Research Center for Medical Sciences
Division of Neuroscience

Fusao Kato, *Professor and Director* Ayako M. Watabe, *Associate Professor*

General Summary

The integration and coordination of functions throughout the body is realized mainly through intercommunication via the nervous systems. To understand how the activities of organs affect brain activity and, in turn, how the brain controls the activities of organs to optimize these integrative functions, we must clarify the mechanisms underlying the dynamic cell-to-cell signaling in the central nervous system underlying various specific functions, such as pain and emotion. In particular, plastic changes of the central nervous system "wiring" realized through the variability of synaptic connections in response to various environmental changes form the core mechanism for optimizing human and animal behaviors. In addition, such plastic changes are known to underlie psychosomatic pathological states, such as chronic pain without sustained tissue injury or inflammation, and the posttraumatic stress disorder. We use approaches at the molecular, cellular, and network levels, including the patch-clamp recording of synaptic currents, the real-time imaging of the intracellular Ca^{2+} concentration, and optogenetic approaches to activate a specific set of neurons by light in living brain tissues from normal animals, animal models of various diseases, and animals subjected to experimental manipulation of gene expression and combine them with the detailed analysis of the behavior of these animals.

Research Activities

Central mechanisms of pain-related negative emotion

Using rodent models of chronic pain, such as the diabetic neuropathy model and the formalin-induced inflammatory pain model, we demonstrated robust synaptic potentiation at the excitatory synapses between afferent fibers arising from the lateral parabrachial nucleus and neurons in the central nucleus of the amygdala, a structure playing a principal role in the expression of emotional behaviors. We also demonstrated monosynaptic connection between these nuclei using optogenetics with channel rhodospin-expression systems and measurement of light-evoked postsynaptic responses. Furthermore, we have applied small animal magnetic resonance imaging with an ultrahigh magnetic field scanner to visualize the spontaneous cerebral activities with activity-dependent Mn^{2+} uptake during the establishment of chronic pain. These findings further confirm the notion that the chronification process of pain involves potentiated link between the nociception and emotion in the amygdala.

Synaptic mechanism underlying acquisition and extinction of fear memory

The Pavlovian fear-conditioning paradigm depends on the association between a contiguously applied conditional cue and an unconditional aversive sensation. It has been

unequivocally established that the plasticity in the amygdala network plays the primary role in this associative learning. However, the origin and pathway of the aversive signal in fear conditioning have been only poorly identified. We have demonstrated that optogenetic "artificial" stimulation of the axon terminals in the central amygdala, arising from parabrachial neurons delivered in association with conditional auditory cue, robustly established associative fear/threat learning, even in the absence of aversive sensory inputs. This finding is the first to demonstrate the role of a nonthalamic nociceptive pathway in fear learning.

Publications

Sato M, Ito M, Nagase M, Sugimura YK, Takahashi Y, Watabe AM, Kato F. The lateral parabrachial nucleus is actively involved in the acquisition of fear memory in mice. *Mol Brain.* 2015; **8:** 22.

Nagano Y, Kaneda K, Maruyama C, Ide S, Kato F, Minami M. Corticotropin-releasing factor enhances inhibitory synaptic transmission to type III neurons in the bed nucleus of the stria terminalis. *Neurosci Lett.* 2015; **600:** 56-61.

Ohkawa N, Saitoh Y, Suzuki A, Tsujimura S, Murayama E, Kosugi S, Nishizono H, Matsuo M, Takahashi Y, Nagase M, Sugimura YK, Watabe AM, Kato F, Inokuchi K. Artificial association of pre-stored information to generate a qualitatively new memory. *Cell Rep.* 2015; **11:** 261-9.