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

Integrated Science and Innovative Science (Comprehensive fields)

Title of Project：Molecular Anatomy of Synaptic Structure

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Research Area：Comprehensive fields

Keyword：Molecular neurobiology

【Purpose and Background of the Research】

Researches on synapse dynamics using optical techniques have revealed molecular rearrangement associated with synaptic plasticity. To precisely monitor molecular reorganization in synapses, new optical methods with a high spatial resolution should be developed. To correlate findings on detailed molecular distribution in single synapses with mechanism of network remodeling, experimental data obtained from high resolution microscopy in vitro should be combined with identification of dynamic synapses in vivo by using two-photon microscopy. However, this strategy will require new tissue processing technology.

To combine high resolution mapping of molecules in synapses with in vivo imaging, we set two research goals in this project.

1. Development of high resolution optical imaging of the postsynaptic density (PSD)
2. Application of the above method to the analyses of in vivo synapse dynamics

【Research Methods】

It has been shown recently that super resolution of less than 20 nm can be achieved in optical microscopy by using detection of single fluorescent molecules. Single PSD is a disk-like structure with its diameter of 400 nm and its internal structure can be theoretically resolved by using a single molecule detection method. In this study, we first test the possibility of applying the high resolution optical mapping of single fluorescent molecules to fluorescently labeled PSDs and spines. Second, we will develop a new embedding method of brain tissue without losing activity of fluorescent proteins and subsequent thin-sectioning of the embedded tissue with thickness of 1 μm. Third, by combining these technical elements, we attempt to obtain high resolution molecular mapping within single synapses identified by in vivo two-photon imaging. By correlating in vivo behavior of single synapses and molecular distribution, we expect to delineate essential molecular events associated with synapse remodeling in vivo.

【Expected Research Achievements and Scientific Significance】

We expect to clarify the molecular mechanisms of synapse formation and stabilization by detecting distribution of signaling molecules within newly formed synapses identified in vivo. It is possible to identify difference in spatial organization of glutamate receptors, scaffolding proteins, and protein kinases between stabilized synapses and synapses under dynamic reorganization. Synapse stabilization and elimination may be related to memory consolidation and extinction. Our study provides molecular characteristics of stable synapses, which will help identification of neural networks supporting long-term storage of information in the brain.

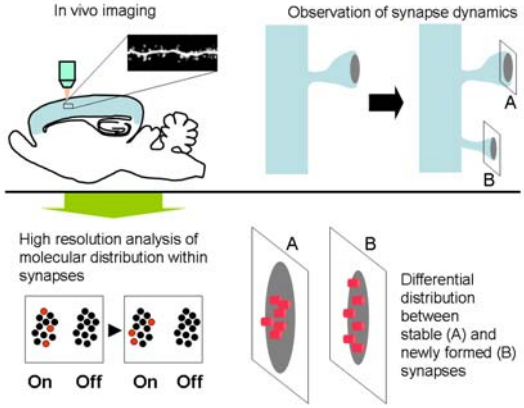

Figure 1 Experimental Design

【Publications Relevant to the Project】

- Sugiyama, Y., Kawabata, I., Sobue, K., and S. Okabe Determination of absolute protein numbers in single synapses by a GFP-based calibration technique. Nature Methods 2, 677-684, 2005.
- Kuriu, T., Inoue, A., Bito, H., Sobue, K., and S. Okabe Differential control of postsynaptic density scaffolds via actin-dependent and independent mechanisms. Journal of Neuroscience 26, 7693-7706, 2006.

【Term of Project】 FY2009-2013
【Budget Allocation】 109,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://synapse.m.u-tokyo.ac.jp/