Research Center for Medical Sciences
Division of Neuroscience

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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 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. In particular, the plastic changes of the central nervous system are the key mechanism allowing the brain to coordinate whole body functions and adapt to the continuously changing environments.
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 behavioral analyses combined with optogenetic and chemogenetics approaches in healthy animals, animal models of various diseases, and animals subjected to experimental manipulation of gene expression.

Research Activities

Pain is “unpleasant sensory and emotional experience”. Lines of evidence indicate that establishment of chronic pain involves plastic changes in the “pain network” in the central nervous system playing roles in sensory, emotional and cognitive aspects 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 channelrhodopsin-expression systems. This would advance our understanding of how nociceptive information modulates the output from the amygdala emotional circuit.
2. We created rats expressing cre recombinase under promoter activities for dopamine-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 decreased nociception sensitivity. In contrast, their suppression with the same technique 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 would help understand the role of descending pain modulation

system, through which the brain controls the nociception sensitivity in acute and chronic pain.

3. We have applied small animal magnetic resonance imaging (MRI) with an ultrahigh magnetic field scanner to visualize the spontaneous cerebral activities with activity-dependent Mn^{2+} entry to the activated neurons during chronic pain establishment. We found that widely distributed brain areas, such as the limbic systems, are strongly activated in the course of chronic pain establishment. In addition, using the DREADD system, we have demonstrated that the amygdala is the hub structure that regulates this chronic pain-associated activation of the limbic systems.

4. We have examined roles played by calcitonin gene-related peptide (CGRP) in the central association between nociception and emotion. In the brain, CGRP is rich in the projection fibers from the parabrachial nucleus to the central amygdala and the central amygdala is rich in CGRP1 receptor proteins. First, in brain slices acutely isolated from mice, we have demonstrated that exogenously applied CGRP enhances NMDA receptor-mediated postsynaptic currents in a PKA-dependent manner without affecting AMPA receptor-mediated currents. Then we demonstrated in CGRP-deficient mice that inflammatory pain-induced synaptic potentiation and ectopic hypersensitization do not occur in mice lacking CGRP, indicating its essential role in chronic pain-associated enhancement of the nociception-emotion link.

5. As a core team of the Center for Neuroscience of Pain, a research center established with the support from MEXT-Supported Program for the Strategic Research Foundation at Private Universities (S1311009; FY2012-2017), we have advanced collaborations with departments and laboratories for clinical and basic medicine. The details are described in the section "Center for Neuroscience of Pain".

Publications

Shinohara K, Watabe AM, Nagase M, Okutsu Y, Takahashi Y, Kurihara H[I], Kato F ([I]University Tokyo). Essential role of endogenous calcitonin gene-related peptide in pain-associated plasticity in the central amygdala. *Eur J Neurosci.* 2017; **46:** 2149-60.

Okutsu Y, Takahashi Y, Nagase M, Shinohara K, Ikeda R, Kato F. Potentiation of NMDA receptor-mediated synaptic transmission at the parabrachial-central amygdala synapses by CGRP in mice. *Mol Pain.* 2017; **13:** 1-11.

Yokose J[I], Okubo-Suzuki R[I], Nomoto M[I], Ohkawa N[I], Nishizono H[I], Suzuki A[I], Matsuo M[I], Tsujimura S[I], Takahashi Y, Nagase M, Watabe AM, Sasahara M[I], Kato F, Inokuchi K[I] ([I]Univ Toyama). Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science* 2017; **355:** 398-403.