Balancing connections for proper brain function

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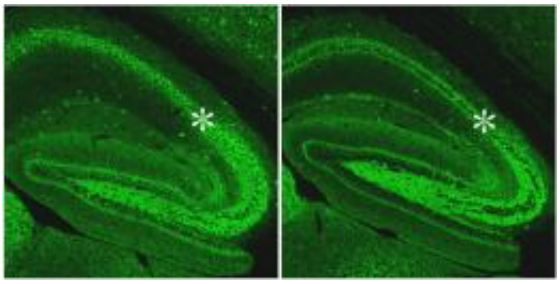

Figure 1: Compared with the brains of normal animals (left), mice lacking the Slitrk3 gene (right) have a reduced density of inhibitory synapses in the hippocampus. Reproduced from Ref. 1 © 2012 Jun Aruga, RIKEN Brain Science Institute

Neuropsychiatric conditions such as autism, schizophrenia and epilepsy involve an imbalance between two types of synapses in the brain: excitatory synapses that release the neurotransmitter glutamate, and inhibitory synapses that release the neurotransmitter GABA. Little is known about the molecular mechanisms underlying development of inhibitory synapses, but a research team from Japan and Canada has reported that a molecular signal between adjacent neurons is required for the development of inhibitory synapses.

In earlier work, the researchers—led by Jun Aruga of the RIKEN Brain Science Institute, Wako, and Ann Marie Craig of the University of British Colombia, Vancouver—showed that a membrane protein called

Slitrk2 organizes signaling molecules at synapses. They therefore tested whether five related proteins are involved in inhibitory synapse development. They cultured immature hippocampal neurons with non-neural cells expressing each of the six Slitrk proteins. They found that Slitrk3, but not other Slitrk proteins, induced clustering of VGAT, a GABA transporter protein found only at inhibitory synapses.

The researchers also examined the localization of Slitrk3 by tagging it with yellow fluorescent protein and introducing it into cultured hippocampal cells. This revealed that Slitrk3 co-localizes in the dendrites of neurons with gephyrin, a scaffold protein found only in inhibitory synapses. They then blocked Slitrk3 synthesis, and found that it led to a significant reduction in the number of inhibitory synapses.

To confirm these findings, the researchers generated a strain of genetically engineered mice lacking the Slitrk3 gene. These animals had significantly fewer inhibitory synapses than normal animals (Fig. 1), and therefore impaired neurotransmission of GABA. They were also susceptible to epileptic seizures. From a screen for proteins that bind to Slitrk3, Aruga, Craig and colleagues identified the protein PTPδ as its only binding partner. Introduction of PTPδ fused to yellow fluorescent protein to cultured hippocampal neurons showed that it is expressed in neuronal dendrites and cell bodies, but not in axons. Blocking PTPδ synthesis prevented the induction of inhibitory synapses by the Slitrk3 protein.

These results demonstrated that the interaction between Slitrk3 on dendrites and PTPδ on axons of adjacent cells is required for the proper development of inhibitory synapses and for inhibitory neurotransmission in the brain.

“We are now examining whether the balance of excitatory and inhibitory synapses is affected by other members of the Slitrk protein family,” says

Aruga. “It is possible that Slitrk3 and other Slitrk proteins are acting synergistically or antagonistically. We are also clarifying whether Slitrk3 is involved in any neurological disorders.”

More information: Takahashi, H., Katayama, K., Sohya, K., Miyamoto, H., Prasad, T., Matsumoto, Y., Ota, M., Yasuda, H., Tsumoto, T., Aruga, J. & Craig, A.M. Selective control of inhibitory synapse development by Slitrk3-PTPδ trans-synaptic interaction. Nature Neuroscience 15, 389–398 (2012). www.nature.com/neuro/journal/v …/n3/abs/nn.3040.html

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