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RESEARCH NEWS

Clearing the way for synaptic vesicle release

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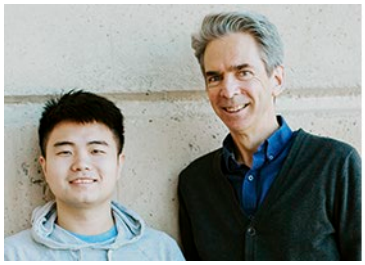
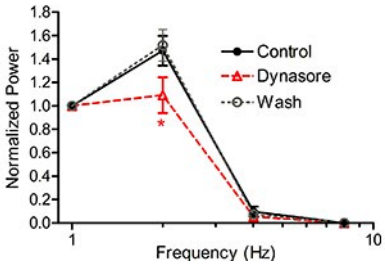
JGP study shows that endocytosis aids synaptic vesicle release at ribbon synapses.

The neuronal synapse is a specialized structure that forms where one neuron contacts another. Information is conveyed across the gap between cells by neurotransmitters, special chemicals that are stored inside vesicles in the presynaptic neuron. In the central nervous system, neurotransmitters are released in pulsatile fashion when an action potential arrives at the synapse and prompts synaptic vesicles to dock and fuse at the plasma membrane. In contrast, sensory neurons, such as the photoreceptor cells of the eye, release synaptic vesicles continuously and produce graded responses to environmental stimuli by varying the intensity of vesicle release (1). In this issue of the *Journal of General Physiology*, Wen et al. explore how sensory neurons prepare their synapses for continual vesicle release (2).

Reflecting their functional differences, the synapses of sensory neurons are structurally different from those of the central nervous systems; they contain a proteinaceous structure called a "ribbon." In photoreceptor cells, the ribbon hovers just above the synaptic plate, where it collects and organizes synaptic vesicles to ready them for rapid release at the nearby plasma membrane (3). The rate at which vesicles are released at ribbon sites depends strongly on how quickly vesicles are delivered to the bottom of the ribbon (4), but other processes may also affect how quickly vesicles are released. For example, in brain neurons, endocytic processes can limit vesicle release rate at synapses (5).

"It's thought that neurons need to remove all the previous crud—the proteins and lipids that have been deposited at the membrane by vesicle fusion—to prepare that site for new release, and that cleaning of the release site occurs as a consequence of endocytosis," explains Dr. Wallace Thoreson, a professor at the University of Nebraska Medical Center's Truhlsen Eye Institute. "That process of clearing out debris can restrict the rate of release at conventional synapses when they're stimulated at high frequencies, like 100 Hz. It can become a problem because they can't clean up fast enough. I thought this could be more of a problem at ribbon synapses, which have continuous release."





Xiangyi Wen (left), Wallace Thoreson (right), and colleagues show that synaptic vesicle release from salamander rod ribbon synapses is sensitive to inhibition of endocytosis at stimulation frequencies as low as 2 Hz. Photo courtesy of the authors.

> "I thought this could be more of a problem at ribbon synapses"

Thoreson's group, led by graduate student Xiangyi Wen, investigated this question in salamander eyes by studying currents in horizontal cells, which collect inputs from rod cell ribbon synapses. The researchers observed that the drug dynasore, which impairs the endocytic GTPase dynamin, strongly inhibited light-evoked currents in horizontal cells at stimulation frequencies as low as 2 Hz, suggesting that rod cell ribbon synapses are actually more sensitive to inhibition of endocytosis than are conventional synapses. Additional experiments with other dynamin inhibitors also supported a strong impact of endocytosis upon vesicle release.

Earlier work suggested release site clearance promotes vesicle docking at the plasma membrane in central neurons (6). However, vesicle release also involves the separate step of fusion with the plasma membrane. The large size of salamander rod cells allowed Wen et al. to determine which step is affected by observing the behavior of fluorescently labeled synaptic vesicles using total internal reflection microscopy.

"We found that when endocytosis was impaired, vesicles could dock just fine but wouldn't fuse," notes Thoreson. Unexpectedly, dynasore treatment also reduced the numbers of vesicles arriving at the synapse from the ribbon in the first place. "It's not obvious to me why this should be the case," says Thoreson. "Dynasore should only be affecting proteins on the membrane. Maybe it's influencing a network of proteins further up in the cell, or it could be an artifact of the drug."

More studies are needed to understand how blockade of endocytosis affects vesicle release at ribbon synapses. Thoreson's group wants to study mouse retina to identify what molecules are involved in vesicle fusion in rods, how these proteins are affected by endocytosis, and the importance of endocytosis in cones or other sensory cell types.

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