【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)

Title of Project : Molecular physiological study for the elucidation of mechanisms for modulation of neurotransmitter release

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Research Area : Neuroscience (general)
Keyword : Molecular and cellular neuroscience

【Purpose and Background of the Research】

The induction and expression mechanism for synaptic plasticity in postsynaptic cells has been examined extensively; however, the mechanism for presynaptic plasticity of neurotransmitter release, which is also critical for postsynaptic plasticity, is largely unclear. In this research plan, we will try to elucidate (1) the mechanism for modulation of neurotransmitter release by Ca^{2+} dynamics in presynaptic terminals and (2) the mechanism by which the content of neurotransmitters in one synaptic vesicle is determined. For these purposes, we will perform functional analyses using mutant mice in which only presynaptic functional molecules are modified. Specifically, we will analyze functional molecules and intracellular organelles related to the regulation of Ca^{2+} dynamics and presynaptic plasticity of neurotransmitter release. Furthermore, we will try to elucidate the molecular mechanism for the determination of quantal size in the presynaptic terminal.

【Research Methods】

We will study electrophysiologically the mechanism for modulation of neurotransmitter release using mouse hippocampal slice preparations. We will focus on the molecules that regulate intracellular Ca^{2+} dynamics as well as the molecules whose functions are modulated by Ca^{2+}. We will also deal with intracellular organelles related to these modulations. In addition, we will generate mutant mice in which only presynaptic functional molecules are modified and analyze synaptic transmission using these mice. Furthermore, by analyzing miniature excitatory postsynaptic currents, which are the smallest unit of synaptic transmission, and evaluating quantal size using a low-affinity antagonist of AMPA receptors that mediate excitatory synaptic transmission, we will try to identify functional molecules that determine quantal size and analyze the functions of these molecules. Following these analyses, we will also perform neural behavioral analyses using mutant mice in which the molecules that we analyze are genetically modified.

【Expected Research Achievements and Scientific Significance】

In previous studies, the mechanism of neurotransmitter release itself has been examined extensively. In this research plan, we will be able to elucidate the mechanism for plastic modulation of neurotransmitter release processes. It is also unique and original that we will be able to elucidate the regulation mechanism of neurotransmitter release, which is mediated by accumulation and release of Ca^{2+} via intracellular organelles. As for quantal size, it is well known that glutamate is filled into synaptic vesicles by glutamate transporters; however, it is largely unknown how the content of glutamate in each synaptic vesicle is determined. In this study, we will be able to understand the molecular and cellular mechanism for the determination of quantal size by presynaptic factors for the first time in the world. These expected research achievements would provide novel insights into presynaptic plasticity.

【Publications Relevant to the Project】

- Sakisaka, T., Yamamoto, Y., Mochida, S. et al. Dual inhibition of SNARE complex formation by tomosyn ensures controlled neurotransmitter release. ***J. Cell Biol.*** 183:323-337, 2008.
- Shimizu, H., Fukaya, M., Yamasaki, M., et al. Use-dependent amplification of presynaptic Ca^{2+} signaling by axonal ryanodine receptors at the hippocampal mossy fiber synapse. ***Proc. Natl. Acad. Sci. USA*** 105:11998-12003, 2008.

【Term of Project】 FY2011-2015

【Budget Allocation】 165,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/NeuronalNetwork/Neuronal_Network/Index.html