The Role of Metabotropic Glutamate 7 in the Etiology and Treatment of Rett Syndrome

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PUBLIC ABSTRACT

The trauma suffered by our military personnel, often the result of a traumatic brain injury (TBI), can result in seizures, repetitive behaviors, anxiety, post-traumatic stress disorder, insomnia, and breathing problems. It has been proposed that the study of genetic models that also manifest the above abnormalities may provide insight into new treatments that might impact members of the US military. One such disorder is Rett syndrome. Rett syndrome (RTT) is a disease that results from mutations in a specific gene that encodes a protein called Methyl CpG Binding Protein 2 (MeCP2). This protein binds to DNA and regulates the production of genetic messages that are translated into proteins. RTT is usually characterized by a period of relatively normal early development; after this point, patients undergo a regression period where they lose previously acquired skills such as talking and walking. RTT patients usually exhibit autistic-like features, repetitive movements such as wringing of the hands, motor delays, problems with cognition, seizures, anxiety, insomnia, and breathing abnormalities. In mice, loss of the Mecp2 gene results in many RTT symptoms and, excitingly, re-expression of Mecp2 protein in the adult mouse brain corrects numerous symptoms, suggesting that at least some symptoms may be reversible in humans. Based on these findings, one therapeutic strategy scientists are exploring in RTT is attempting to replace lost MeCP2. As MeCP2 has many functions in the brain, it is hoped that correction of the root deficit will have the biggest impact on symptoms in patients. However, expression of too much MeCP2 results in a different syndrome, called MECP2 Duplication syndrome. This suggests that either too much or too little MeCP2 causes disease. Such precise requirements for MeCP2 levels present a significant challenge for gene therapy approaches, and many investigators have looked to downstream MeCP2 targets for therapeutic opportunities. Additionally, downstream targets may also be amenable to cross over to distinct patient populations, suggesting that study of a downstream RTT target may also have relevance to TBI.

We have found that expression of the metabotropic glutamate receptor 7 (mGlu7) is controlled by MeCP2. Metabotropic glutamate receptor 7 (mGlu7) belongs to a family of receptors that is the target of the majority of Food and Drug Administration-approved drugs. mGlu7 is expressed on the cell surface of neurons where it regulates the release of neurotransmitters, important molecules that communicate signals between neurons. Differences in the DNA encoding mGlu7, GRM7, among the human population have been linked to depression, attention deficit hyperactivity disorder, schizophrenia, bipolar disorder, epilepsy, and autism. We have found dramatically reduced mGlu7 protein levels in the motor cortex and cerebellum of RTT autopsy samples, and we have also observed decreases in mGlu7 expression in Mecp2-deficient mice. Interestingly, we have now found evidence that mice lacking mGlu7 exhibit previously unrecognized symptoms that are strikingly similar to those observed in RTT-model mice. Characteristic phenotypes of RTT-model mice include clasping of the paws, seizures, cognitive deficits, and apneas, and our preliminary data show that mice lacking mGlu7 exhibit a profound clasping phenotype, spontaneous seizures, and apneas that parallel those in RTT model mice. In Aim 1, we will test the hypothesis that a primary loss of mGlu7 mimics aspects of RTT by comparing mGlu7 knockout and Mecp2 knockout animals to determine which domains of the RTT phenotype are observed with a primary reduction of mGlu7. In Aim 2, we will expand this analysis to test the hypothesis that genetic reductions in mGlu7 signaling will worsen or accelerate disease in RTT mice, whereas genetic increases in mGlu7 will reverse RTT phenotypes. These experiments will help us to better characterize the involvement of mGlu7 in multiple symptom domains of RTT.

Based upon our findings that mGlu7 levels are decreased in RTT patients as well as in a rodent model of RTT, we tested the hypothesis that symptoms in these animals might be corrected using small molecules that potentiate the activity of mGlu7. These compounds are called positive allosteric modulators (PAMs), and they increase the response of mGlu7 to its normal activator, glutamate. Due to the current lack of selective tools to activate or potentiate mGlu7 activity, we began our studies using a PAM, VU0422288, that is active at mGlu7 but also at other targets. We found that VU0422288 could correct deficits in neuronal function and reverse impairments in cognitive and social memory tests. Additionally, we can reverse apneas in RTT model animals with a single acute dose of VU0422288, and control experiments suggest that this effect is mediated by potentiation of mGlu7. Overall, these results provide support for mGlu7 as a relevant RTT target and one that may correct multiple symptoms. One of the strengths of the Vanderbilt Center for Neuroscience Drug Discovery is the ability to optimize small molecules for receptors such as mGlu7. In Aim 3, we proposed to conduct a chemical optimization campaign to develop highly selective tool compounds to continue to validate mGlu7 potentiation as a therapeutic strategy in RTT, particularly in the domains that impact our military personnel suffering from TBIs, such as seizures, apneas, and stress-related symptoms.