Insights into Synapse Nanostructure from Analysis of SNARE Disease Variants

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Soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins drive synaptic transmission in a temporally and spatially precise manner. Recent studies have identified several disease-causing SNARE variants that give rise to developmental and epileptic encephalopathies (DEEs), defined as SNAREopathies. In this presentation, I will discuss our ongoing work into the mechanisms dictating functional impact of these SNARE variants. The neurotransmission deficits we observe with these variants parallel the symptomatic heterogeneity of the patients, with some variants displaying a disproportionate augmentation of spontaneous neurotransmitter release. When we examined the spatial organization of this excessive spontaneous release at nanoscale, we found that SNARE complexes composed of these variants formed exclusively outside of nano-column scaffolding, revealing a preserved exclusion zone sparing evoked release from pathophysiology. These findings reveal shared patterns of aberrant neurotransmission across different SNARE variants, highlighting the necessity for a functional classification of SNAREopathies to develop therapeutic interventions. The use of clinically relevant genetic manipulations to challenge the synapse provides mechanistic insight into rare diseases while simultaneously revealing fundamental aspects of synaptic physiology.