons. Thus, we have disclosed a novel mechanism by which the muscarinic system regulates striatal output and may contribute to motor control.

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