Role of Cholinergic-Glutamatergic Co-transmission in Forebrain Circuits

https://neurodegenerationresearch.eu/survey/role-of-cholinergic-glutamatergic-co-transmission-in-forebrain-circuits/

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Country

USA

Title of project or programme

Role of Cholinergic-Glutamatergic Co-transmission in Forebrain Circuits

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NIH (NIA)

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01/04/2013

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

SLC17A8 gene, cholinergic, Prosencephalon, cholinergic neuron, basal forebrain cholinergic neurons

Research Abstract
DESCRIPTION (provided by applicant): Basal forebrain and striatal cholinergic neurons have a critical role in many aspects of brain function including learning and memory, attention, reward

and motor function and their dysregulation contributes to neuropsychiatric disorders such as Parkinson’s disease, schizophrenia and Alzheimer’s disease. For decades, it was assumed that these cells release only one classical transmitter, acetylcholine, however it is now known that they express the vesicular glutamate transporter 3 and release glutamate. While we have data showing that VGLUT3 in striatal cholinergic neurons mediates fast glutamatergic transmission and modulates cholinergic transmission, not much is known about its role in basal forebrain neurons or its behavioral role in either population. Thus, the goal of this grant is to determine te functional and behavioral role of VGLUT3 in forebrain cholinergic neurons. In Aim 1 we will determine the cellular distribution of VGLUT3 in basal forebrain nuclei and map their axonal projections using our BAC transgenic cre recombinase and reporter mice together with cre-dependent viral tracing methods. These new tools provide higher sensitivity and selectivity over more traditional methods. In Aim 2 we will determine mechanisms of VGLUT3-mediated synaptic signaling by basal forebrain cholinergic neurons. We will use a biochemical approach to assess whether VGLUT3 and VAChT reside on the same vesicles, which would suggest synergistic co-packaging increases cholinergic transmission by those cells. We will use cre-dependent viral expression of channelrhodopsin together with patch clamp electrophysiology to detect fast glutamatergic transmission by cholinergic cells. In Aim 3 we will determine the behavioral role of VGLUT3 in striatal and basal forebrain cholinergic neurons. Using our conditional VGLUT3 knockout mice, we now have evidence of behaviors definitively linked to VGLUT3 in cholinergic neurons. Deletion of the transporter in these neurons produces nocturnal hyperlocomotor activity as well as deficits in two working memory tasks, novel arm recognition and spontaneous alternation. Work in this aim will determine which population of cholinergic neurons mediates these phenotypes and if there is a behavioral role for the glutamate signaling by these cells. Cholinomemetics that target signaling by forebrain cholinergic neurons are commonly used to treat a number of neurological disorders. Our work here suggests that glutamate signaling by these cells could provide novel therapeutic targets.

Lay Summary
PUBLIC HEALTH RELEVANCE: Cholinergic neurons in the striatum and basal forebrain are important for cognition and motor function. These cells were known to use acetylcholine as a transmitter and now there is evidence that they also use the major excitatory transmitter glutamate. Our work explores the role of this glutamate signaling in normal brain function and in conditions of neurological dysfunction such as Parkinson’s disease and Alzheimer’s disease.

Further information available at:

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Alzheimer's disease & other dementias

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