Investigating the Exocyst as an Insulin-Sensitive Regulator of Amyloid-beta Synthesis in Neurons

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ABSTRACT
Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects over six million Americans. A hallmark of AD is an imbalance between production and clearance of amyloid-β peptides (Aβ), resulting in the buildup of neurotoxic amyloid plaques in the brain. These Aβ are generated from proteolytic processing of the amyloid precursor protein (APP) in neurons, and we hypothesize that the exocyst trafficking complex is a novel regulator of APP processing and Aβ generation. Additionally, the exocyst is known to be activated by insulin, representing a potentially new mechanistic connection between insulin signaling and APP processing in neurons. We are investigating this insulin-exocyst-APP connection with two widely utilized neuronal cell models: mouse primary hippocampal neurons and the SH-SY5Y cell line. Using advanced fluorescent microscopy and proximity-ligation assays, we are mapping the association between the exocyst and APP within neurons and found that insulin signaling reduced exocyst-APP interactions, specifically in the axons and dendrites. Proteomic analysis revealed reduced cell-surface APP in neurons treated with the exocyst inhibitor, endosidin 2. These recent findings suggest that the exocyst does play a specific role in Aβ production by neurons, and this may be under the direct regulation of insulin signaling. Further understanding of how the exocyst regulates Aβ in neurons may lead to new potential targets for AD treatment.

KEYWORDS: Amyloid-β peptides, Amyloid precursor protein, Exocyst, insulin, Neurons, Alzheimer's disease

ACKNOWLEDGEMENTS
The STEP-UP High School program is supported by the Nation Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, Grant Number: 5R25DK078386-18