

Exercise combined with methamphetamine regimen could be a powerful new way to treat addiction

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Exercise coupled with a regimen of methamphetamine could help addicts get clean, according to a pre-clinical study published today in the *FASEB Journal*. The reason lies in the mechanism through which exercise and methamphetamine affect circadian rhythms, the roughly 24-hour cycles that drive all organisms.

Researchers in the Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo based their hypothesis on the fact that both methamphetamine and running wheel activity target the same reward centers in the brain, which are also involved in daily synchronization of physiological rhythms.

"Our experiments show that it might be possible to use methamphetamine to treat meth addiction itself, by associating drug usage with a stimuli that's not harmful: exercise," explained Oliver Rawashdeh, PhD, co-first author, formerly a postdoctoral researcher in the Jacobs School of Medicine and Biomedical Sciences and now a lecturer and head of the Chronobiology lab in the School of Biomedical Sciences at the University of Queensland in Australia. Shannon J. Clough, PhD, a [postdoctoral researcher](#) in the UB Department of Pharmacology and Toxicology, is co-first author with Rawashdeh.

The UB researchers were interested in [circadian rhythms](#) because addiction upsets them, increasing craving for the drug and making

relapse after treatment more likely.

"Since various aspects of circadian rhythms are conserved among mammals, these findings may be directly translatable to humans," said Margarita Dubocovich, PhD, senior author and chair of the Department of Pharmacology and Toxicology in the Jacobs School of Medicine and Biomedical Sciences.

Circadian rhythms out of sync

"The circadian system is negatively impacted by drugs of addiction and it doesn't necessarily recover," said Rawashdeh. "We also know that the success of rehabilitation and prevention of relapse is linked to the degree of circadian disturbance in addicts."

To better understand the relationship between addiction and circadian rhythms, the researchers studied mice from whom the suprachiasmatic nucleus (SCN), a small region in the brain's hypothalamus that acts as the master circadian clock, was removed.

"Metabolism and sleep cycles are all off kilter when someone is addicted," Rawashdeh explained, "just like an animal whose master circadian clock has been removed."

"It's like being in a constant state of jet lag," said Dubocovich. "You are in a constant transition state and the same goes for these animals," she said.

That's what happens when the SCN, the master circadian driver, becomes decoupled from the so-called "slave" oscillators that it controls, one of which is the methamphetamine-sensitive circadian oscillator or MASCO.

Exercise as meth substitute

The researchers found that running wheel access and methamphetamine reinstate circadian rhythmicity in animals with no SCN, providing periodic feedback to a newly activated circadian brain clock, which could be the MASCO.

"Our idea was that if you pair a reward, in this case access to the running wheel, along with methamphetamine in 24-hour intervals over a period of time, the animal's fragmented sleep/wake cycles would acclimatize to the 24-hour cycles, a process we call entrainment and consolidation," explained Rawashdeh. Even more fascinating, he added, is the fact that the re-established circadian rhythm in sleep/wake cycles persists even after removing methamphetamine.

Tapping into brain plasticity

"We created a new homeostatic state," he said. "By using the principles of learning and memory, we may have rewired the brain's circuitry, activating a new clock – a form of plasticity – using the same stimulus that caused addiction in the first place, methamphetamine," said Rawashdeh. "This was necessary in order to transfer the euphoric and pleasurable characteristics associated with the drug over to a healthy stimulus – exercise."

Exercise stimulates the growth of new neurons, which may also play a role in the successful brain rewiring that takes place, the researchers said.

If this association can be duplicated in people, Rawashdeh added, it might be very possible to accelerate the efficiency of drug rehabilitation, decreasing the chances for relapse and re-establishing healthy circadian

rhythms after withdrawal.

The team's immediate next step is to understand how the pairing of exercise with methamphetamine activates a new circadian clock in the brain to induce robust rhythms and drug withdrawal, explained Dubocovich.

More information: O. Rawashdeh et al. Learned motivation drives circadian physiology in the absence of the master circadian clock, *The FASEB Journal* (2016). [DOI: 10.1096/fj.201600926R](https://doi.org/10.1096/fj.201600926R)

Provided by University at Buffalo

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