# v-SNARE-based protein-lipid interactions catalyze membrane fusion

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$Ca^{2+}$-triggered fusion of vesicles with the plasma membrane enables neurotransmitters release, underlying information processing in the central nervous system. Overcoming electrostatic repulsion, shedding of hydration shells, bending of membranes etc. put an energetic toll on the fusion process. While this energy threshold is actively surmounted by membrane bridging interactions between vesicular and target SNARE (*soluble N-ethylmaleimide-sensitive factor attachment protein receptors*) proteins, SNARE: phospholipids interactions may help catalyzing membrane merger. In this work, we have investigated the role of vesicular SNARE synaptobrevin-2 (syb-2) and phospholipid interactions in $Ca^{2+}$-triggered neurotransmitter release. Using a combination of photolytic 'uncaging' of intracellular $Ca^{2+}$ with membrane capacitance measurement and analysis of single amperometric spikes in chromaffin cells, we found that structural flexibility of the syb-2 transmembrane domain (TMD) positively affects the extent of membrane fusion and rate of cargo release from single granules. Amperometric measurement of chromaffin granule fusion also showed that membrane-active agents that either alters curvature (e.g. lysophosphatidyl choline, oleic acid) or membrane fluidity (e.g. cholesterol) regulate fusion. Furthermore, we could show that the slow fusion pore expansion in syb-2-TMD mutants can be rescued with membrane-active agents, demonstrating that the protein and lipid functions converge on the same intermediate steps to promote exocytosis. Thus, our results demonstrate that SNARE TMDs play an active role in the fusion process that goes beyond simple anchoring of the protein, and their functional *pas de deux* with lipids determines $Ca^{2+}$ triggered neurotransmitter release.