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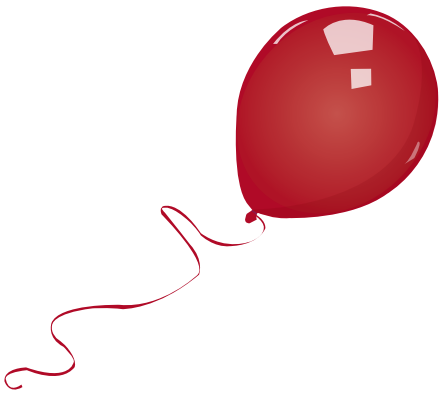

NEUROTRANSMISSION

Timing the release

At chemical synapses, neurotransmission involves calcium-triggered fusion of neurotransmitter-containing synaptic vesicles (SVs) with the plasma membrane, and it frequently comprises fast and slow components. The mechanisms underlying fast and slow neurotransmitter release are incompletely understood, but now Kaplan and colleagues show in *Caenorhabditis elegans* that they require different combinations of exocytic proteins.

Previous studies showed that, at the cholinergic neuromuscular junction (NMJ) in *C. elegans*, loss of the active zone protein UNC-13 reduced the number of docked SVs at the presynaptic terminal, whereas loss of UNC-10, another active zone protein, only impaired SV docking at a small region within the terminal, at the site of highest calcium channel density. This suggested that different proteins might promote the fusion of different SV populations.

UNC-13 is in fact expressed as long and short isoforms (UNC-13L and UNC-13S). The authors found that UNC-13L co-localized with UNC-10 at presynaptic sites at the worm NMJ, whereas UNC-13S had a more diffuse axonal distribution, indicating that the two UNC-13 isoforms may be involved in different forms of neurotransmitter release.

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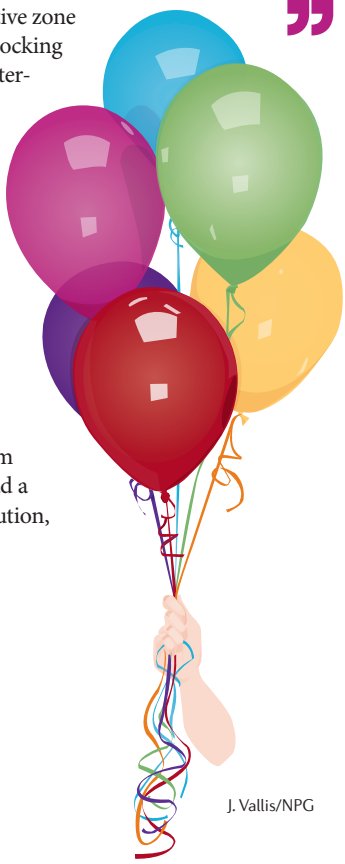

J. Vallis/NPG

Expression of UNC-13L or UNC-13S, via transgenes, fully or partially rescued, respectively, the endogenous excitatory postsynaptic current (EPSC) deficits that are observed in *unc-13(s69)* mutant worms, which do not express either UNC-13 isoform. This confirmed the role of the UNC-13 isoforms in synaptic transmission. By recording stimulus-induced EPSCs in body wall muscle, the authors also showed that EPSC kinetics were faster in UNC-13L-rescued worms than in wild-type worms, whereas they were slower in UNC-13S-rescued animals, suggesting that UNC-13L and UNC-13S mediate fast and slow neurotransmitter release, respectively.

The results described above might have been influenced by protein overexpression effects. Thus, to test whether the UNC-13 isoforms influence synaptic function independently of each other, as the results above suggested, the authors examined synaptic transmission in worms in which endogenous UNC-13L expression was selectively inactivated. These animals had synaptic transmission deficits, as revealed by their endogenous and stimulus-induced EPSCs, that were less severe than those in *unc-13(s69)* worms but more severe than those in UNC-13S-rescued worms. This suggested that UNC-13L not only mediates fast neurotransmission but also regulates slow neurotransmitter release.

Last, the authors examined whether other proteins may be involved in mediating fast versus slow neurotransmitter release. Worms with a mutation in the gene encoding tomosyn (*tom-1*) showed more prolonged, slower acetylcholine release at the NMJ than did wild-type worms, and worms lacking both tomosyn and UNC-13L showed an increase in acetylcholine release compared with worms in which UNC-13L expression was inactivated. Together, these data suggest that tomosyn inhibits the promotion of slow neurotransmitter release by UNC-13S.

This study shows that at the worm NMJ, fast and slow neurotransmitter release require different sets of exocytic proteins. Similar mechanisms may govern fast and slow neurotransmitter release in mammals, as UNC-13 and tomosyn homologues are found across phyla.

Darran Yates

ORIGINAL RESEARCH PAPER Hu, Z., Tong, X.-J. & Kaplan, J. M. UNC-13L, UNC-13S, and Tomosyn form a protein code for fast and slow neurotransmitter release in *Caenorhabditis elegans*. *eLife* **2**, e00967 (2013)