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General Summary

We are aiming to clarify the mechanisms underlying dynamic cell-to-cell signaling in the central nervous system. We use approaches at the molecular, cellular, and network levels, including the patch-clamp recording of synaptic currents and the real-time imaging of the intracellular Ca^{2+} concentration in living brain tissues from normal animals, animal models for various types of disease, and animals with experimental manipulation of gene expression.

Research Activities

Regulation of synaptic transmission in the brain network

1. Molecular mechanism of neurotransmitter release

To clarify the roles played by specific molecules in transmitter release in brain synapses, we developed a novel method for *in-vivo* gene silencing with RNA interference against the genes encoding presynaptic proteins which is followed by functional analysis of synaptic transmission with patch-clamp recording in brain slices.

2. Glia-neuron interaction at synapses

We have demonstrated that pharmacological activation of astrocyte-specific P2Y1 receptors in brainstem slices facilitates glutamate release in a manner sensitive to P2X receptor blockade and gliotoxin (fluoroacetate) pretreatment. To our knowledge, this is the first study to demonstrate direct excitatory action of ATP of astrocyte origin on synaptic transmission.

3. Central mechanism of frequency-dependent decoding of afferent information

To understand how the brain analyzes sensory signals from internal organs, we analyzed the postsynaptic responses of second-order neurons in the nucleus of the solitary tract and the dorsal motor nucleus of the vagus nerve to repeated stimulation of afferent fibers. These synapses showed distinct types of short-term plasticity with distinct Ca^{2+}-dependency, which might underlie the frequency-dependent "tuning-in" of visceral information.

Central mechanisms of pain-related negative emotion

Using a rat model of chronic neuropathic pain, we demonstrated that the synaptic potentiation at excitatory synapses between afferent fibers arising from the nucleus parabrachialis and neurons in the central nucleus of the amygdala, a structure playing a principal role in the expression of emotional behavior, involves structural consolidation.

The role of monocarboxylate transport in the synaptic function

To clarify the role played by lactate uptake in synaptic transmission, we analyzed the effect of a selective inhibitor of monocarboxylate transporters on postsynaptic transmission in neurons of the nucleus of the solitary tract. We found that lactate transport is essential for maintaining postsynaptic responses mediated by alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors.

Molecular target of volatile anesthetics

We presented evidence that sevoflurane directly excites neurons in the locus coeruleus through an opening of gap-junction channels, a mechanism that might underlie the aberrant excitatory effect of this anesthetic frequently reported in clinical practice.

Publications

Yasui Y, Masaki E, Kato F. Sevoflurane directly excites locus coeruleus neurons in the rat. *Anesthesiology* 2007; **107:** 992–1002.

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