Nature Reviews Neuroscience | AOP, published online 2 September 2011; doi:10.1038/nrn3108

SYNAPTIC PLASTICITY

A key player in presynaptic plasticity

> short-term plasticity at excitatory and inhibitory synapses was not affected in *Rab3b* knockout mice, suggesting a role for RAB3B in forms of synaptic plasticity that occur over longer timescales

Presynaptic forms of long-term plasticity involve changes in probability of transmitter release. They can occur at both excitatory and inhibitory synapses and contribute to behaviours such as learning and memory. One common form of such plasticity at inhibitory synapses is endocannabinoid-dependent presynaptic long-term depression (LTD). Whether or not a member of the RAB3 synaptic vesicle protein family is involved in this form of plasticity was unknown. Now, Tsetsenis et al. show that RAB3B is crucial for endocannabinoid-dependent LTD at inhibitory hippocampal CA1 synapses (termed i-LTD) and plays a part in spatial memory retention.

There are four RAB3 isoforms. Using immunohistochemical techniques, the authors found that RAB3B is enriched at inhibitory hippocampal CA1 synapses. Thus, RAB3B might be an important contributor to plasticity at these synapses. The authors generated Rab3b knockout mice and used electrophysiological recordings to determine changes in synaptic transmission. Basal neurotransmission at both excitatory and inhibitory synapses seemed to be normal in these mice; however, i-LTD was markedly attenuated in knockout animals compared with wild-type controls. Importantly, short-term plasticity at excitatory and inhibitory synapses was not affected in Rab3b knockout mice, suggesting a role for RAB3B in forms of synaptic plasticity that occur over longer timescales.

Interestingly, in tests that involved the Morris water maze, the authors found that the initial rate of learning of the submerged platform's location was similar in knockout mice and their wild-type littermates. When the position of the platform was changed to the opposite side of the pool, however, the knockout mice adjusted to the new position of the platform more quickly than control animals, which suggests an enhanced reversal of spatial learning. In other words, the knockout mice more readily 'forgot' the previous location of the platform. Similarly, Rab3b knockout mice more effectively erased fearful memories that were established in a previously aversive environment.

These findings indicate that RAB3B is an important player in endocannabinoid-dependent LTD in the inhibitory synapses of the hippocampal CA1, and that i-LTD contributes to learning and memory, possibly by enhancing the stability of synapses and circuits that have previously been modified by a learning stimulus.

Sian Lewis

ORIGINAL RESEARCH PAPER Tsetsenis, T. *et al.* Rab3B protein is required for long-term depression of hippocampal inhibitory synapses and for normal reversal learning. *Proc. Natl Acad. Sci. USA* 15 Aug 2011 (doi:10.1073/pnas.1112237108)