Mechanical Control of Neurotransmission

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During neurotransmission, a process that is central to our ability to move, eat, think, and sense, tiny 40 nm-sized synaptic vesicles (SVs) undergo rapid exocytotic fusion with the plasma membrane. SV exocytosis is tightly coupled to compensatory endocytosis of an equal amount of membrane to homeostatically maintain synaptic plasma membrane area and to prevent neurodegeneration. How such exo-endocytic coupling is accomplished, remains incompletely understood. In my talk, I will present evidence that neurotransmission is controlled by sensing vesicle fusion-triggered changes in membrane properties via the phase-separating intrinsically disordered region (IDR) of the endocytic protein FBP17. Exocytosis-induced alterations in membrane packing are translated into changes in FBP17 conformation and oligomerization-dependent endocytic membrane remodelling, revealing a mechanism of mechanotransduction wherein the IDR of FBP17 directly senses the physical properties of the membrane. Loss of FBP17 or its ability to sense membrane mechanics leads to endocytic defects, increased spontaneous vesicle fusion, and failed network synchronization in engineered human neurons. Our results unravel a molecular mechanism for the mechanical control of neurotransmission that enables synapses to maintain plasma membrane homeostasis and to plastically adapt network properties. We predict similar mechanisms to operate at other subcellular sites and in other types of exo-endocytosis in diverse cells and tissues and, possibly, in membrane traffic in general.