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SYNAPTIC TRANSMISSION

Short-term consequences for calyces

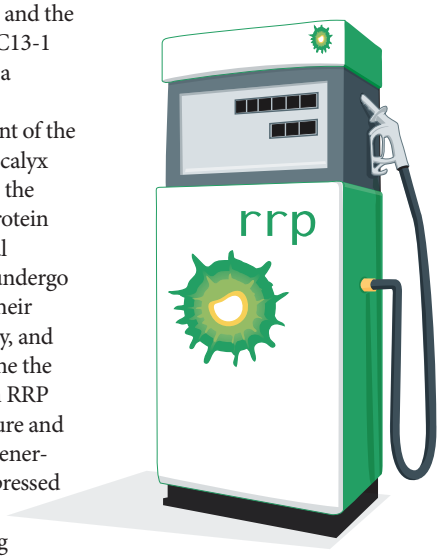
> The fast-releasing pool of immature calyces from MUNC13-1^{W464R} mice was much slower to recover from depletion compared with wild-type mice

Short-term synaptic depression (STD) is a type of plasticity that occurs at many synapses in response to high-frequency stimulation (HFS). STD is mainly caused by depletion of the readily releasable pool (RRP) of synaptic vesicles. The recovery from STD is controlled by the Ca^{2+}/calmodulin-dependent replenishment of the RRP, but the mechanism by which this occurs is not known. A new study by Lipstein *et al.* shows that an interaction between Ca^{2+}/calmodulin and the vesicle priming protein MUNC13-1 (also known as UNC13A) has a crucial role.

A key stage of replenishment of the RRP is vesicle priming, and at calyx of Held synapses, this involves the Ca^{2+}-dependent active zone protein MUNC13-1. Early in postnatal development, calyx synapses undergo maturation, which improves their processing speed and reliability, and the authors sought to determine the involvement of MUNC13-1 in RRP replenishment in both immature and mature calyx synapses. They generated a knockin mouse that expressed a variant of MUNC13-1 in which Ca^{2+}-dependent binding to Ca^{2+}/calmodulin was disrupted (MUNC13-1^{W464R} mice). Patch-clamp recordings of calyx of Held synapses in brainstem slices enabled estimation of the rate of RRP recovery using a paired-pulse protocol.

It is known that vesicle release from the RRP of calyces consists of two phases — a fast component and a slow component, reflecting fast- and slow-releasing pools of vesicles. The fast-releasing pool of immature calyces from MUNC13-1^{W464R} mice was much slower to recover from depletion compared with wild-type mice, whereas recovery time of the slow-releasing pool was the same in both groups. At mature calyces, both the fast- and slow-releasing vesicle pools of MUNC13-1^{W464R} mice were affected. In addition, recovery of the fast-releasing pool in wild-type mice (both immature and mature) was reduced by exposure to an inhibitor of calmodulin, further implicating Ca^{2+}/calmodulin and MUNC13-1 signalling in RRP recovery. Finally, the authors found that disruption of the interaction between Ca^{2+}/calmodulin and MUNC13-1 in MUNC13-1^{W464R} mice resulted in aberrant STD.

These findings demonstrate, in an intact preparation, the importance of Ca^{2+}/calmodulin–MUNC13-1 signalling for RRP replenishment and for STD at calyx synapses throughout development.



J. Vallis/NPG

Sian Lewis

ORIGINAL RESEARCH PAPER Lipstein, N. *et al.* Dynamic control of synaptic vesicle replenishment and short-term plasticity by Ca2+-Calmodulin-Munc13-1 signaling. *Neuron* http://dx.doi.org/10.1016/j.neuron.2013.05.011 (2013)