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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 (CNS) underlying various specific functions, such as autonomic regulation and pain sensation. In particular, plastic changes of the CNS "wiring" realized through the variability of synaptic connections in response to various environmental changes form the core mechanism for optimizing human and animal behaviors. 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 types of disease, and animals subjected to experimental manipulation of gene expression and combine them with the behavior of these animals.

Research Activities

Central mechanisms of pain-related negative emotion

Using a rat model of chronic neuropathic pain, we demonstrated that 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 the principal role in expression of emotional behaviors, involves structural consolidation. We also demonstrated that in the streptozocin-induced model of painful diabetes neuropathy, the synaptic potentiation in the amygdala is established selectively in the parabrachial-central amygdalar synapses, unlike in other models. This finding further confirms the notion that the mechanism of synaptic potentiation in the central amygdala, which underlies the enhanced link between nociception and negative emotions, depends largely on the modality and duration of chronic pain.

Synaptic mechanism underlying acquisition and extinction of fear memory

The Pavlovian fear-conditioning paradigm depends on the association between a contiguously applied cue (e.g., tone) and an aversive signal (e.g., electric shock). 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 hypothesized that the spino-parabrachio-amygdaloid pathway, which carries information arising from the nocicep-

tion-specific neurons in the spinal dorsal horn to the central amygdala by way of pontine parabrachial relay nucleus, would be one of the pathways for such aversive signals. We have shown that fear learning not only potentiates the indirect nociceptive pathway (basolateral amygdala to the central amygdala) but also the direct nociceptive pathway (parabrachial to the central amygdala). This finding is the first to demonstrate direct involvement of the plasticity in the spino-parabrachio-amygdaloid pathway in fear-learning.

Glia-neuron interaction at central synapses

To clarify the role played by the transfer of lactate from astrocytes to neurons in synaptic transmission, we analyzed the effects of selective inhibitors of monocarboxylate transporters on synaptic transmission in neurons of the nucleus of the solitary tract. We found that lactate transport is essential for maintaining the postsynaptic responses both in the presence and the absence of glucose supply.

Publications

Nakao A, Takahashi Y, Nagase M, Ikeda R, Kato F. Role of capsaicin-sensitive C-fiber afferents in neuropathic pain-induced synaptic potentiation in the nociceptive amygdala. *Mol Pain*. 2012; **8:** 51.

Watabe AM, Ochiai T, Nagase M, Takahashi Y, Sato M, Kato F. Synaptic potentiation in the nociceptive amygdala following fear learning in mice. *Mol Brain*. 2013; **6:** 11.