

Elucidation of mechanisms and physiological meanings of endocannabinoid-mediated retrograde modulation of synaptic transmission

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【Outline of survey】

It is well known that inhalation of marijuana causes various psychiatric and neurological effects. These actions of marijuana are mediated by “cannabinoid CB1 receptor”, a target protein of an active component of marijuana. The CB1 receptor is present on presynaptic terminals and axons of neurons in various regions of the brain. The activation of this receptor causes suppression of neurotransmitter release from presynaptic terminals. However, many important points remain to be determined as to what stimuli can produce endocannabinoids (i.e., endogenous ligands that bind to the CB1 receptor) in the brain and what physiological meanings the endocannabinoid system has. We have disclosed that endocannabinoids act as a retrograde messenger from postsynaptic neurons to presynaptic terminals in the brain. In the present study, we will examine in detail how endocannabinoids modulate synaptic transmission by combining multiple methodological approaches including electrophysiology, molecular biology and mouse genetics. We are particularly interested in the following two major issues; (1) molecular mechanisms of biosynthesis, release and degradation of endocannabinoids under physiological conditions and (2) roles of the endocannabinoid system in synaptic plasticity and higher brain function. Through this 5-year project, we expect to make a significant contribution to elucidating mechanisms and physiological meanings of endocannabinoid-mediated retrograde modulation of synaptic transmission.

【Expected results】

From previous studies including those on CB1 receptor deficient mice, it is known that the endocannabinoid system plays important roles in memory extinction and motor control, as well as regulation of pain and anxiety, hunger and vomiting. Through the present studies, it is expected that detailed mechanisms of these aspects of endocannabinoid-mediated neural regulation become clear at the synapse level. Furthermore, since cannabinoids and related compounds have long been thought as candidates of drugs for anxiety, pain, vomiting and obesity, the outcome of the present studies may contribute significantly to developing new therapeutic drugs.

【References by the principal researcher】

- Ohno-Shosaku, T., Maejima, T. and Kano, M.: Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron* 29: 729-738, (2001).
- Maejima, T., Hashimoto, K., Yoshida, T., Aiba, A. and Kano, M.: Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. *Neuron* 31: 463-475, (2001).

【Term of project】 FY 2005 - 2009

【Budget allocation】 81,200,000 yen

【Homepage address】 <http://web.kanazawa-u.ac.jp/~med05/>