Nature Reviews Neuroscience | AOP, published online 12 October 2011; doi:10.1038/nrn3127

SYNAPTIC PLASTICITY

Transporting memories

In humans, polymorphisms in the gene encoding KIBRA have been linked to variation in memory performance; however, the neural function of this protein has been unclear. Now, Huganir and colleagues report that KIBRA regulates AMPA receptor (AMPAR) trafficking and synaptic plasticity.

Fast excitatory synaptic transmission in the brain mainly occurs through AMPARs, and the trafficking of such receptors to and from synapses is integral to the various mechanisms of synaptic plasticity that are linked to learning and memory, including long-term potentiation (LTP) and long-term depression (LTD).

Protein interacting with C kinase 1 (PICK1; also known as PRKCA-binding protein) is implicated in the regulation of AMPAR trafficking, and the authors identified KIBRA as a PICK1-binding partner in a yeast two-hybrid screen. Subsequently, they co-immunoprecipitated these proteins from mouse brain samples using an anti-KIBRA antibody, confirming that KIBRA and PICK1 interact *in vivo*. Two AMPAR subunits and several other proteins that are associated with AMPAR trafficking were also detected in the immunoprecipitate, suggesting that KIBRA has a role in this process.

To test this assertion, the authors used an AMPAR subunit (glutamate receptor 2 (GluR2)) recycling assay in cultured hippocampal neurons. In this assay, NMDA receptor activation leads to rapid internalization of cell surface GluR2 in the soma and dendrites. GluR2 is then recycled to the plasma membrane when NMDA is removed. Knockdown of KIBRA expression by specific short hairpin RNAs had no effect on GluR2 internalization but did increase the rate at which this subunit was recycled, indicating that KIBRA has a role in retaining internalized AMPARs following neural activity.

Next, the authors generated *Kibra*$^{-/-}$ mice. Electrophysiological recordings in hippocampal slices from these animals revealed that adult knockout mice had defects in LTP and LTD but young knockout mice did not, consistent with a role for KIBRA in activity-dependent AMPAR trafficking.

Finally, the authors assessed hippocampus-dependent learning and memory in adult *Kibra*$^{-/-}$ mice through use of fear conditioning. These animals took longer to learn associations between a shock and a tone or context than did wild-type animals, and showed marked deficits in retaining memories for these associations 24 hours after training.

Together, these results suggest that KIBRA affects learning and memory through modulation of AMPAR trafficking and synaptic plasticity.

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ORIGINAL RESEARCH PAPER Makuch, L. *et al.* Regulation of AMPA receptor function by the human memory-associated gene KIBRA. *Neuron* **71**, 1022–1029 (2011)