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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 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. 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 underlying chronic pain

Lines of evidence indicate the establishment of chronic pain involves plastic changes in the "pain matrix" in the central nervous system playing roles in sensation, emotion and cognition of pain. We analyzed the cellular and network mechanisms underlying this process.

1. We demonstrated that the monosynaptic inputs from the parabrachial nucleus to the central amygdala not only activates the central amygdala neurons but also gives rise to sustained post-excitation inhibition using selective activation of these inputs using optogenetics with channel rhodospin-expression systems.

2. We created rats expressing cre recombinase under promotor activities for dopa-β-hydroxylase (DBH) and vesicular GABA transpoter (VGAT). Using these rats, we have demonstrated that pharmacogenetical excitation of central amygdala neurons with DREADD (designer receptor exclusively activated by designer drug) expression technique results in hyperalgesia and their suppression in attenuated nocifensive behaviors in inflammatory pain model. Also using these rats with channelrhodopsin2 expression, we have directly measured the synaptic transmission from the central amygdala to the periaqueductal grey neurons, which had been otherwise impossible. These results provide basis

for understanding the role of descending pain modulation system, through which the brain controls the nociception sensitivity especially in the chronic pain.
3. 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. We found that during the development of inflammatory chronic pain, widely distributed brain areas, such as the limbic systems, are strongly activated.
4. We have demonstrated in mice that an artificial suppression of the amygdala neurons which had been activated commonly in distinct memory forming tasks, using activity-dependent expression of archeorhodopsin and its optogenetic stimulation, reduces behaviors depending on associative memories.

Mechanism underlying motor neuron vulnerability
In motor neuron degenerative diseases such as the amyotrophic lateral sclerosis (ALS), the vulnerability of the neurons against metabolic stress differs between distinct motor neuron pools. To elucidate the mechanism underlying such region-dependent vulnerability, we compared the responses to experimental chemical hypoxia in brain slices between hypoglossal, facial and oculomotor neurons. In the hypoglossal and facial motor neurons, which are highly vulnerable in ALS, glycine release was increased. In contrast, in the oculomotor neurons, which are most resistant in the ALS, GABA release was increased instead. Because we have already demonstrated that an increase in extracellular glycine concentration leads to enhanced excitotoxity through activation of NMDA receptors, this particularity would underlie the distinct vulnerability of different motor neurons.

Publications

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