

Scientists show molecule in brain may drive cocaine addiction

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A new study from scientists at The Scripps Research Institute (TSRI), funded by the National Institutes of Health's (NIH) National Institute on Drug Abuse (NIDA) and National Institute on Alcohol Abuse and Alcoholism (NIAAA), suggests that increased levels of a molecule in the brain, called hypocretin, may contribute to cocaine addiction.

The research, published recently online ahead of print in the journal *Biological Psychiatry*, shows that blocking hypocretin may reduce compulsive drug-seeking behavior in rat models of cocaine addiction.

"Cocaine addiction is a disorder that affects millions of people worldwide," said Marisa Roberto, professor in TSRI's Committee on the Neurobiology of Addictive Disorders (CNAD) and co-author of the study with Brooke Schmeichel, a former TSRI researcher now at NIDA, George Koob, the CNAD chairman currently on a leave of absence to direct the NIAAA, and Melissa Herman, a senior research associate at TSRI. "Understanding the mechanisms underlying cocaine addiction is important for identifying potential new targets for therapeutic use."

"The results of this study would suggest that the hypocretin system could be considered a pharmacological target, with the hopes that such a medication could be used in combination with cognitive behavioral therapies," added Schmeichel.

What Fuels Addiction?

Addiction seems like a simple concept—taking a drug motivates a person to continue to take that drug.

But the molecular mechanisms in the brain that drive addiction are more complex. To design treatments for addiction and relapse, scientists need to understand what motivates a person to transition from occasional drug use to compulsive drug use.

In the new study, the researchers, led by Schmeichel, focused on changes in the central amygdala, a brain region associated with stress and negative emotions during drug withdrawal.

Their goal was to better understand the role of a neurotransmitter called hypocretin in the central amygdala. Hypocretin is a main player in the brain's hypothalamic hypocretin/orexin (HCRT) system, a network that sends signals between brain regions and has been shown to influence the brain's reactions to cocaine, nicotine, alcohol and opioids and the desire to relapse. Until now, however, scientists did not fully understand the HCRT's role in [cocaine addiction](#).

For the study, one group of rats was given the option to self-administer cocaine for one hour a day, mimicking conditions of short-term, occasional drug use. A second group had the option to self-administer cocaine for six hours a day, which mimicked the conditions that lead to compulsive drug use and addiction.

The researchers found that compulsive cocaine use triggers a dangerous cycle in the brain, with cocaine sensitizing the HCRT system, which motivates further drug-seeking.

Specifically, compulsive [cocaine](#) use leads to increased hypocretin, which contributes to overactivity in the central amygdala. This overactivity corresponds with an anxiety-like state in rat models that

appears to help maintain the motivation to continue to seek the drug.

"The rats escalate their daily intake as many human users would," said Roberto.

Interestingly, giving the rats an "antagonist" to block HCRT activity at one of the two HCRT receptors in the central amygdala helped reduce their [drug](#)-seeking behavior, suggesting a potential role for these compounds in treatments for addiction and relapse.

More information: Brooke E. Schmeichel et al, Hypocretin Neurotransmission within the Central Amygdala Mediates Escalated Cocaine Self-Administration and Stress-induced Reinstatement in Rats, *Biological Psychiatry* (2016). [DOI: 10.1016/j.biopsych.2016.06.010](https://doi.org/10.1016/j.biopsych.2016.06.010)

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