Nature Reviews Neuroscience | Published online 5 Oct 2017; doi:10.1038/nrn.2017.127

SYNAPTIC PLASTICITY

Strength through movement

> whereas STP involves movement of AMPARs from extrasynaptic locations, eLTP requires exocytosis of new AMPARs first, followed by diffusion of these receptors to synaptic locations

High-frequency stimulation (HFS) of hippocampal CA3→CA1 synapses results in a potentiation process that involves several stage: short-term potentiation (STP), which occurs immediately after stimulation; early long-term potentiation (eLTP), which occurs at time points less than 1 h later; and late LTP, which occurs after 1 h; each stage involves different cellular processes. Various mechanisms have been suggested for eLTP at these synapses, including recruitment of additional AMPA receptors (AMPARs) either from an intracellular pool or from extrasynaptic locations, but direct evidence remains elusive. In this study, Penn *et al.* show that AMPAR trafficking from extrasynaptic sites plays a crucial role in STP and eLTP.

Gary Waters / Alamy Stock Photo

To investigate the role of extrasynaptic AMPAR diffusion in synaptic strength increases at CA3→CA1 synapses, the authors developed a technique in which biotin-tethered GluA2 could be autonomously expressed in brain slices; exposure of these surface-expressed proteins to a biotin-binding protein could then induce crosslinking and AMPAR immobilization. They showed that in biotin-tethered GluA2-expressing hippocampal slices from mice that lack endogenous GluA2 subunits, acute pretreatment with the biotin-binding protein did not affect basal synaptic transmission but abolished HFS-induced STP. This suggests that diffusion of surface AMPARs plays an important role in the expression of STP.

Interestingly, although STP was blocked, eLTP still occurred in these slices. The authors hypothesized that eLTP relied on a different mechanism to that of STP (at least initially): exocytosis of new AMPARs into the postsynaptic membrane. Indeed, application of tetanus toxin light chain (TeTx), which prevents exocytosis, blocked eLTP but not STP, which suggests that whereas surface diffusion of existing AMPARs seems to be crucial for STP, eLTP requires exocytosis of intracellular AMPARs. It has been reported that AMPAR exocytosis occurs at extrasynaptic locations, and the authors reasoned that for these AMPARs to participate in synaptic strengthening, they would need to traffic to synaptic locations. In support of this notion, the authors found that ongoing exposure of slices to the biotin-binding protein following HFS prevented both STP and eLTP.

Through the use of a different approach to restrict AMPAR surface mobility — that is, anti-GluA2 antibody-mediated crosslinking — in acute hippocampal slices, the authors found that, again, pretreatment with the crosslinking antibody followed by HFS reduced STP, and that continual anti-GluA2 infusion abolished eLTP. *In vivo* confirmation of these findings was obtained by anti-GluA2 antibody injection into dorsal hippocampal CA1 followed by HFS of commissural CA1 input; this produced a substantial reduction in field excitatory postsynaptic potentials in this region. These findings suggest that whereas STP involves movement of AMPARs from extrasynaptic locations, eLTP requires exocytosis of new AMPARs first, followed by diffusion of these receptors to synaptic locations.

Contextual fear learning is thought to involve AMPAR trafficking and synaptic plasticity in the dorsal hippocampus. If this hypothesis is correct, then crosslinking AMPARs in this brain region should impair the formation of contextual fear memories. Mice were injected with either anti-GluA2 antibodies or a control solution into the dorsal hippocampus and exposed to a fear-conditioning paradigm. The following day, re-exposure to the fear-conditioned context produced around 50% less freezing in antibody-treated mice compared with controls.

Together, these findings suggest that diffusion of extrasynaptic AMPA receptors is crucial for hippocampal synaptic plasticity and for contextual memory formation in mice.

Sian Lewis

ORIGINAL ARTICLE Penn, A. C. *et al.* Hippocampal LTP and contextual learning require surface diffusion of AMPA receptors. *Nature* **549**, 384–388 (2017)