Exploration of metabotropic glutamate receptor 3 as a target for MeCP2-related disorders

Colleen Niswender, PhD
Vanderbilt University
$150,000.00

Precise levels of the transcriptional regulator Methyl CpG Binding Protein 2 (MeCP2) are required for proper neurological function. The neurodevelopmental disorders Rett syndrome (RS) and MECP2 Duplication syndrome (MDS) result from opposing changes in levels of MeCP2. The loss or gain of MeCP2 results in distinct phenotypes in these disorders as well as a subset of overlapping symptoms, including stereotypy, seizures, cognitive deficits, and autism. Encouragingly, both disorders can be corrected post-development in animal models, providing hope for patients and their families. Rodent models of RS and MDS have provided evidence for significant and reciprocal impairments in hippocampal synaptic plasticity as well as responses in contextual fear conditioning, suggesting potentially maladaptive hippocampal learning in these animals. These findings suggest that these mice represent models to study the etiology and treatment of cognitive deficits and intellectual disabilities relevant to RS and MDS patients. Levels of metabotropic glutamate receptor 3 (mGlu3) are decreased in neurons from RS model mice; in contrast, our preliminary data suggest that protein levels mGlu3 are upregulated in the hippocampus of mice overexpressing a human MECP2 transgene (MECP2-Tg1). These results suggest that mGlu3 expression levels may be directly regulated by MeCP2. Given that mGlu3 plays a crucial role in normal synaptic plasticity and cognitive function, we anticipate that decreases in mGlu3 signaling in Mecp2-deficient animals, as well as increases in mGlu3 resulting from overexpression of MeCP2, may contribute to synaptic plasticity and cognitive impairments seen in these animals. We present data suggesting that hippocampal long-term depression (LTD) at Schaffer collateral-CA1 (SC-CA1) synapses in the hippocampus is reduced in MECP2-Tg1 mice and show that this deficit is reversed by a novel mGlu3-selective negative allosteric modulator (NAM). We will now test the hypothesis that reciprocal changes in mGlu3 protein lead to corresponding changes in mGlu3 signaling in the hippocampus and determine if this contributes to synaptic plasticity deficits in mice under or overexpressing MeCP2. We will then determine if opposing mGlu3 changes contribute to hippocampally-mediated cognitive deficits in these lines of animals. We further hypothesize that abnormal mGlu3 signaling, electrophysiological, and behavioral responses will be sensitive to administration of highly selective mGlu3 negative allosteric modulators (NAMs), potentially providing evidence for a new drug target in these disorders.