Title of Project : Imaging analysis of signaling mechanisms in the central nervous system cell-cell networks

Masamitsu Iino
(The University of Tokyo, Graduate School of Medicine, Professor)

Research Area : Medicine, dentistry, and pharmacy
Keyword : Central nervous system, Receptor, channel system, and signal transduction system

【Purpose and Background of the Research】

Neurons and glial cells in the central nervous system (CNS) form complex networks to serve their functions, and the understanding of CNS functions requires the clarification of the basic network mechanisms. We will address the network mechanism using the following strategies. First, the CNS cells have very complex morphology and subcellular signaling mechanisms determine the properties of the network. Therefore, we will develop new imaging methods for signaling molecules to clarify the cell-cell signaling mechanisms. Second, among many signaling molecules in the CNS, Ca^{2+} regulates many important CNS functions including synaptic transmission and plasticity. There must remain numerous unknown functions of Ca^{2+} signaling. Therefore, we will elucidate unknown functions of Ca^{2+} signaling in neurons and glial cells to understand the network mechanism. Imaging signaling molecules and finding novel functions of Ca^{2+} signaling, we will advance our understanding of CNS network mechanisms.

【Research Methods】

Focusing on the neuron-neuron and neuron-glia interaction in the CNS, we will study the network mechanisms as follows:

1) New functions of IP_3-Ca^{2+} signaling. Inhibiting IP_3-Ca^{2+} signaling by IP_3 5-phosphatase, we found a neuron-astrocyte interaction mechanism and a synaptic maintenance mechanism. We will apply the same method to other network mechanisms.

2) Imaging analysis of glutamate dynamics. Glutamate is the major excitatory transmitter mediating rapid synaptic transmission. Glutamate may escape from the synapses to mediate intercellular interaction outside the synaptic cleft. However, there has been no direct analysis of the spatiotemporal features of extrasynaptic glutamate dynamics. Using new fluorescent glutamate indicators, we will visualize extrasynaptic glutamate dynamics.

3) NO signal-Ca^{2+} signal coupling mechanism. We have found that NO signal couples to Ca^{2+} signal at synapses. We will clarify the molecular mechanism, as well as physiological and pathophysiological roles of the NO-Ca^{2+} coupling mechanism.

【Expected Research Achievements and Scientific Significance】

We will carry out the present study using innovative methods that are based on our previous achievements, and our study is expected to greatly contribute to the understanding of CNS functions. We expect the following results. (1) Glutamate dynamics imaging will clarify the spatiotemporal features of the extrasynaptic glutamate dynamics, and will produce a milestone work that will provide essential information to understand the neurotransmission. (2) NO-Ca^{2+} coupling mechanism analysis is expected to clarify physiological and pathophysiological mechanisms of NO-related signaling in the brain. (3) Elucidation of new roles of IP_3-Ca^{2+} signaling in neurons and glial cells is expected to result in new findings in important network mechanisms. These new findings in the basic network mechanisms will have a major impact on the related fields.

【Publications Relevant to the Project】

・Furutani, K., Okubo, Y., Kakizawa, S. and Iino, M. Postsynaptic inositol 1,4,5-trisphosphate signaling maintains presynaptic function of parallel fiber-Purkinje cell synapses via BDNF. **Proc. Nat. Acad. Sci. U.S.A.** 103, 8528-8533, 2006.

・Okubo, Y., Kakizawa, S., Hirose, K., and Iino, M. Visualization of IP_3 dynamics reveals a novel AMPA receptor-triggered IP_3 production pathway mediated by voltage-dependent Ca^{2+} influx in Purkinje cells. **Neuron** 32, 113-122, 2001.

【Term of Project】 FY2009-2013
【Budget Allocation】 183,800 Thousand Yen

【Homepage Address and Other Contact Information】
http://calcium.cmp.m.u-tokyo.ac.jp