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Preclinical inquiry into 1 mutation sheds light on addiction and a birth defect

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When a certain protein is mutated or missing, symptoms of the neurodevelopmental disorder Rett syndrome arise, causing a gradual loss of brain function during early development.

This fact led Duke University Medical Center researchers to test a theory that the protein might also contribute to nerve-cell connection (synapse) changes in a fully formed adult mouse brain when exposed to psychostimulant use.

In two experiments with mice, Anne West, M.D., Ph.D., an assistant professor of neurobiology, and Duke colleagues found that virally manipulating levels of the methyl-binding protein MeCP2 in the brains of adult mice affected their place preference, a measure of the rewarding properties of the amphetamines the mice consumed in that location. The mice that had less of the MeCP2 protein kept returning to the same location in hope of getting more of the drug.

The study was published Aug. 15 in Nature Neuroscience.

Scientists have speculated that psychostimulant drugs make long-lasting changes to synapses that lead to addictive types of behavior. When the researchers changed the expression levels of MeCP2, they noticed a proportional relationship.

"The body may increase MeCP2 as a way to reset the reward threshold," West said. "You decrease the sense of reward when you increase

MeCP2. It might be the body's compensation and way to maintain balance."

These studies show that MeCP2 is involved in the process through which repeated amphetamine use changes both the structure and the function of the brain, West said.

"Until now, nobody had experimentally linked MeCP2 to the effects of stimulant drugs," West said. "I was surprised that subtle manipulations of the protein in adult mice had effects on behavior that were profound. In addition there are multiple effects of losing MeCP2 in mutant mice and we could see the effects on brain development in the young mice."

The study suggests that the methyl-DNA binding protein MeCP2 is important in regulating the rewarding properties of psychostimulant drugs, which may lead to treatments for people who overuse stimulants, West said.

"MeCP2 is a transcriptional regulator that responds to an extracellular stimulus like an amphetamine, and we showed that it can modulate synapses in the part of the brain (nucleus accumbens) that is responsible for reward," she said.

She said the next step is to learn what is happening on a molecular level to cause these effects.

Provided by Duke University Medical Center

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