Department of Pharmacology

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General Summary

The research interests of the Department of Pharmacology include:
1. Synaptic transmission and its modulation in the basal ganglia and basal forebrain (Toshihiko Momiyama)
2. Neural control of breathing in aquatic vertebrates (Naofumi Kimura)
3. Peripheral benzodiazepine receptors on adrenal cells (Yuji Ohno)
4. Research on the function of G protein-coupled purinergic receptors in mast cells (Haruhisa Nishi)
5. Analysis of the cerebro-cerebellar interaction using optogenetics (Taro Ishikawa and Misa Shimuta)
6. Mild hypothermia-mediated neuroprotection for experimental ischemia through adenosine receptors (Masahito Kawamura)
7. Presynaptic plasticity at cerebellar parallel fiber terminals (Yukihiro Nakamura)
8. Cholinergic modulation of central synaptic transmission (Etsuko Suzuki)

Research Activities

Synaptic transmission and its modulation in the basal ganglia and basal forebrain
Electrophysiological studies using slice patch-clamp recording techniques were performed to analyze synaptic transmission and its modulation by neuromodulators, mediated by dopamine serotonin and muscarine receptors in the nigrostriatal or mesolimbic dopaminergic system and in the cholinergic system of the basal forebrain. Developmental changes in the modulation are also under investigation. These systems are involved in various psychological functions as well as their disorders, including Parkinson's disease and Alzheimer's disease. Furthermore, optogenetic activation techniques for neurones in these brain areas have been introduced to analyze neuron type-specific synaptic transmission as well as its modulation. These basic analyses can lead to the identification of the mechanisms underlying the related disorders mentioned above, as well as to the development of novel therapeutic tools.

Neural control of breathing in aquatic vertebrates
The neural respiratory output of the isolated brainstem of *Xenopus laevis* displayed two motor patterns, the lung ventilation-like large bursts and the functionally unidentified small bursts. The lung ventilation-like bursts were abolished by bath application of the low concentration (0.1 μM) of μ-opioid receptor agonist, DAMGO and restored by 1-5 μM naloxone. While, the small bursts were resistant to the low concentration of DAMGO.

The small bursts might have a common origin with the buccal rhythm of terrestrial frogs.

Peripheral benzodiazepine receptors on adrenal cells
Peripheral benzodiazepine receptor (PBR) localizes in the outer mitochondrial membrane and not only transfer cholesterol in steroidogenic organs under physiological conditions but also is readily upregulated under various pathological conditions such as cancer, inflammation and neurological disease. We would like to investigate whether endozepine and its metabolite, which we prepared from bovine adrenocortical cells, could be related to these pathological conditions.

Research on the function of G protein-coupled purinergic receptors in mast cells
Using a human-derived mast cell line, the enhancement system via G protein-coupled purinergic receptor (P2YR) stimulation on IgE receptor-induced allergic histamine release was further analyzed. As a result, it was discovered that the enhancement of allergic histamine release by stimulation of the P2YR was caused by an unusual phosphorylation cascade that includes activation of phosphatidylinositide 3-kinase type delta (PI3Kδ), an isoform of PI3K. It was also shown that this enhancement occurred without the induction of intracellular Ca^{2+} mobilization, which is usually required for degranulation in mast cells.

Analysis of the cerebro-cerebellar interaction using optogenetics
The cerebro-cerebellar communication is important in a wide range of brain functions, including sensory information processing. We investigated the somatosensory-signaling pathways to the cerebellar cortex, using transgenic mice whose cerebral cortex can be suppressed by light illumination, and revealed that the direct signals from the trigeminal nucleus and the indirect ones via the somatosensory cortex are integrated not only in the Purkinje cells but also in the granule cells in the cerebellar cortex. Furthermore, we examined how such integration is affected by various types of anaesthetics and revealed that the cerebro-cerebellar communication is rather enhanced by the ketamine anaesthesia in comparison to a non-anaesthetic state.

Mild hypothermia-mediated neuroprotection for experimental ischemia through adenosine receptors
The therapeutic hypothermia for acute stroke might play an important role in neuroprotection, however, the key mechanism of this therapy is still undetermined. We examined the role of adenosine in hypothermia-induced neruoprotection with using extracellular and patch clamp recordings. Mild hypothermia (32°C) causes protection for ischemia-induced loss of synaptic transmission through activation of adenosine A1 receptors, but deep hypothermia (28°C)-induced neruoprotection is not caused by adenosine receptors. This study might reveal the involvement of adenosine in the therapeutic hypothermia (usual 32-33°C) for acute stroke.

Presynaptic plasticity at cerebellar parallel fiber terminals
Plasticity at the parallel fiber-Purkinje cell synapse is an underlying mechanism for cere-

bellar motor learning. Recent immunocytochemical studies have shown that intense photo stimulation of cerebellum from channelrhodopsin-expressing transgenic rats induced a transient increase in the number of voltage-gated Ca^{2+} channels expressed at the parallel fiber terminal. We measured excitatory postsynaptic current from Purkinje cells before and after the photo stimulation, and found that the photo stimulation induced long-term synaptic depression. However there were no electrophysiological indexes of presynaptic changes. Further study is necessary to uncover physiological functions of the change in presynaptic Ca^{2+} channels at the parallel fiber terminal.

Cholinergic modulation of central synaptic transmission

Acetylcholine is known to be a neurotransmitter involved in learning and memory. In the central nervous system, several studies have reported that synaptic transmission and firing property of neurons are modulated by acetylcholine. We elucidated the cholinergic modulation in striatum using electrophysiological technique. In the striatum, we have found that GABA release from striatal medium spiny neurons onto cholinergic interneurons is inhibited by activation of presynaptic muscarinic M1 receptors.

Publications

Park J, Masaki T, Mezaki Y, Yokoyama H, Nakamura M, Maehashi H, Fujimi TJ[1], Gouraud SS[2], Nagatsuma K, Nakagomi M[3], Kimura N, Matsuura T ([1]Bunkyo Univ, [2]Ochanomizu Univ, [3]Food and Drug Safety Center). Alpha-1 antichymotrypsin is involved in astrocyte injury in concert with argininevasopressin during the development of acute hepatic encephalopathy. *PLoS ONE.* 2017; **12:** e0189346.

Nakamura Y, Reva M[1], DiGregorio DA[1] ([1]Institut Pasteur). Variations in Ca^{2+} influx can alter chelator-based estimates of Ca^{2+} channel-synaptic vesicle coupling distance. *J Neurosci.* **38**: 3971-87.

Reviews and Books

Momiyama T, Nishijo T. Dopamine and Serotonin-Induced Modulation of GABAergic and Glutamatergic Transmission in the Striatum and Basal Forebrain. *Front Neuroanat.* 2017; **11:** 42.