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Meeting abstract

Peptide-based interactions with calnexin target misassembled GABA transporter-1 molecules into organized smooth endoplasmic reticulum compartments*

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Correct assembly of neurotransmitter transporters, e.g. GABA transporter-1 (GAT1) in the ER is a prerequisite for their delivery and function at the neuronal synapse. We have previously identified a GAT1 residue, E101, substitution of which disrupts assembly and causes retention of the transporter molecules in the ER. Here, we show that chemical modulation of ER Ca^{2+} by thapsigargin or inhibition of ER glucosidases suffices to partially rescue the misassembled GAT1 mutant (E101D). Moreover, we identify an ER chaperone calnexin as a key participant in recognition and retention of the E101D-GAT1 molecules. Interactions with calnexin lead to accumulation of the transporter in the multilamellar organized smooth ER structures. We show that the function of calnexin as a chaperone is preserved in this compartment. Despite the defective E101D-GAT1 assembly, within the multilamellar membranes it is in a non-aggregated state and fully mobile, confirming our previous suggestion that the overall folding of the protein is not greatly perturbed by mutation. Furthermore, using FRAP and FRET methods we show that GAT1 and E101D-GAT1 recognition by calnexin occurs largely in a glycan-independent manner and, at least in part, on a transmembrane domain level. Our findings with GAT1 are likely relevant for other neurotransmitter transporters containing SNPs linked to genetic disorders (e.g. transporters for dopamine or norepinephrine).

Author's Note

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