REGULATION OF ALPHA-SYNUCLEIN MEMBRANE BINDING BY RAB3A/GDI/HSP90

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Introduction: Alpha-synuclein (a-syn) is an abundant nerve terminal protein and a primary component of Lewy bodies. While the precise biological and pathological role of a-syn remains unclear, its ability to bind to and dissociate from synaptic membranes may be linked to its function in these states.

Aim: The aim of this study is to identify and characterize synaptic vesicle proteins that regulate a-syn membrane binding and dissociation.

Methods/results: Using an in vitro a-syn binding assay to identify vesicle proteins that regulate a-syn's interaction with synaptic membranes, we observed that antibodies to rab3a and its chaperone GDI inhibited a-syn membrane binding. Glycerol gradient analysis indicated that a-syn co-eluted with rab3a in high-molecular weight fractions and co-immunoprecipitation experiments confirmed that membrane-bound, but not cytosolic, a-syn interacts with rab3a. Furthermore, expression of mutant constitutively GTP-bound rab3a in SH-SY5Y cells increased a-syn sequestration on membranes. Although neither GDI nor Hsp90 (the regulatory complex essential for rab3a membrane dissociation) were identified in this complex, we found that the Hsp90 inhibitors radicicol and geldanamycin, which disrupt rab3a dissociation from membranes, also inhibit alpha-synuclein membrane dissociation in both cells and synaptosomal membranes.

Conclusion: We propose that GTP- and membrane-bound rab3a stabilizes a-syn binding to synaptic vesicles and that the GDI/Hsp90 machinery regulating rab3a membrane dissociation also regulates a-syn dissociation during synaptic activity.