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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 diseases, 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 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 unequivocally demonstrated monosynaptic connections between these nuclei using optogenetics with channelrhodopsin-expression systems and measurement of light-evoked postsynaptic responses. These findings further confirm the notion that the chronification process of pain involves potentiated links 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 cue and an 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 transient pharmacological inactivation of the lateral parabrachial nucleus at the time of association significantly perturbs fear learning. This finding is the first to demonstrate the role of a nonthalamic nocicep-

tive 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, the lateral amygdala, cerebellum, hippocampus, and the hypoglossal nucleus. We found that lactate transport is essential for maintaining the postsynaptic responses both in the presence and the absence of glucose supply in most of the brain synapses.

Publications

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