

Review of: "Synaptic vesicle proteins are selectively delivered to axons in mammalian neurons"

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The main concern is the unbalanced approach in Introduction. For many axonal proteins, selective direct delivery is a dominant pathway and can hardly be called a novel idea as mentioned in lines 98, 153, 388. The Introduction (lines 43-60) needs to be more balanced to include more of the work citing direct sorting of SV proteins into axons (to name a few: Fletcher et al., 1991, J Neuroscience; Ahmari et al., 2000, Nature Neuroscience; Bonanomi et al., 2006, Progress in Neurobiology; Horton & Ehlers, 2003, Neuron). What the authors did here is not showing direct axonal sorting as a novel idea but using a new technique to document it.

The second concern is the unbalanced view in line 65 that "how these proteins are incorporated into SVs once they make their way into axons remains completely unknown". Local recycling of these SV proteins along axons, prior to SV formation, has been well documented (e. g., Matteoli et al., 1992, J CB; Krueger et al., 2003, Neuron), and should be incorporated into Introduction, the relevant section in Results, and Discussion.

Citation on two references (Nabb and Bentley 2022; Sampo et al. 2003) in lines 143, 171 (and other places) should be reworded to avoid misunderstanding. These papers showed both selective delivery and selective retention. The way these references were cited in the text could be misinterpreted as if they only showed selective retention.

Some other comments:

Line 150, "suggest the existence of a selective and specific pathway that targets SYT1 to presynaptic boutons." Is over interpreted. At this stage of the presentation, synapse did not even come into play yet.

Lines 203-224 on the necessity of "low levels of expression"... The authors nicely demonstrated the caveats on mis-sorting of proteins due to overexpression. However, it would have been helpful to also cite more older studies of immunolabeling of endogenous proteins which did not involve overexpression of these proteins.

