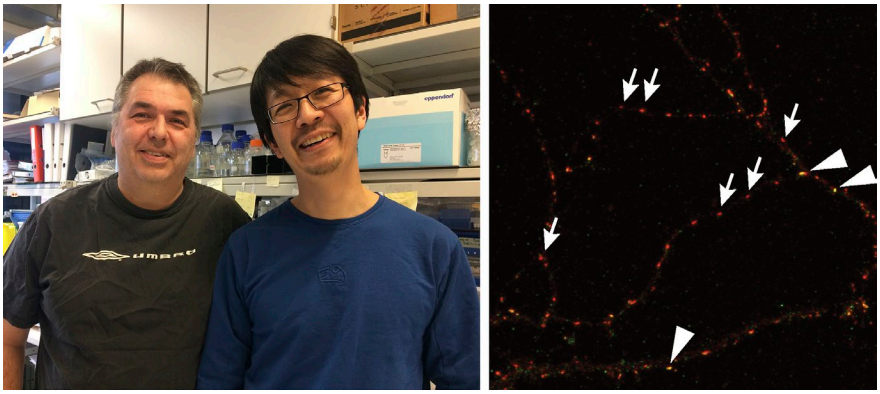
ELKS1 helps neuronal synapses diversify

Ben Short

Study reveals how neurons vary the properties of individual synapses by recruiting different Munc13 proteins to presynaptic active zones.



Focal Point Nils Brose (left), Hiroshi Kawabe (right), and colleagues reveal how individual presynapses recruit different active zone proteins to endow themselves with distinct functional properties. Most of the presynapses in hippocampal neurons (arrows) use RIM proteins to recruit the synaptic vesicle priming protein Munc13-1 (red), which depresses synaptic vesicle release during repetitive stimulation. But a small subset of presynapses (arrowheads) also use the active zone protein ELKS1 to recruit bMunc13-2 (green), which augments synaptic transmission during sustained activity. This synaptic heterogeneity is crucial for the overall behavior of neuronal networks. Photo courtesy of the authors.

Presynaptic active zones contain a network of proteins that control the tethering, priming, and fusion of synaptic vesicles to ensure that neurotransmitters are released at the right time and place. Yet the properties of individual presynapses can vary even within a single neuron, suggesting that different synapses can recruit distinct active zone proteins. In this issue, Kawabe et al. describe how a subset of synapses in hippocampal neurons specifically recruit the synaptic vesicle priming protein bMunc13-2 (1).

Researchers have long recognized that individual synapses in the same neuron can have distinct properties. During repetitive stimulation, for example, some synapses may become progressively less active while others in the same cell may show an increase in activity (2). These differences in short-term plasticity are crucial for determining the overall behavior of a neuronal network. "But," says Nils Brose, from the Max Planck Institute of Experimental Medicine in Göttingen, Germany, "nobody really knows the cause of these differences or how synapses might be equipped with distinct proteins to make them different."

One component of active zones known to influence short-term plasticity is the Munc13 family of synaptic vesicle priming proteins. These proteins are absolutely required for synaptic transmission because of their ability to regulate the conformation of the SNARE proteins that mediate synaptic vesicle fusion (3). However, the vesicle-priming activity of Munc13 proteins is modulated by various second messengers including Ca^{2+}/calmodulin and diacylglycerol. Some family members, like Munc13-1, are only moderately activated by these second messengers upon neuronal stimulation, resulting in a depression of synaptic vesicle release, whereas others, such as bMunc13-2, are activated strongly to augment further synaptic transmission (4).

Electrophysiological studies have suggested that Munc13-1 and bMunc13-2 are targeted to different subsets of synapses within hippocampal neurons (3, 4), and Brose and colleagues, led by Hiroshi Kawabe, confirmed by fluorescence microscopy that, although most presynapses contain Munc13-1, ~10% also contain bMunc13-2 (1).

"We have the first glimpse of the molecular mechanisms by which synapses can be equipped with different proteins."

Munc13-1 is recruited to presynaptic active zones by RIM proteins, which bind to a domain in Munc13-1's N terminus. bMunc13-2 has a distinct N-terminal domain, however, so Kawabe et al. performed a yeast two-hybrid screen to identify proteins that might recruit bMunc13-2 to presynapses (1). Using this approach, the researchers discovered that a coiled-coil domain in bMunc13-2's N terminus binds to a coiled-coil sequence in the active zone protein ELKS1.

The two proteins colocalized at a subset of synapses in the brain, and bMunc13-2's recruitment to presynapses was reduced in ELKS1 conditional knockout mice. Similarly, a bMunc13-2 mutant lacking the ELKS1-binding domain failed to efficiently localize to presynaptic active zones in Munc13-1/2 double knockout hippocampal neurons.

Unlike full length bMunc13-2, the mutant version unable to bind ELKS1 could only partially restore neurotransmission between these double knockout neurons; the cells contained a lower number of primed, readily-releasable synaptic vesicles and were less able to augment synaptic transmission upon repetitive stimulation.

Thus, although most presynapses in hippocampal neurons use RIM proteins to recruit Munc13-1, a small subset also use ELKS1 to recruit bMunc13-2. These two types of presynapse are therefore endowed, respectively, with the ability to depress, or facilitate, synaptic vesicle release during repeated stimulation. "So, we have the first glimpse of the molecular mechanisms by which synapses can be equipped with different proteins that endow them with different functional characteristics," Kawabe says. "But, of course, the next question is how ELKS1 is localized to some presynaptic active zones but not others."

One possibility, Kawabe and Brose suggest, is that the postsynaptic neuron signals via adhesion molecules to determine which proteins are recruited to the presynaptic site.

1. Kawabe, H., et al. 2017. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201606086
2. Reyes, A., et al. 1998. *Nat. Neurosci.* 1:279–285.
3. Varoqueaux, F., et al. 2002. *Proc. Natl. Acad. Sci. USA.* 99:9037–9042.
4. Rosenmund, C., et al. 2002. *Neuron.* 33:411–424.

bshort@rockefeller.edu