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SYNAPTIC TRANSMISSION

A hare as well as a tortoise

> DA axons can exhibit fast exocytosis, probably from RIM-containing active zones

Presynaptic release of fast neurotransmitters such as glutamate and GABA can be precisely timed at the submillisecond level and operates over short distances. In the striatum, dopamine (DA) is thought to signal by a different mechanism — volume transmission, which is generally considered to be slower and less precisely timed; whether DA is released via fast exocytosis has not been clear. In this study, Liu and colleagues find that mouse dorsal striatal DA axons have varicosities containing active zones that can mediate fast DA release. DA may therefore rapidly code information in addition to its slower-acting roles.

Fast synaptic transmission requires active zones, which are specialized regions that contain molecular machinery involved in exocytosis (including scaffolding proteins such as RIM, ELKS and bassoon), vesicle docking and priming (such as MUNC13 and MUNC18), and vesicular SNARE proteins (such as synaptobrevin 2).

First, the authors used antibodies against tyrosine hydroxylase (TH) and antibodies against bassoon to identify neurons expressing DA and any putative active zones, respectively. Then, using super resolution microscopy (which enabled localization of proteins at the level of individual synapses), they found that bassoon clusters were often localized within DA neurons. In addition, TH-expressing striatal synaptosomes were found to contain bassoon, RIM and ELKS, further supporting the existence of active zone-like structures in these neurons.

Next, the authors investigated whether these active zone-like sites release DA. They applied amperometry in acute brain slices from mice in which RIM had been conditionally and selectively knocked out in DA neurons (RIM cKODA mice). DA release was almost entirely abolished in these mice, even at high stimulation intensities or following short stimulus trains; this was unexpected because at most other fast synapses removal of RIM produces only a partial decrease in neurotransmitter release. Moreover, microdialysis showed that extracellular levels of DA in the striatum of these mice were reduced, but this effect was lost when action potentials were blocked with tetrodotoxin, suggesting that, in these neurons, RIM is crucial for evoked DA release.

The authors noticed that DA release evoked by a short stimulus train diminished rapidly, and reasoned that this effect could be caused by depletion of the pool of readily releasable synaptic vesicles. To test this hypothesis, the authors expressed a fast channelrhodopsin selectively in dopamine neurons of wild-type mice. Light-induced activation of these neurons produced DA release that was tetrodotoxin sensitive, and occurred on a timescale similar to that observed at classical fast synapses and that indicates a high release probability. By contrast, optogenetically triggered DA release in RIM cKODA mice was strongly impaired. Together, these findings suggest that DA axons can exhibit fast exocytosis, probably from RIM-containing active zones.

Comparison of the distribution of active zone-like sites relative to DA-containing vesicle clusters in DA axons showed that 30% of varicosities that contained clusters of DA vesicles also contained bassoon, RIM or ELKS. Moreover, 25–30% of synaptosomes that were positive for TH and synaptobrevin 2 also expressed bassoon or RIM.

Taken together, these findings suggest that around a third of DA-containing axonal varicosities of striatal neurons contain active zones that are capable of fast DA release followed by a rapid attenuation of release, which might play a role in DA coding with subsecond precision.

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ORIGINAL ARTICLE Liu, C. *et al.* Dopamine secretion is mediated by sparse active zone-like release sites. *Cell* https://doi.org/10.1016/j.cell.2018.01.008 (2018)

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