Abstract Submitted
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Energetics and Kinetics of *trans*-SNARE Zippering[1] ALEKSANDER A. REBANE, TONG SHU, Yale Univ, SHYAM KRISHNAKUMAR, JAMES E. ROTHMAN, YONGLI ZHANG, Yale School of Medicine — Synaptic exocytosis relies on assembly of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins into a four-helix bundle to drive membrane fusion. Complementary SNAREs anchored to the synaptic vesicle (v-SNARE) and the plasma membrane (t-SNARE) associate from their N-termini, transiting a half-assembled intermediate (*trans*-SNARE), and ending at their C-termini with a rapid power stroke that leads to membrane fusion. Although cytosolic SNARE assembly has been characterized, it remains unknown how membranes modulate the energetics and kinetics of SNARE assembly. Here, we present optical tweezers measurements on folding of single membrane proteins in phospholipid bilayers. To our knowledge, this is the first such report. We measured the energetics, kinetics, and assembly intermediates of *trans*-SNAREs formed between a t-SNARE inserted into a bead-supported bilayer and a v-SNARE in a nanodisc. We found that the repulsive force of the apposed membranes increases the lifetime of the half-assembled intermediate. Our findings provide a single-molecule platform to study the regulation of *trans*-SNARE assembly by proteins that act on the half-assembled state, and thus reveal the mechanistic basis of the speed and high fidelity of synaptic transmission.

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