Research Center for Medical Sciences
Division of Neuroscience

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General Summary

The mission of the Department of Neuroscience has 3 parts. The first part is to advance and promote research on the roles played by the brain neuronal network in various aspects of biological functions in health and disease. The functions of the central nervous system undergo plastic, adaptive, and allostatic changes that play essential roles in the development and persistence of many diseases caused by the dysfunction of peripheral organs. An example is pain, which is a biologically necessary function that detects aversive situations in the body and urges reactions to improve the situation. At the same time, however, pain is highly distressing and disturbs the daily life and thoughts of patients. Despite the cause of pain often being in the periphery (but not always for chronic pain), the plastic changes in the brain, particularly in the regions of survival/defence, emotion, and cognition, alter the perception of pain and modulate the sensitivity of pain. These changes in perception and sensitivity affect the autonomic, endocrine, and cognatic systems. To identify the mechanisms underlying the plastic changes, we use electrophysiological, behavioural, imaging, and genetic tools in various models of diseases with pain.

The second part of the mission is to develop novel technologies that would help the first part be achieved. An example of a novel technology is a combination of chemogenetics and manganese-enhanced magnetic resonance imaging of the brain from models of chronic inflammatory pain. This approach allows the limitations of magnetic resonance imaging of the brain in animal models, such as the necessity of anesthesia, the lack of causality-related information, and the difficultly in imaging brain activity associated with spontaneous behaviour, to be surpassed.

The third part of the department's mission is to provide an opportunity for young researchers and students to participate in studies with updated technology and tools used in modern brain sciences and to experience the planning, practicing, summarizing, presenting, and publishing of novel findings. Because of the complexity of its targets and the extremely rapid progress being made, neuroscience is an advanced domain of integrative biology.

To achieve the department's mission, we use approaches at the molecular, cellular, synaptic, and network levels, including the patch-clamp recording of synaptic currents, the real-time imaging of intracellular Ca^{2+} concentration, and behavioral analyses combined with optogenetic and chemogenetics approaches in healthy animals and animal models of various diseases.

As of March 2019, the department is composed of 1 professor/director, 2 research assistant professors (Dr. Yukari Takahashi and Dr. Yae K Sugimura), 1 part-time lecturer, 8 Ph.D. students, 1 foreign visiting student (Iran), 1 research supporter, and many other visiting researchers. At The Jikei University we give lectures in neurophysiology and pro-

vide practical laboratory work to medical students and give lectures to graduate students. We also participate in a wide range of social activities, including being board members of scientific societies and members of the Science Council of Japan.

Research Activities

In the 2018 fiscal year, we have examined the following subjects.

1. Establishment of transgenic rats expressing cre recombinase under vesicular GABA transporters (VGATs) and dopamine-β-hydroxylase (DBH) promotors. These are now deposited at the National BioResource Project - Rats.
2. Identification of the role of the central amygdala in widespread hypersensitivity through selective activation and inhibition of GABAergic neurons using VGAT-cre rats and chemogenetics.
3. Identification of the role of endogenous noradrenaline released in response to light stimulation of terminals in the central amygdala arising from the nucleus of the solitary tract using DBH-cre rats and channelrhodopsin expression.
4. Analysis of the activation patterns of the lateral parabrachial nucleus and the basolateral/central amygdalae using c-Fos immunohistochemistry in a newly developed, formalin-induced model of latent inflammatory pain.
5. Analysis of the role of inflammatory factors in the plastic changes of the central pain network during the shift from acute pain to chronic pain.
6. Development of methods of selective gene expression in the trigeminal ganglion using adeno-associated viruses.
7. Evaluation of spontaneous/voluntary behaviors in animals with collagen-induced rheumatoid arthritis using a wheel-running paradigm and temperature-dependent choice.
8. Visualization of neuronal activation and dopamine receptor expression in the brain reward system in response to acute itch using multiple single RNA imaging.
9. Fast intracellular Ca imaging for comparing the neuroglial responses to exogenous oxytocin in the central amygdala of female mice from before pregnancy to before and after delivery.
10. Behavioral analysis of the relationships of the social rank order of individual mice to glucose tolerance and insulin release regulation.

Publications

Yamauchi N*[1]*, Takahashi D, Sugimura YK, Kato F, Amano T*[1]*, Minami M*[1] *(*[1]*Hokkaido Univ). Activation of the neural pathway from the dorsolateral bed nucleus of the stria terminalis to the central amygdala induces anxiety-like behaviors. *The European Journal of Neuroscience.* 2018; **48:** 3052-61.

Soma S*[1]*, Yoshida J*[1]*, Kato S*[1]*, Takahashi Y, Nonomura S*[1]*, Sugimura YK, Ríos A*[1]*, Kawabata M*[1]*, Kobayashi K*[1]*, Kato F, Sakai Y*[1]*, Isomura Y*[1] *(*[1]*Tamagawa Univ). Ipsilateral-Dominant Control of Limb Movements in Rodent Posterior Parietal Cortex. *J Neurosci.* 2019 Jan 16; **39:** 485-502.

Igarashi H*[1]*, Ikeda K*[2]*, Onimaru H*[3]*, Kaneko R*[4]*, Koizumi K*[1]*, Beppu K*[1]*, Nishizawa K*[5]*, Takahashi Y, Kato F, Matsui K*[2]*, Kobayashi K*[5]*, Yanagawa Y*[4]*, Muramatsu SI*[6]*, Ishizuka T*[1]*, Yawo H*[1] *(*[1]*Tohoku Univ,* [2]*International Univ Health and Welfare,* [3]*Showa Univ Sch Med,* [4]*Gunma Univ Graduate Sch Med,* [5]*Fukushima Med Univ Sch Med,* [6]*Jichi Med Sch). Targeted expression of step-function opsins in transgenic rats for optogenetic studies. *Scientific Reports.* **8:**

5435.

Reviews and Books

Kato F, Sugimura YK, Takahashi Y. Pain-associated neural plasticity in the parabrachial to central amygdala circuit. *Adv Exp Med Biol.* 2018; **1099:** 157-66.