Scientists show how gene expression controls synaptic plasticity in the aging human brain

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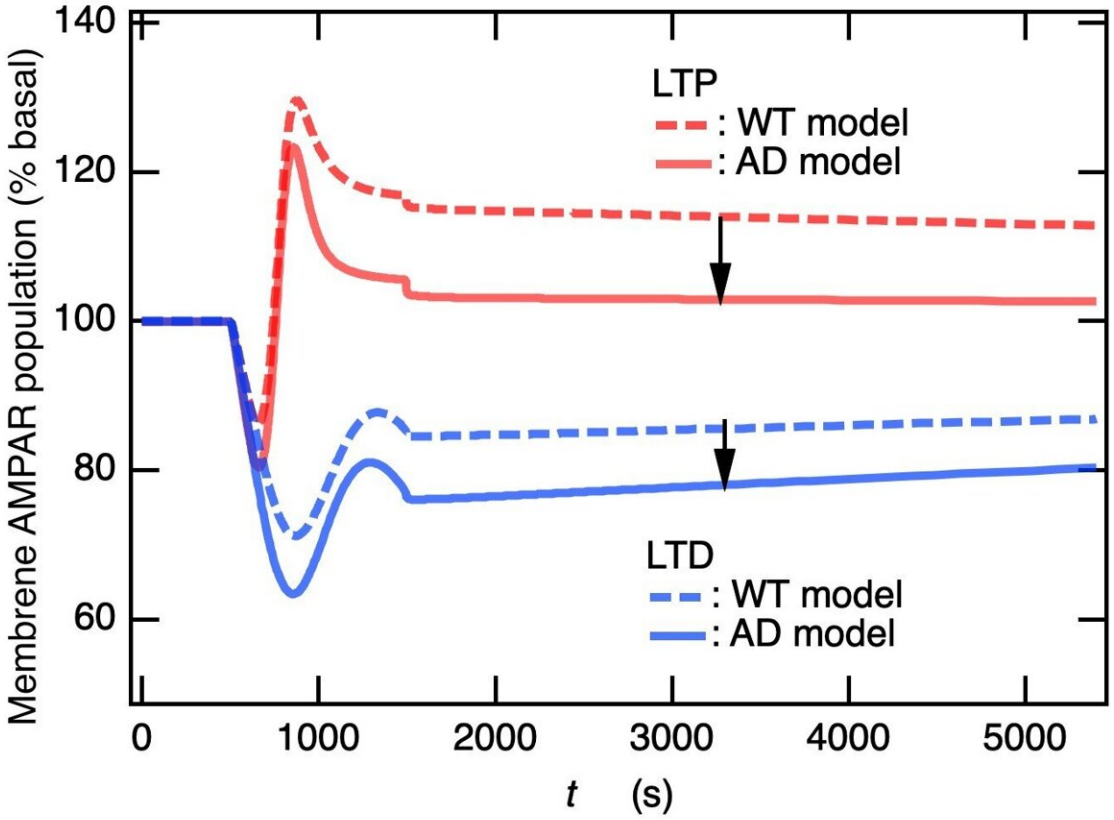

The graph shows involvement of the percentage of basal membrane AMPAR population in long term potentiation and differentiation in wild type and Alzhiemer's disease animal models. The study demonstrates that M1-mAChR- and NMDAR-dependent long term potentiation and differentiation share a common pathway. Credit: Tomonari Sumi and Kouji Harada from Okayama University

Scientific evidence shows how the cognitive decline in Alzheimer's disease (AD) is caused by the buildup of amyloid beta proteins, which promote synaptic malfunction. One of the neuropathological features in the brains of patients with AD is the degeneration of the basal forebrain cholinergic neurons, leading to a decrease in the number of cholinergic projections to the hippocampus.

As a symptomatic treatment of AD, cholinergic neurotransmission is enhanced by the use of certain drugs, known as acetylcholinesterase inhibitors. For better prevention and treatment of cognitive disorders like AD and schizophrenia, it is necessary to understand how acetylcholine regulates synaptic transmissions.

Higher brain functions, like learning and memory, are partly regulated by signaling through the M1 muscarinic acetylcholine receptor (mAChR). The mAChR also induces long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmission in the hippocampus. During hippocampus-controlled learning activities, extracellular levels of acetylcholine (Ach) increase by 4 times in the hippocampus, driven by mAChR signal transmission.

Activation of the mAChR by agonists (activator chemicals) is known to induce LTP and LTD in the hippocampus, but the underlying molecular mechanisms are not well understood.

To study these molecular mechanisms, scientists from Japan have recently designed a model to track hippocampal synaptic plasticity. Their study has been published in *iScience*.

Associate Professor Tomonari Sumi from Okayama University, Japan, who led the study, explains, "Here, we propose the hypothesis that M1 mAChR-dependent LTP and LTD share the common a-amino-3-hydroxy5-methyl-4-isoxazolepropionic acid receptor

(AMPAR) trafficking pathway associated with NMDAR dependent LTP and LTD."

For the hippocampal neurons, an AMPA receptor (AMPAR) trafficking model was proposed to simulate N-methyl-D-aspartate receptor (NMDAR)-dependent synaptic plasticity. The findings of this study prove the validity of the hypothesis that the mAChR-dependent LTP and LTD share a common AMPAR trafficking pathway.

The difference between the two pathways is that in the M1-mAChR activation, Ca^{2+} ions stored in the endoplasmic reticulum of the neurons are released into the spine cytosol. A competition between Ca^{2+} dependent exocytosis and endocytosis regulates LTP and LPD.

"Therefore, it can be concluded that the M1 mAChR-dependent induction of LTP and LTD shares the common AMPAR trafficking pathway with NMDAR-dependent synaptic plasticity, and new gene expression is not necessary, at least in the early stages of LTP and LTD," says Kouji Harada from the Center for IT-Based Education, Toyohashi University of Technology.

These findings show how the reduction in the number of AMPARs due to varying gene expression levels affects the induction of LTP and LTD. These results will be useful to understand the dominant factors resulting in alterations of LTP and LTD in animal models of AD, which can ultimately be greatly helpful for the development of AD therapy targeting synaptic plasticity for humans.

Aging of the human brain causes a marked reduction in the expression of a number of neurotransmitter receptors, like GluA1, which induces the integration of AMPA receptors inside synaptic membranes. The AMPAR trafficking model shows that alterations in LTP and LTD observed in AD could be due to age-related reduction in AMPAR

expression levels.

"Taken together, these observations suggest that either upregulation of neurotransmitter receptor genes or suppression of the downregulation could improve synaptic dysfunction during AD," says Dr. Sumi.

More information: Tomonari Sumi et al, Muscarinic acetylcholine receptor-dependent and NMDA receptor-dependent LTP and LTD share the common AMPAR trafficking pathway, *iScience* (2023). DOI: 10.1016/j.isci.2023.106133

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