THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Albert Orock

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
Neuroscience

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Biomedical Research Center, Room 109

NOVEL PRESYNAPTIC PATHWAY IN COGNITIVE IMPAIREMENT: THE ROLES OF SYNAPTOBREVIN2 AND MUNC18-1

COMMITTEE IN CHARGE: Ferenc Deak, MD, PhD; Beverley Greenwood - Van Meerveld, PhD; Jose Rizo-Rey, PhD; Robert E Anderson, MD, PhD; Rheal Towner, PhD; William E Sonntag, PhD

ABSTRACT: Cognitive impairment is a hallmark of multiple neurological disorders with many different underlying causes. The vast etiology of these disorders has also made it very difficult to decipher the underlying causes of cognitive impairment. Even without classical neurodegeneration, normal brain aging is known to impair cognitive function. In special cases synaptic protein mutations have been identified as causes of learning and memory defects. The question arises, does altered synaptic protein expression play a role in learning and memory deficits associated with these diseases. Specifically, my hypothesis is that reduced expression of the synaptic proteins involved in synaptic vesicle release, synaptobrevin2 (syb2) and munc18-1, cause impaired synaptic transmission and cognitive impairment. Syb2, the major vesicular SNARE in the brain, has been shown to decrease in patients with dementia, making it a candidate mechanism for age related cognitive decline. Point mutations in the munc18-1 gene, a SNARE associated protein essential for synaptic vesicle fusion, was also implicated in Early Infantile Epileptic Encephalopathy-4, which also presents with cognitive impairment. We tested this hypothesis by using heterozygous knockout mice of syb2$^{+/-}$ and munc18-1$^{+/-}$. I used behavioral and synaptic plasticity assays to assess learning and memory. I also performed live fluorescence assays to assess the vesicular release rates of syb2$^{+/-}$ and munc18-1$^{+/-}$ neurons. My data from syb2$^{+/-}$ mice revealed that reduced syb2 expression led to learning and memory deficits in adult mice, which was exacerbated in old mice. Syb2$^{+/-}$ animals also had impaired long-term potentiation and reduced vesicle release probability and this caused syb2$^{+/-}$ neurons to have reduced vesicular release rates in the FM assays. Munc18-1$^{+/-}$ animals also displayed impaired spatial learning and memory caused by reduced hippocampal LTP. Munc18-1$^{+/-}$ neurons had significantly decreased readily releasable pools and reduced release rates of synaptic vesicles. From these results I conclude that reduced expression of specific synaptic protein affect different parts of the synaptic release machinery, which causes reduced vesicle release rates. This novel finding about the presynaptic molecular mechanism that leads to dysfunction and learning impairment highlight that reduced synaptic protein expression could be as a novel pathway to focus on and to prevent cognitive impairment.