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Study shows how exercise could reduce relapse during meth withdrawal

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Scientists at The Scripps Research Institute (TSRI) have found that even brief workouts can reduce the risk of relapse in rats withdrawing from methamphetamine. In addition, the team found that exercise affected the neurons in a brain region that had never before been associated with meth withdrawal, suggesting a new direction for drug development.

"There was no correlation between length of workout and risk of relapse—it's the mere involvement in the activity of physical fitness, rather than how much time you can put in," said TSRI Associate Professor Chitra Mandyam, senior author of the new study, published in the journal *Brain Structure and Function*. "That's really important if we are going to translate this to humans."

These research results come as the number of methamphetamine users rises in the United States, according to the U.S. Department of Health and Human Service's 2013 National Survey on Drug Use and Health. In San Diego County, this rise has had dire consequences, with the county reporting a 55-percent increase in meth-related deaths since 2008.

"Right now, there is no FDA-approved medicine for methamphetamine addiction," Mandyam noted. "Discovering novel pathways in the brain that could be associated specifically with the withdrawal and relapse stage may lead to new avenues for therapeutics."

The Impact of Exercise

In a 2013 study, Mandyam and her colleagues had shown that running during methamphetamine use reduced the amount of methamphetamine that rats chose to consume. By investigating the brain chemistry involved, the team found that both running and drug use activated the brain's reward system—apparently rats that exercised didn't need as much methamphetamine to be satisfied.

For the current study, the researchers wanted to see whether running could play a similar protective role in methamphetamine withdrawal.

To find out, they set up an experiment using two groups of rats. One group had access to running wheels during withdrawal; the other did not. During the addiction stage, the rats were allowed to choose how much methamphetamine to consume. During the withdrawal stage, they could also choose how often to run on a wheel.

"Right off the bat, we noticed that the rats going through withdrawal did get on the running wheels when given access to them, but they didn't run as much as drug-naïve rats," said Mandyam.

The rats given access to running wheels, however, showed a reduction in drug-seeking behavior, meaning that they were less likely to press a lever to request a dose of methamphetamine after the drug had been withdrawn. This finding echoes observations of decreased drug-seeking in cocaine and nicotine-addicted rats given access to running wheels during withdrawal.

How the Brain Changes

The researchers went on to determine the brain region associated with this difference in behavior.

They measured neurotoxicity and the activity of neurons in the brain,

and were surprised to find that running reduced the number of dopamine neurons in the periaqueductal grey (PAG), an area of the brain associated with pain-sensing. Scientists had long known that opiates, such as heroin, affected the PAG, but a change had never been seen during the withdrawal stage from a stimulant such as methamphetamine.

The researchers suggest that the connection between the dopamine neurons in the PAG and neurons in a region of the brain called the central nucleus of the amygdala, which is associated with negative reinforcement, could be driving relapse behavior in methamphetamine -addicted animals.

Mandyam said that more experiments are needed to determine exactly how the PAG and central nucleus of the amygdala interact. Mandyam is also studying whether changes in the PAG occur in rats withdrawing from alcohol and is interested in whether any significant differences can be found in the brain structure.

More information: "Chronic wheel running-induced reduction of extinction and reinstatement of methamphetamine seeking in methamphetamine dependent rats is associated with reduced number of periaqueductal gray neurons," *Brain Structure and Function*, Date: 02 Oct 2014

Provided by The Scripps Research Institute