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. Peripheral benzodiazepine receptors on adrenal cells (Yuji Ohno)
3. Mast cells and homeostasis: involvement in melatonin synthesis (Haruhisa Nishi)
4. Analysis of the cerebro-cerebellar interaction using optogenetics (Taro Ishikawa and Misa Shimuta)
5. Mild hypothermia-mediated neuroprotection for experimental ischemia through adenosine receptors (Masahito Kawamura)
6. Theoretical characterization of chemical probes used in the study of synaptic transmission (Yukihiro Nakamura)
7. Cholinergic modulation of central synaptic transmission (Etsuko Suzuki)

Research Activities

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

Peripheral benzodiazepine receptors on adrenal cells
Peripheral benzodiazepine receptors localize in the outer mitochondrial membrane, transfer cholesterol in steroidogenic organs under physiological conditions, and are 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, are related to these pathological conditions.

Mast cells and homeostasis: involvement in melatonin synthesis

Some studies suggest that mast cells release melatonin, which might play key roles in the prevention of viral and bacterial infections and the development of tumors. The present study focused on 2 enzymes for melatonin synthesis in mast cells because of their roles in the immune response. Messenger (m) RNA expression from LAD2, a human mast cell-derived cell line, was examined for key enzymes in melatonin synthesis. The LAD2 cells were positive for mRNA expression of both enzymes. The mRNA levels were enhanced by cyclic adenosine monophosphate elevation without LAD2 activation. In contrast, an increase in calcium did not enhance mRNA levels but did activate LAD2. These results suggest that melatonin release from mast cells is involved in maintaining homeostasis and is not involved in allergic responses.

Analysis with optogenetics of the cerebrocerebellar interaction

Cerebrocerebellar communication is important in a wide range of brain functions, including sensory information processing. We investigated the somatosensory-signaling pathways to the cerebellar cortex in transgenic mice whose cerebral cortex can be suppressed by light illumination. We found that direct signals from the trigeminal nucleus and indirect signals via the primary somatosensory cortex are integrated in both Purkinje cells and granule cells in the cerebellar cortex. We also found that spontaneous signals are transmitted from the somatosensory cortex to the cerebellum.

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 has not been determined. We examined the role of adenosine in hypothermia-induced neuroprotection by using extracellular and patch-clamp recordings. Mild hypothermia (32°C) causes protection for ischemia-induced loss of synaptic transmission through activation of adenosine A_1 receptors, but deep hypothermia (28°C)-induced neuroprotection is not caused by adenosine receptors. This study suggests that adenosine is involved in the therapeutic hypothermia (usually 32°C to 33°C) for acute stroke.

Theoretical characterization of chemical probes used in the study of synaptic transmission

Although chemical probes are essential in cellular biology, they are often used without a correct understanding of their characteristics and mechanisms of action. Using numerical simulations, we examined the properties of the two chemical probes used in the study of synaptic transmission.

The Ca chelator ethyleneglycol bis-(β-aminoethylether) N,N,N',N'-tetraacetic acid (EGTA) is widely used to probe the coupling distance between voltage-gated Ca channels and vesicles in the active zone. Our simulation showed that the effectiveness of EGTA also depends on factors other than the distance. We made the calibration curves for EGTA.

Due to slow dissociation rate constant, fluorescence signal from glutamate probe EOS

does not directly show the time course of the glutamate concentration transient. Deconvolution of EOS fluorescence is being developed to make more precise measurement of glutamate release.

Cholinergic modulation of central synaptic transmission

Acetylcholine is a neurotransmitter involved in learning and memory. In the central nervous system, several studies have shown that acetylcholine modulates the synaptic transmission and the firing property of neurons. We used an electrophysiological technique to elucidate the cholinergic modulation in adult mice striatum. We have found that GABA release from striatal medium spiny neurons onto cholinergic interneurons is inhibited by carbachol application.

Publications

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