Why Do Hair Cells Have Ribbons? Focus on “Synaptic Ribbon Enables Temporal Precision of Hair Cell Afferent Synapse by Increasing the Number of Readily Releasable Vesicles: A Modeling Study”

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Hair cells, like retinal photoreceptors and bipolar cells, encode stimuli with graded changes in membrane potential and transmit that signal through ribbon synapses to drive action potentials in associated afferent neurons (Sterling and Matthews 2005). Thus one would expect transmitter release from ribbons to vary in interesting ways from that evoked by action potentials at conventional chemical synapses. For example, it was observed early on that hair cells (Fuchs 1996) and retinal cells (Tachibana 1999) use L-type, dihydropyridine-sensitive calcium channels to couple vesicular release to membrane potential rather than the usual mix of non-L-type channels found elsewhere. Consistent with their support of spontaneous afferent activity, these channels, encoded by members of the CaV1 gene family, inactivate very little in hair cells. This, however, has been one of the few successful gene/function identities, and a host of unresolved questions remain. Many of these are prompted by the unusual ultrastructure of the ribbon synapse, composed of an electron-dense core a fraction of a micron in diameter, around which small clear vesicles are attached through fibrillar tethers. This very appearance begs the question of what specialized functions such peculiar structure might confer. And yet, there is still precious little information about the molecular composition of the ribbon, and functional measures are only slowly teasing apart the process of transmitter release. Thus in the recent article by Wittig and Parsons, they turn to an anatomically realistic model of the ribbon synapse in frog saccular hair cells to probe its contribution to one particular feature of release: the latency and precision of spike timing in the postsynaptic afferent neurons.

Like others, Wittig and Parsons took note of what might be regarded as the most obvious structure/function relation of the ribbon, that it accumulates vesicles in the vicinity of an active zone. If vesicles attached to the ribbon are available for release, then these constitute a reservoir to sustain synaptic transmission. The authors show that this would have specific benefits for spike timing: briefer first spike latencies and reduced temporal jitter. This arises from the statistics of random variables, the underlying multiplication accentuates the asymmetry of the release probability function as has been exploited to model spike-timing elsewhere (Xu-Friedman and Regehr 2005). Deeper insights were acquired by moving from this theoretical expression to an anatomically based model in which the contribution of ribbon-associated synaptic vesicles was assayed explicitly. The authors chose the anatomically detailed ribbon synapse of frog saccular hair cells (Lenzi et al. 1999) for which temporal coding data also exist (Feng 1982). The number of docked and tethered vesicles, the number of voltage-gated calcium channels and their gating properties and the concentration and efficacy of calcium buffer are known entities for this synapse. From this basis, the authors developed a stochastic computational model that included randomized calcium channel gating, local calcium flux, and the calcium-dependent release probability of single vesicles. Critical to this exercise was the assignment of vesicles to one of several classes: docked to the plasma membrane but not tethered to the ribbon, docked and tethered, tethered only, or neither (“outliers”). The relative numbers and distribution of each were drawn from previous ultrastructural studies (Lenzi et al. 1999). Finally, the cluster of 84 voltage-gated calcium channels composing the active zone lay entirely under the shadow cast by the ribbon (Roberts 1994). Therefore docked and tethered vesicles (40 of 50 total docked) dominated the active zone center and constituted the majority of the 30 vesicles released during each 10-ms step to the peak of the calcium channel activation curve. As predicted, having multiple vesicles ready for release improved temporal accuracy. The mean first latency was 0.88 ms, with a jitter of 0.28 ms—comparable to first latencies of ~1 ms in frog saccular afferents (Feng 1982). This corresponded to a peak release rate of nine vesicles/ms.

From this baseline the authors could then explore the effect of specific changes in synaptic structure or function. For example, the model required ≥15 vesicles docked in the active zone to replicate the temporal precision of frog nerve fiber data. With respect to the central question of this work, they showed that first latency slowed and was more variable without ribbon-associated vesicles, supporting the contention that the ribbon specifically increases the release-ready pool (Khimich et al. 2005).

The additional benefit of the model is that other questions can begin to be addressed. Thus a topic of some interest presently is the ability of ribbon synapses to perform multivesicular release—the simultaneous fusion of multiple vesicles (in the absence of action potentials). Very large synaptic currents recorded in cochlear (Glowatzki and Fuchs 2002; Goutman and Glowatzki 2007) and papillar (Keen and Hudspeth 2006) afferents, as well as retinal cells (Maple et al. 1994; Singer et al. 2004), are thought to arise from the coordinate release of multiple vesicles. Recent capacitance measurements from cochlear hair cells also have been interpreted as resulting from multivesicular release (Neef et al. 2007). The Wittig and Parsons model implies multivesicular release, at least at the stated maximum of nine vesicles/ms. However, that high rate occurred when coordinate gating of multiple calcium channels was imposed by the voltage step. Experimentally, large (multivesicular) synaptic currents can be observed even when the hair cell’s membrane potential is held constant by voltage clamp (Goutman and Glowatzki 2007; Keen and Hudspeth 2006) or potassium depolarization (Glo-
watzki and Fuchs 2002). It will be of interest to learn whether the present model can replicate such “stochastic” multivesicular release. Even if the answer is negative it will motivate efforts to find the missing elements.

Another idea associated with multivesicular release is that ribbon-tethered vesicles might fuse prior to release at the plasma membrane. Such vesicle sausages have been proposed as one method to produce large, multivesicular, synaptic currents (Matthews and Sterling 2008). The present model argues that intervesicular fusion would have to occur without benefit of calcium influx because buffered diffusion ensures that only the very closest tethered vesicles see even as much as 1 μM free calcium.

The Wittig and Parsons study provides a well-constructed hair cell ribbon model for posing questions that complement ongoing experimental work. Of course the strength of the model depends on choice of parameters; this work benefits from ultrastructural and functional studies that justify those choices. But in addition, the present formulation and clarity of presentation promise further revelations as this tool is used to probe the mysteries of ribbon function.

REFERENCES

Wittig Jr JH, Parsons TD. Synaptic ribbon enables temporal precision of hair cell afferent synapse by increasing the number of readily releasable vesicles. J Neurophysiol doi:10.1152/jn.90322.2008.