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Simon Bradbrook/NPG

SYNAPTIC PHYSIOLOGY

Seventh sense

Closely spaced action potentials can cause an increase in neurotransmitter release known as facilitation. The underlying mechanism for this has remained elusive, but now Jackman *et al.* show that the calcium sensor synaptotagmin 7 (SYT7) has a crucial role in mediating this response.

SYT7 presynaptic action potentials produce a large, localized increase in presynaptic intracellular calcium (Ca^{2+}) that triggers neurotransmitter release through binding of the Ca^{2+} to fast synaptotagmin isoforms such as SYT1 and SYT2. This is followed by a smaller residual Ca^{2+} signal (Ca^{2+res}) that lasts for several tens of miliseconds and has been implicated in synaptic facilitation. SYT7 is present presynaptically and binds Ca^{2+} with high affinity and slow kinetics, making it a promising candidate sensor for Ca^{2+res}.

The authors found that *Syt7*-knockout mice do not exhibit facilitation, and used a combination of electrophysiology, pharmacology and optogenetics to determine why. They focused their attention on the hippocampal CA1–CA3 Schaffer collateral synapse, which exhibits facilitation following a paired-pulse facilitation (PPF) protocol (that is, the application of closely spaced stimuli). They found that, following synaptic stimulation, the amplitude and time course of Ca^{2+} influx and Ca^{2+res} were similar in wild-type mice and *Syt7*-knockout mice. This suggests that the loss of facilitation in *Syt7*-knockout mice is not due to a change in the Ca^{2+} signal.

The authors then turned their attention to measuring the initial release probability (p), as an increase in p could produce synaptic depression that would obscure facilitation. They compared p in *Syt7*-knockout and wild-type mice using the use-dependent blocker of NMDA receptors (NMDARs), MK-801. In the presence of this agent, higher p results in more glutamate release and faster blockade of NMDARs; thus, the rate of attenuation of NMDAR-mediated synaptic responses can be used to assess changes in p. Following single stimuli, the rate of NMDAR blockade in the presence of MK-801 was similar between *Syt7*-knockout and wild-type mice, indicating a similar initial p. However, NMDAR-mediated responses evoked by brief trains of stimuli decayed more quickly (indicative of greater glutamate release) in wild-type than in *Syt7*-knockout mice, suggesting that the mutant mice lacked the ability to increase release probability and thus produce facilitation.

Finally, the authors co-expressed SYT7 and channelrhodopsin-2 (ChR2) in CA3 terminals enabling optogenetic activation of SYT7-expressing neurons. SYT7 expression in hippocampal CA3 terminals of *Syt7*-knockout mice restored facilitation in a cell-autonomous manner. In wild-type mice, expression of a mutant SYT7 that lacked the calcium-sensing C2A domain substantially attenuated facilitation. These data suggest that SYT7 is likely to be the calcium sensor that mediates the increase in p during facilitation.

Sian Lewis

> “SYT7 is likely to be the calcium sensor that mediates the increase in p [synapse initial release probability] during facilitation”

ORIGINAL ARTICLE Jackman, S. L. *et al.* The calcium sensor synaptotagmin 7 is required for synaptic facilitation. *Nature* **529**, 88–91 (2016)