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Okayama University research: Making memories—the workings of a neuron revealed

(Okayama, 27 October) **In a study published in *Scientific Reports* researchers at Okayama University use simulations to depict changes that occur within neurons during the processes of learning and memory formation.**

Two antagonist phenomena in the brain are known to drive learning and memory. Long-term potentiation (LTP) strengthens communication between adjacent neurons to facilitate the integration of new memories. Long-term depression (LTD) weakens such interactions to relieve the brain of redundant information. However, the molecular changes driving these processes are still unclear to neuroscientists. Now, in a collaboration between Associate Professor SUMI Tomonari from Okayama University and Assistant Professor HARADA Kouji from Toyohashi University of Technology, a pair of scientists has revealed how the competitive shuttling of one molecule between in and out of synapses play an important role in this regard.

LTP and LTD are initiated by flux of calcium ions into neighbouring (post-synaptic) neurons when those receive signals from the pre-synaptic ones. The post-synaptic neurons then do so by presenting a signal reader known as the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) on their surface during LTP, which fades away during LTD. To understand the dynamics of AMPAR increase and decrease on post-synaptic membranes better, the duo created a mathematical model of post-synaptic neuron that closely mimicked physiological LTP and LTD. Neurons of the hippocampus—the seat of learning and memory within the brain—were used as a model system.

Influxes of calcium ions were applied as the input of the simulations, and successfully trigger LTP and LTD. As expected, calcium-induced LTP stimulus resulted in AMPAR being shuttled out of the post-synaptic neurons, whereas LTD resulted in AMPAR being shunted back in. A deeper dive revealed that two opposing calcium sensors, namely synaptotagmin 1/7 (Syt1/7) and protein interacting with C-kinase 1 (PICK1), were driving these movements. Both sensors were active during LTP and LTD albeit in varying amounts. The Syt1/7 activity overtook the PICK1 during LTP resulting in a release of AMPAR from vesicles, whereas the former was overtook by the latter during LTD resulting in a recapture of the released AMPAR. A competition between Syt1/7 and PICK1 was thus behind the increase and decrease of AMPAR on the post-synaptic membranes.

The research duo then closely examined the fate of AMPAR once it was shunted back into post synaptic neurons. Instead of degrading, AMPAR was stored in little vesicles near the neuron surface and kept ready for the next LTP signal. This resulted in an almost instantaneous incorporation of AMPAR into the postsynaptic membranes upon LTP

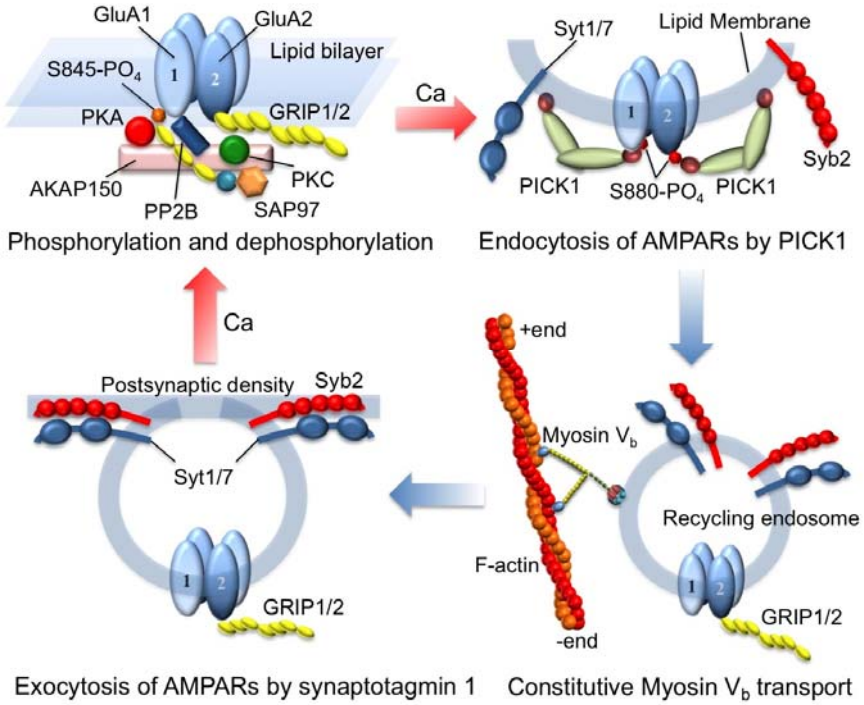
stimulus. Myosin V_b, a molecular motor protein, was responsible for this dynamic recycling of AMPAR within the neuron.

This study showed two competing mechanisms underlying LTP and LTD instead of two mutually exclusive processes. Additionally, the role of key molecules driving this dynamic competition was revealed. Deciphering the complexities of LTP and LTD is instrumental in understanding memory related disorders such as Alzheimer's disease and amnesia.

Background

LTP, LTD, and AMPAR: Long-term potentiation (LTP) is the strengthening, and long-term depression (LTD) is the weakening of inter-neuron connections in response to chemicals known as neurotransmitters. The chemically induced inflow of calcium ions into adjacent (post-synaptic) neurons warns to prepare for either LTP or LTD. Subsequently, the initiating (pre-synaptic) neuron fires neurotransmitters such as glutamate to communicate with the post-synaptic neurons.

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is a molecule that closely resembles glutamate. Thus, the post-synaptic neuron presents the AMPA receptor (AMPAR) on its surface to read glutamate signals. LTP leads to more AMPAR incorporation into postsynaptic membranes and better glutamate binding, whereas LTD leads to the opposite. The increase and decrease of AMPAR on post-synaptic membranes is a key factor in facilitating neuronal connections. Understanding the dynamics of AMPAR shuttling is vital for research on the normal development of learning and memory and disorders that implicate them.



Caption

AMPAR transport system in postsynapse reproducing LPT/LTD of hippocampal excitatory neurons.

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Reference

Tomonari Sumi, Kouji Harada. Mechanism underlying hippocampal long-term potentiation and depression based on competition between endocytosis and exocytosis of AMPA receptors. *Scientific Reports*, volume.10, Article number: 14711 (2020)
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Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html

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