NEUROSCIENCE April 2004 Vol 5 No 4 HIGHLIGHTS

Nature Reviews Neuroscience **5**, 256 (2004); doi:10.1038/nrn1371

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[694K]

SYNAPTIC PHYSIOLOGY

Freedom for vesicles

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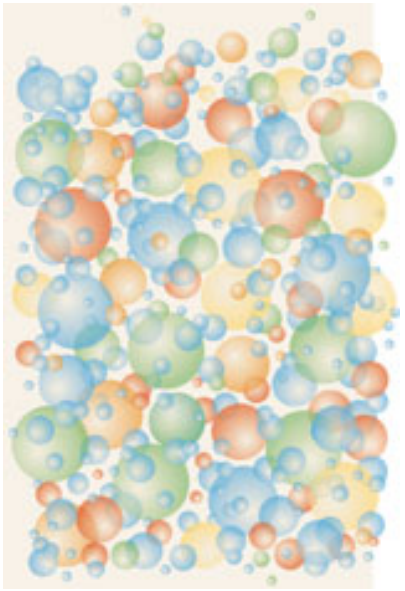
Unlike most neurons, photoreceptors release neurotransmitter continuously, except when they are stimulated by light. Rea and colleagues, writing in *Neuron*, describe some of the specialized features that allow cone photoreceptors to keep up this tonic release.



We know that the synapses of cones have a number of unusual charateristics, including structures called 'synaptic ribbons' that bind large numbers of vesicles near the synaptic membrane. Exocytosis in cones is particularly sensitive to levels of Ca^{2+}, and endocytosis is unusually rapid and precise. But it has been difficult to study further details of the vesicle cycle. Rea *et al*. have developed a way to load the marker dye FM1-43 specifically into the synaptic terminals of cones, by labelling cells in the intact retina rather than when dissociated. Cones are labelled in the dark, and the retina is then transferred to a Ca^{2+}-free solution (to prevent unloading of the dye during exocytosis) and washed with Advasep-7, which helps to remove the dye from surface membranes. The authors show that the dye is present only in synaptic vesicles, and use this technique to explore vesicle cycling.

Loading cone terminals with FM1-43 in this way produced cones in which the terminal was entirely filled with dye after as little as 2 min of loading time, indicating that endocytosed vesicles could move throughout the terminal very quickly. Vesicles also seem to remain mobile, rapidly redistributing after a short period of dye unloading in a high-Ca^{2+} solution. This mobility was quantified using FRAP (fluorescence recovery after photobleaching). A small area in the cone terminal is scanned with a laser for a short time, to bleach the FM1-43 in that area. Vesicle mobility can then be quantified by how quickly the bleached area becomes fluorescent again. In the case of cones, the results indicated that about 87% of vesicles were able to move between the bleached and unbleached areas, and that the recovery reached a steady

state within 25 s. By contrast, vesicles in the neuromuscular junction show very little mobility in this type of test, even over the course of an hour.

The mobility of cone vesicles was not affected by changes in intracellular Ca^{2+} or cyclic AMP. In addition, the diffusion coefficient of synaptic vesicles in this study is similar to the rate of diffusion of an inert particle of a similar diameter, indicating that the vesicles might diffuse freely within the terminal. The reason why vesicles are so much more mobile in cones than in other neurons might relate to the fact that photoreceptors lack a membrane-associated protein called synapsin, which normally tethers synaptic vesicles to the cytoskeleton.

The authors also investigated whether endocytosed vesicles coalesce and reform during recycling, as can happen in other synapses when release rates are high. By comparing sequential loading of FM1-43 and a related dye, FM4-64, with simultaneous loading, they established that vesicles loaded with one dye or the other do not intermix. Although in other synapses, endocytosis can involve bulk membrane retrieval followed by budding of individual vesicles, it seems that this does not occur in cones. Based on these results, the authors propose a model of vesicle cycling in cones in which individual vesicles are endocytosed, diffuse throughout the terminal and then encounter a synaptic ribbon, to which they bind. After moving along the ribbon and being primed for release, vesicles dock and undergo exocytosis in response to elevated Ca^{2+}.

The highly mobile population of vesicles in cone terminals, which contrasts sharply with the presence of a large, immobile reserve pool in most types of synapse, might ensure that the synaptic ribbons in cones are always fully charged with vesicles, allowing the continuous and high rate of neurotransmitter release in the dark that is characteristic of photoreceptors.

References and links

ORIGINAL RESEARCH PAPER
Rea, R. *et al*. Streamlined synaptic vesicle cycle in cone photoreceptor terminals. *Neuron* 12 February 2004 (10.1016/S0896-6273(04)00088-1) | PubMed |

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