

## 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. Living environments may exacerbate allergic stimulation (Haruhisa Nishi)
5. Analysis of the cerebro-cerebellar interaction using optogenetics (Taro Ishikawa and Misa Shimuta)
6. The basic mechanism underlying anticonvulsant effects of 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 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  $\mu$ M) of  $\mu$ -opioid receptor agonist, DAMGO and restored by 1-5  $\mu$ M 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.

*Living environments may exacerbate allergic stimulation*

Environmental exacerbation of allergic stimuli was investigated using a human mast cell-derived cell line as a screening tool. The results revealed that even non-allergen-composed materials could indirectly enhance allergic-induced degranulation. This enhancement was the result of excessive PI3K activation. These results demonstrate that environmental objects may enhance allergic symptoms in patients with type I allergies. This study was supported by the LIXIL JS Foundation and the reports of the study had been presented on the web site of the LIXIL JS Foundation.

*Analysis of the cerebro-cerebellar interaction using optogenetics*

The cerebro-cerebellar communication is important in a wide range of brain function 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 signals via the somatosensory cortex are integrated not only in the Purkinje cells but also in the granule cells in the cerebellar cortex. In addition, in collaboration with a group of Edinburgh University, we showed that the balance of excitatory and inhibitory synaptic inputs are crucial in action potential generation in Purkinje cells and that disturbance of this balance results in a disorder of locomotive activity of mice.

*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 ketogenic diet-fed animals showed reduced excitability, and the effects of the ketogenic diet could be reversed with blockers of adenosine A<sub>1</sub> receptors. These results suggest that the reduction of neuronal activity through activation of adenosine A<sub>1</sub> receptor is one of the key mechanisms underlying anticonvulsant effects of ketogenic diet.

*Coupling distance between presynaptic Ca<sup>2+</sup> channels and synaptic vesicles*

Coupling distance between voltage-gated Ca<sup>2+</sup> channels and synaptic vesicles critically determines the probability and timing of neurotransmitter release. Although the coupling distance has been estimated based on the inhibition of transmitter release by Ca<sup>2+</sup> chelator EGTA, other presynaptic factors other than coupling distance can affect the EGTA effect.

My simulations of buffered  $\text{Ca}^{2+}$  diffusion and transmitter release revealed that the inhibitory effect of EGTA is potentiated for a brief  $\text{Ca}^{2+}$  influx like action potential-induced  $\text{Ca}^{2+}$  elevation. Time course of presynaptic  $\text{Ca}^{2+}$  influx is mandatory biophysical parameters to estimate the coupling distance using EGTA.

#### *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 has reported that synaptic transmission and firing property of neurons are modulated by acetylcholine. We elucidated the cholinergic modulation in striatum and hippocampus using electrophysiological technique. In the striatum, we have found that GABA release onto cholinergic interneurons is inhibited by activation of muscarine M1 receptors.

#### Publications

**Nishijo T, Momiyama T.** Serotonin 5-HT<sub>1B</sub> receptor-mediated calcium influx-independent presynaptic inhibition of GABA release onto rat basal forebrain cholinergic neurons. *Eur J Neurosci.* 2016; **44**: 1747–60.

**Hamada N<sup>1</sup>, Ito H<sup>1</sup>, Nishijo T, Iwamoto I<sup>1</sup>, Morishita R<sup>1</sup>, Tabata H<sup>1</sup>, Momiyama T, Nagata K<sup>1</sup> (Aichi Human Service Center).** Essential role of the nuclear isoform of RBFOX1, a candidate gene for autism spectrum disorders, in the brain development. *Sci Rep.* 2016; **6**: 30805.

**Nishi H, Pelleg A<sup>1</sup>, Schulman ES<sup>1</sup> (Drexel Univ).** IgE Receptor-Mediated Histamine Release in Human Lung Mast Cells: Modulation by Purinergic Receptor Ligands. *Ann Clin Lab Sci.* 2016; **46**: 463–9.

**Kawamura MJ, Ruskin DN<sup>1</sup>, Masino SA<sup>1</sup> (Trinity Coll).** Metabolic Therapy for Temporal Lobe Epilepsy in a Dish: Investigating Mechanisms of Ketogenic Diet using Electrophysiological Recordings in Hippocampal Slices. *Front Mol Neurosci.*

2016; **9**: 112.

**Jelitai M<sup>1</sup>, Puggioni P<sup>1</sup>, Ishikawa T, Rinaldi A<sup>1</sup>, Duguid I<sup>1</sup> (Univ Edinburgh).** Dendritic excitation-inhibition balance shapes cerebellar output during motor behavior. *Nat Commun.* 2016; **7**: 13722.

#### Reviews and Books

**Yamada K<sup>1</sup>, Takahashi S<sup>2</sup>, Karube F<sup>2</sup>, Fujiyama F<sup>2</sup>, Kobayashi K<sup>3</sup>, Nishi A<sup>4</sup>, Momiyama T (Hiroasaki Univ, <sup>2</sup>Doshisha Univ, <sup>3</sup>Fukushima Med Univ, <sup>4</sup>Kurume Univ).** Neuronal circuits and physiological roles of the basal ganglia in terms of transmitters, receptors and related disorders. *J Physiol Sci.* 2016; **66**: 435–46.

**Kawamura M, Jr.** Chapter 21, Ketogenic diet in a hippocampal slice: models and mechanisms. In: Ketogenic Diet and Metabolic Therapies: Expanded Roles in Health and Disease. Oxford: Oxford University Press; 2016. p. 186–95.