Experimental small molecule shows potential in preventing meth relapse

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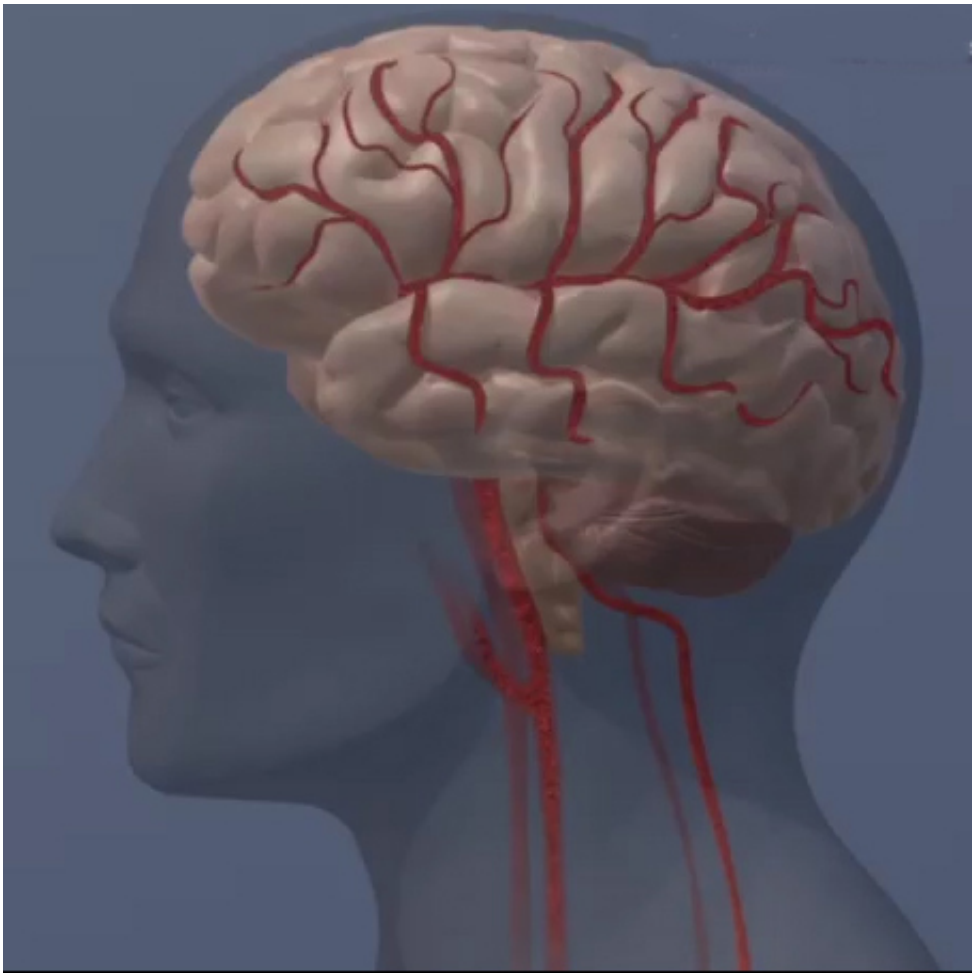

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New research from The Scripps Research Institute (TSRI) suggests that

the reason methamphetamine users find it so hard to quit—88 percent of them relapse, even after rehab—is that meth takes advantage of the brain's natural learning process. The TSRI study in rodent models shows that ceasing meth use prompts new neurons to form in a brain region tied to learning and memory, suggesting that the brain is strengthening memories tied to drug-seeking behavior.

"New neuronal growth is normally thought of as a good thing, but we captured these new neurons assisting with 'bad' behaviors," said Chitra Mandyam, who led the research as an associate professor at TSRI before starting a new position at the Veterans Medical Research Foundation and the University of California, San Diego.

The scientists discovered that they could block relapse by giving animals a synthetic small molecule to stop new neurons from forming. This molecule, called Isoxazole-9 (Isx-9), also appeared to reverse abnormal neuronal growth that developed during meth use.

The new research was published this week in the journal *Molecular Psychiatry*.

Young Neurons Gone Bad

Neurons are born all the time in a process called neurogenesis. In a 2010 study, Mandyam and her colleagues at TSRI showed that increased neurogenesis is tied to a higher risk of drug relapse, but they weren't sure of the new neurons' role in the process. The researchers were especially curious about a "burst" of neurogenesis that occurs during abstinence from meth.

The new study may explain why the brain is so eager to make neurons during abstinence: meth hijacks the natural neurogenesis process.

Normally, new neurons help us learn by forming new circuits to connect rewards, like food, to reward-associated memories. For example, we learn early on that the refrigerator holds food. "In a non-drug environment, this is a healthy process," said Mandyam. But the brain isn't good at separating healthy rewards from the dangerous high of drug use.

Using rat models of meth addiction, the researchers showed that forced abstinence prompted the development of new neurons called granule cell neurons in a brain region called the dentate gyrus, which is associated with memory formation. These new neurons drove compulsive-like drug seeking and relapse by strengthening drug-associated memories. The rats learned to associate a particular location in their environment with meth use. Returning to this location during abstinence later served as a triggering cue—prompting a recovering addict to relapse.

A Potential Way to Stop Relapse

Next, the researchers tested whether the synthetic small molecule Isx-9 could inhibit this process. Previous studies had shown that Isx-9 could block cell division of some types of cells, but it had not been tested as a way to block neurogenesis and fight meth relapse. Working closely with Professor Kim Janda's lab at TSRI, which supplied the molecule, Mandyam and her colleagues found that meth-addicted rats given Isx-9 during abstinence were less likely to relapse into drug use. Isx-9 indeed blocked neurogenesis, appearing to keep their brains from strengthening drug-associated memories. For these rats, the environment where they took the drug was no longer a strong trigger for relapse.

Interestingly, the researchers only saw the benefits of Isx-9 in rats that were "high responders" to meth. From the beginning of the experiment, some of the rats were simply not as interested in the drug—Mandyam called them the "casual users." "Just like humans, animals also show

remarkable individual differences in drug seeking," said Mandyam. She plans to further study these individual differences to better understand how to address addiction and recovery.

Isx-9 also appears to repair some of the structural changes seen in neurons exposed to meth. In high-responder rats, Isx-9 restored the neuronal structures crucial for normal cell signaling.

The researchers also plan to further investigate potential side effects of Isx-9, and Mandyam hopes future studies will set the stage to test Isx-9 in clinical trials for meth addiction.

More information: "A synthetic small molecule Isoxazole-9 protect against methamphetamine relapse," *Molecular Psychiatry*, 2017.

Provided by The Scripps Research Institute