Department of Pharmacology

Toshihiko Momiyama, *Professor*
Yuji Ohno, *Assistant Professor*
Taro Ishikawa, *Assistant Professor*
Naofumi Kimura, *Professor*
Haruhisa Nishi, *Assistant Professor*
Masahito Kawamura, *Assistant Professor*

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. Study of the mast cell allergic response (Haruhisa Nishi)
5. Analysis of the cerebrocerebellar interaction using optogenetics (Taro Ishikawa, Misa Shimuta)
6. The basic mechanism underlying anticonvulsant effects of a ketogenic diet (Masahito Kawamura)
7. Coupling distance between presynaptic Ca^{2+} channels and synaptic vesicles (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, such as dopamine and serotonin, and their 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 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 local neural circuits.
These basic analyses could 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
Aquatic turtles, amphibians, and air-breathing fishes, unlike aves and postnatal mammals, never open their glottis while yawning. Elasmobranches that lack lungs and a glottis also show yawn-like behavior. Therefore, the central pattern generator of yawns is considered phylogenetically older than that of pulmonary ventilation. Coupling between lung-ventilation and yawning might have evolved as a result of the change into air-aspirating

breathing.

Peripheral benzodiazepine receptors on adrenal cells
Peripheral benzodiazepine receptors localize in the outer mitochondrial membrane; they 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.

Study of the mast cell allergic response
An increase of the intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) is recognized as being essential for mast cell activation, leading to the release of histamine. However, the release of the histamine dependencies of the different pathways leading to the rise in intracellular Ca^{2+} in activated mast cells is unknown. To investigate this association, the relationship between the $[Ca^{2+}]i$ increase and the release of histamine caused by variable stimulation, was examined in LAD2 cells, a human mast cell line that can be activated to the release of histamine. The results indicate that extracellular Ca^{2+} influx is more critical to release of histamine than to Ca^{2+} mobilization from the intracellular organelles in LAD2. These results suggest that controlling the Ca^{2+} influx pathways could be a useful way to mitigate the allergic symptoms caused by activated mast cells.

Analysis of cerebrocerebellar interaction by means of optogenetics
The circuit that connects the cerebrum and the cerebellum is important in a wide range of brain functions, including sensory information processing. We are investigating the neural circuits involved in the orofacial sensory signal processing of mice. We found that, among the signals recorded in the cerebellar granule cells, signals that had a long latency were specifically suppressed by cerebral optogenetic inhibition. In contrast, signals that had a short latency, which originated from the trigeminocerebellar pathway, were not suppressed. These results suggest that direct trigeminal signals and indirect cerebral signals are integrated in cerebellar granule cells.

The basic mechanism underlying anticonvulsant effects of ketogenic diet
A ketogenic diet has been used successfully to treat medically refractory epilepsy. The mechanisms underlying the success of ketogenic diet therapy, however, are not well understood. We fed rats a ketogenic diet, prepared hippocampal slices, and performed electrophysiology in the seizure-prone CA3 region. Slices from animals fed a ketogenic diet showed reduced excitability, and the effects of the ketogenic diet could be reversed with blockers of adenosine A1 receptors. These results suggest that the reduction of neuronal activity through activation of adenosine A1 receptor is a key mechanism underlying the anticonvulsant effects of a ketogenic diet.

Coupling distance between presynaptic Ca^{2+} channels and synaptic vesicles
The coupling distance between voltage-gated Ca^{2+} channels and synaptic vesicles criti-

cally determines the probability and timing of neurotransmitter release. The presynaptic terminal of the calyx of Held in the auditory brainstem is composed of stalks connecting to the axon and of swellings extended from stalks, both of which form release sites onto the postsynaptic neuron. Electrophysiological measurements combined with numerical simulations of transmitter release at this synapse revealed that the coupling distance is longer in swellings than in stalks. This result suggests that the coupling distance between Ca^{2+} channels and vesicles varies among release sites within the same synapse, thereby diversifying the method of transmitter 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 synaptic transmission and the firing property of neurons are modulated by acetylcholine. We examined cholinergic modulation in the striatum and the hippocampus with an electrophysiological technique. In the striatum, we have found that the GABAergic inhibitory transmission onto cholinergic interneurons is inhibited by the activation of muscarine receptors.

Publications

Ishikawa T, Shimuta M, Häusser M (Univ Coll London). Multimodal sensory integration in single cerebellar granule cells in vivo. *Elife.* 2015; **4:** e12916.