Title of Project : Research on the roles of endocannabinoid-mediated retrograde synaptic transmission in physiology and pathophysiology of the brain

Masanobu Kano
(The University of Tokyo, Graduate school of Medicine, Professor)

Research Area : Neuroscience

Keyword : Molecular/Cellular Neuroscience, Synaptic Plasticity

【Purpose and Background of the Research】

Marijuana affects neural functions through the binding of its active component (Δ^9-THC) to cannabinoid CB_1 receptor in the brain. Recent studies have elucidated that endogenous ligands for cannabinoid receptors, endocannabinoids (eCBs), serve as retrograde messengers at synapses in various regions of the brain. We have revealed that eCBs are released from postsynaptic neurons and cause transient and long-lasting reduction of neurotransmitter release through activation of presynaptic cannabonoid receptors. eCB release is induced by either postsynaptic Ca^{2+} elevation or activation of $G_{q/11}$-coupled receptors. When these two stimuli coincide, eCB release is markedly enhanced, which is attributed to the Ca^{2+} dependency of phospholipase Cβ (PLCβ). Besides these cellular studies on eCB-mediated synaptic modulation, many behavioral studies have clarified the roles of the eCB system in various brain functions, including learning and memory, anxiety, depression, drug addiction, appetite, feeding behavior, pain and anti-convulsant effect.

This research project aims at elucidating how retrograde eCB signaling regulates synaptic transmission, influences neuronal activity to physiological relevant stimuli, and contributes to various brain functions. For this purpose, we take multidisciplinary approaches at cellular, neural circuit, and behavioral levels.

【Research Methods】

In experiment 1, we perform paired whole-cell recordings from cultured hippocampal neurons from newborn rats or mice. We search for novel receptor systems that can drive eCB release and cause retrograde modulation, and also pursue how eCB signaling is regulated.

In experiment 2, we prepare slices from various brain regions including the cerebellum, hippocampus and nucleus accumbens. We make whole-cell recordings from neurons in brain slices from various knockout mice with deletions of eCB signaling molecules. We study how excitatory/inhibitory synapses in individual brain regions are regulated by eCB signaling. We also identify localizations of eCB signaling molecules by using immunofluorescence and immunoelectron microscopies.

In experiment 3, we make whole-cell recordings from neurons in anesthetized or awake rats or mice *in vivo*. We study how neuronal activities of neurons *in vivo* such as responses to natural sensory stimuli are modulated by eCB signaling.

In experiment 4, we make behavioral analyses of the knockout mice to check whether and how defect in eCB signaling is related to brain functions. We focus on learning and memory, anxiety, and anti-convulsant effect.

【Expected Research Achievements and Scientific Significance】

Our finding that eCB mediates retrograde signaling at synapses has established a new concept in the physiology of synapses. Furthermore, the fact that the eCB system is involved in various aspects of brain functions has provided new targets of drug development. In this respect, the present research project will have impacts also on clinical studies and contribute to the advance of neuroscience significantly. We have generated several knockout mice lacking eCB signaling molecules in collaboration with Prof. Sakimura (Niigata University). By using these mice together with multidisciplinary approaches, we expect to elucidate the roles of eCB signaling in brain functions at cellular, neural circuit, and behavioral levels.

【Publications Relevant to the Project】

・Kano M, Ohno-Shosaku T, Hashimotodani Y, Uchigashima M, Watanabe M: Endocannabinoid-mediated control of synaptic transmission. Physiol Rev, 89, 309-380, 2009.
・Hashimotodani Y, Ohno-Shosaku T, Tsubokawa H, Ogata H, Emoto K, Maejima T, Araishi K, Shin H-S, Kano M: Phospholipase Cß serves as a coincidence detector through its Ca^{2+} dependency for triggering retrograde endocannabinoid signal. Neuron, 45, 257-268, 2005.

【Term of Project】 FY2009-2013

【Budget Allocation】 161,800Thousand Yen

【 Homepage Address and Other Contact Information】

http://plaza.umin.ac.jp/~neurophy/Kano%20lab/Top.html