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Small-molecule therapeutic boosts spatial memory and motor function in Rett syndrome mice

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New research into Rett syndrome therapeutics suggests that a small molecule already reported to improve respiratory problems associated with the disease may also improve spatial memory and motor skill defects.

Girls born with a mutation in the *MECP2* gene initially develop typically, but at 6-18 months a gradual or sudden reversal of development indicates the onset of Rett syndrome. As this rare genetic neurological disease develops, affected girls experience slowed growth, a loss of communication skills and use of the hands, problems with movement and coordination, difficulty breathing, and seizures. The disease almost exclusively presents in girls, as the MECP2 gene is located on the X chromosome. With only a single copy of this chromosome, boys are affected in devastating ways by the mutation and rarely survive early infancy.

The *MECP2* gene encodes methyl-CpG-binding protein-2 (MeCP2), a transcriptional regulator of many genes including brain-derived neurotrophic factor (*BDNF*). Decreased levels of BDNF are associated with a number of neurological disorders, such as depression, schizophrenia, Alzheimer's disease and Huntington's disease. BDNF levels have also been shown to be reduced in the brains of individuals with Rett syndrome and in multiple brain areas of *Mecp2*-deficient mice. Genetic overexpression of BDNF has previously been reported to

improve defective behaviours in *Mecp2* mutant mice. Now, in an article published in *Disease Models & Mechanisms*, a team from the University of Alabama at Birmingham and Stanford University School of Medicine describe the use of a BDNF loop domain mimetic to improve motor function and object location memory in a mouse model of Rett syndrome.

Improving behavioural deficits

Lead investigator Lucas Pozzo-Miller and his lab worked on the role of BDNF in synapse function for several years before entering the MeCP2/Rett field. "In fact, we became interested in Rett due to others groups' observations of MeCP2 regulation of BDNF expression and genetic overexpression of BDNF improving behavioural deficits in *Mecp2* mutant mice," recalls Pozzo-Miller. The lab was working on a method to increase BDNF levels in *Mecp2* mice when they learned that another group had positive results when using LM22A-4, a small-molecule mimetic of the loop domain BDNF and partial agonist of its receptor TrkB, in Rett model mice. This research - by co-author Frank Longo and colleagues - was focused on the neural bases of breathing, the role of BDNF on its proper development and the consequences of *Mecp2* deletion. "My lab works on the neural bases of learning and memory," says Pozzo-Miller, "so we decided to test if LM22A-4 was able to improve spatial discrimination deficits by enhancing synaptic plasticity in the hippocampus, the brain region responsible for spatial learning and memory." He contacted Longo, outlining his group's plan to test LM22A-4 in hippocampal function in Rett model mice. Longo explains that he and collaborator David Katz saw an opportunity to really challenge LM22A-4 and see if it could successfully engage in additional key Rett mechanisms.

Pozzo-Miller and his team found that Rett-like symptoms improved in model mice after treatment with LM22A-4, and the distance the mice

were able to travel in a test field was comparable with normal mice. The group also noted an improvement in the ability of the treated mice to remember where an object had been placed within an arena. They further established that LM22A-4 exerts these effects by subduing excitatory synaptic transmission and network activity in hippocampal slices to levels amenable for the induction of synaptic plasticity and behavioural learning and memory.

Neurodevelopmental disorders need not be considered closed cases

There is a growing body of literature supporting the high therapeutic potential of LM22A-4 for the treatment of Rett syndrome and other diseases associated with lowered levels of BDNF. Pozzo-Miller reflects that this new research on LM22A-4, combined with prior studies from the Katz lab, provides hope that at least some neurological and cognitive deficits in individuals with Rett could be improved by pharmacological treatment even after the onset of symptoms. Neurons, the synapses between them and the networks they build are extremely plastic throughout life, which allows therapeutic intervention to improve neurological and cognitive function. Pozzo-Miller says, "There has been a growing realization that neurodevelopmental disorders need not be considered as closed cases simply because the mutations affect early brain development. Our studies in Rett model mice add to similar studies in mouse models of Down syndrome, neurofibromatosis, tuberous sclerosis and fragile X, which provide rational bases for their treatment in adulthood, providing hope for millions of affected individuals and their families."

More information: Wei Li et al, A small-molecule TrkB ligand restores hippocampal synaptic plasticity and object location memory in Rett syndrome mice, *Disease Models & Mechanisms* (2017). DOI:

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