Opioid users could benefit from meth-relapse prevention strategy, study finds

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The research was led by Courtney Miller, PhD, associate professor on the Florida campus of Scripps Research. Credit: Scripps Research

New research raises the possibility that a wider group of people battling substance use disorders may benefit from a Scripps Research-developed relapse-prevention compound than previously thought.

The research, published recently in the journal *Learning and Memory*, shows that the compound appears to be effective even if multiple drugs of abuse are involved, such as methamphetamine in combination with either opioids or nicotine. Polysubstance use is common among people addicted to methamphetamine, in part because the rate of smoking is high among meth users. In addition, the meth available today is so potent that many users turn to opioids to dampen the high.

The potential medication, a modified form of the compound blebbistatin, works by breaking down methamphetamine-linked memories that can trigger craving and relapse. The opportunity to boost treatment success by modulating emotional memory is a novel concept, and a promising one, says Courtney Miller, Ph.D., associate professor on the Florida campus of Scripps Research and senior author of the study.

For people in recovery from substance use disorder, memories can drive uncontrollable urges to return to drug use. Handling money, tasting certain foods or returning to places linked to their drug use can all trigger those intense cravings.

"A lot of current users aren't even aware of what their triggers are until they encounter them. These triggers can maintain their ability to drive craving for a person's entire life, meaning a lifetime relapse risk. That's what makes this new finding exciting," Miller says. "This would be the first compound to directly target the motivational power of craving triggers."

Importantly, the compound doesn't appear to act on other forms of memory or motivations, and this selectivity is key to its powerful potential.

How the drug works to target cravings

The modified blebbistatin, tested in animal models for this study, works by interfering with storage of memories in the amygdala, the brain's emotional memory center, Miller says. The medication inhibits a protein called nonmuscle myosin II. That protein organizes another, called actin, which is involved in neural plasticity, the extension of brain cells' finger-like projections that form new connections.

Normally, actin and nonmuscle myosin II stabilize within minutes of learning, lending stability to long-term memory storage. However, the actin and myosin supporting meth memories behaves differently. They remain active and, therefore, uniquely vulnerable to a drug designed to inhibit nonmuscle myosin II. In animal models, treatment with the compound eliminated the animals' learned preference for a place where they had ingested addictive drugs.

"What they are losing is that drive to go and drug seek when they see the familiar place," Miller adds.

Miller hopes this sort of treatment could offer long-term relief from drug cravings. Miller explains that while many U.S. insurance plans now cover 30 days of inpatient drug treatment, spontaneous addiction cravings last significantly longer, and at present, no medications exist to reduce the pull of lifelong drug-linked memories.

"The height of drug cravings peaks around 30 days and goes out to about 180 days after cessation of use," Miller says. "That's when they are out of rehab and back in their environment, surrounded by the things that trigger their cravings, so it's a really problematic situation."

A closer look at the role of stress in relapse

Memories aren't the only problem. Studies show that encountering intense stress during that sensitive recovery period can boost relapse risk.

For a related study, published recently in the journal *Addiction Biology*, Miller, research associate Ashley Blouin, Ph.D., and colleagues, developed a novel animal model of social stress-potentiated meth seeking that may provide a more accurate way to test the effectiveness of the modified blebbistatin compound and other therapies in development.

"There is data in humans that social stress—combined with using a small amount of meth—can drive a much stronger craving for the drug," Miller says. "We found we can recapitulate that in an animal model."

The new model measures relapse in animals that had been previously exposed to social defeat and meth. With the model, a rat is placed in the home cage of an aggressive resident rat. Some of these "intruders" handle the aggressive resident in an active way, defending themselves. Others take a more passive approach and rapidly acquiesce to the resident by laying down. The passive rats were consistently more likely to self-administer methamphetamine after the stressful encounter compared to rats that actively defended themselves, Miller says. Interestingly, passive coping strategies have been linked to a host of behavioral and mental disorders, including an increased likelihood of developing addiction, she adds.

"Having a reliable model of social stress in the context of drug use will be important to developing medication strategies to improve treatment response," Miller says.

Depending on many factors, relapse rates following treatment for methamphetamine and heroin addiction can hover between 40 percent and 60 percent, or as high as 90 percent. Studies suggest that people who abuse both methamphetamine and heroin are almost three times more likely to overdose, underscoring the need for innovative solutions. With these two new studies, Miller hopes to bring treatment options closer to

patients as quickly as possible. With funding from the Blueprint Neurotherapeutics Network, a translational research program of the National Institutes of Health, the Miller laboratory is working with Scripps Research colleagues, Pat Griffin, Ph.D., and Ted Kamenecka, Ph.D., to move the modified blebbistatin to the clinic.

More information: Sherri B. Briggs et al, The role of nonmuscle myosin II in polydrug memories and memory reconsolidation, *Learning & Memory* (2018). DOI: 10.1101/lm.046763.117

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