【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Biological Sciences)

Title of Project : Study of Cerebral Synapses and Circuits Using Two-photon Microscopy and Novel Optoprobes

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Research Project Number : 26221001 Researcher Number : 60224375
Research Area : Neuroscience
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【Purpose and Background of the Research】

It is widely accepted that higher-order functions of the brain, particularly of the cerebral cortex, represent our cognition and mind. Recent functional brain imaging has revealed detailed localizations of various brain functions to specific regions in the cortex, indicating that various forms of perception, emotion, and executive functions are caused by the operation of neuronal networks in the corresponding cortical regions. Neurons extend long axons to numerous other neurons in the brain to form extensive neuronal networks, where electrical signals are transmitted via "synapses". These electrical activities, however, exist even in unawakened states of animals and hence, cannot completely account for the awake state of the brain.

We have revealed that synapses in the cerebral cortex change their shapes when their connectivity changes. Such motile synapses (spine synapses) are particularly well developed in the cerebral cortex. The motility of synapses can be induced by synchronous firing of neurons, which represent a coherent operation of neuronal circuits. The motility can be long lasting and leave traces, in a manner consistent with memory formation. A neuron in the cerebral cortex possesses thousands of spine synapses, and their motility, rather than neuronal electrical activity alone, can encode for highly diverse states.

We will develop novel methods for revealing functions of motile synapses in awake behaving animals, and in visualizing the cell-synapse assemblies responsible for various cognitive functions.

【Research Methods】

Cortical synapses can be visualized by two-photon microscopy both *in vitro* and *in vivo*. We have developed optoprobes to label and manipulate spine synapses, which are involved in learning and memory. Thus, we now can identify synapses that are involved in memory, and delineate the circuits involved in cell-synapse assembly in the cortex. We will also visualize the motilities of synapses in awake mice, and study their dependence on vigilance, stimulus selectivity, and so on. The consequences of synapse motility will be also analyzed for the presence of non-classical interactions of synapses.

【Expected Research Achievements and Scientific Significance】

Our study will clarify whether neuronal motilities, in addition to neuronal electrical activity, play essential roles in higher-order brain functions. Based on their influence on the neuronal network activity, we may obtain new insights into the localization of higher-order brain functions in specific regions of the brain and also into the mechanisms behind various mental disorders.

【Publications Relevant to the Project】

- Takahashi, N., Hatakeyama, H., Okado, H., Noguchi, J., Ohno, M. & Kasai, H. (2010). SNARE conformational changes that prepare vesicles for exocytosis. *Cell Metabolism* 12:19-29.
- Hayama, T., Noguchi, J., Watanabe, S., Ellis-Davies, G.C.R., Hayashi, A., Takahashi, N., Matsuzaki, M. & Kasai, H. (2013). GABA promotes the competitive selection of dendritic spines by controlling local Ca^{2+} signaling. *Nature Neurosci.* 16:1409-1416.

【Term of Project】 FY2014-2018

【Budget Allocation】 150,000 Thousand Yen

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