

Synaptic regulatory mechanisms by novel AMPA receptor modulators

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【Outline of survey】

AMPA receptors (AMPA) mediate most fast excitatory synaptic transmission in brain. The activity dependent changes of AMPAR-mediated synaptic transmission are thought to be critical for learning and memory. Therefore, the regulatory mechanisms of AMPAR functions are the foremost issue in modern neuroscience. In this project, we clarify the regulatory mechanisms of synaptic transmission by focusing on novel regulators of AMPARs: 1) the PSD-95 palmitoylating enzyme, which determines the synaptic position of PSD-95 scaffold, and 2) the epilepsy-related ligand/receptor, LGI1/ADAM22. We also elucidate the relationship between AMPARs and Alzheimer's disease-related proteins. Taken together, we clarify regulatory mechanisms for synaptic function and dysfunction.

【Expected results】

The misregulation of synaptic transmission causes various neurological disorders, including dementia and epilepsy. Because AMPARs mediate most excitatory synaptic transmission in brain, clarifying the regulatory mechanisms of AMPARs should contribute to understanding the pathogenesis of above neurological disorders. Because enzymes and ligands/receptors are targets for about two-third of all drugs in use today, our originally identified palmitoylating enzymes and epilepsy-related ligand/receptor could become therapeutic targets for synaptic disorders.

【References by the principal investigator】

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2. Fukata, Y., Iwanaga, T., and Fukata, M. Systematic screening for palmitoyl transferase activity of the DHHC protein family in mammalian cells. *Methods* 40, 177-182, 2006
3. Fukata, M., Fukata, Y., Adesnik, H., Nicoll, R.A., and Brecht, D.S. Identification of PSD-95 palmitoylating enzymes. *Neuron* 44, 987-996, 2004

【Term of project】 FY2008- 2012

【Budget allocation】

78,100,000 yen (direct cost)

【Homepage address】

<http://www.nips.ac.jp/fukata/>