Treating cocaine addiction by reducing our appetite for drugs?

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The hypocretin/orexin (HCRT) system of the brain is best known for promoting wakefulness and appetite. A new paper in *Biological Psychiatry* suggests that blocking hypocretin signaling via the HCRT-1 receptor (HCRT-R1) might also reduce the appetite for cocaine. The study, led by first author Dr. Brooke Schmeichel in George Koob's laboratory at the National Institute on Drug Abuse (NIDA), Intramural Research Program, Baltimore, Maryland, suggests that blocking hypocretin signaling may provide a new avenue for treating cocaine addiction.

"The more that we learn about the brain, the more that we learn that brain signaling mechanisms that play a particular defined function, such as a role in wakefulness or appetite, often play important roles in other functions, such as addiction," said professor John Krystal, Editor of *Biological Psychiatry*.

HCRT signaling has been implicated in stress and high-arousal conditions, linking it to cocaine's strong arousal-inducing effects and stress-induced relapse of drug seeking. To better understand how the HCRT system contributes cocaine addiction, Schmeichel, along with colleagues at The Scripps Research Institute, La Jolla, California, provided rats with short (1 hour) or long (6 hours) access to cocaine, which the rats could self-administer through an IV by pressing a lever. Long access to the drug induces compulsive-like cocaine seeking behavior in the rats, in contrast to more stable use by rats provided short access.

Blocking hypocretin signaling throughout the brain with an HCRT-R1 antagonist reduced cocaine intake only in the rats allowed long access to cocaine self-administration. The researchers saw the same effect when the antagonist was administered directly to the central amygdala, a region of the brain involved in stress and anxiety, which also blocked stress-induced reinstatement of cocaine seeking. The findings finger HCRT neurotransmission within the central amygdala as a key contributor to compulsive-like cocaine taking.

Rats allowed long access to cocaine also had an overactive GABAergic system in the central amygdala, which was modulated by the HCRT system. Importantly, the rampant GABA signaling was restored by blocking HCRT-R1. Reversal of the cocaine-induced neuroadaptations in the central amygdala has important implications for efforts to curb compulsive-like cocaine intake associated with addiction.

"The results of this study would suggest that the hypocretin system could be considered a pharmacological target, with the hopes that a medication designed to target hypocretin receptors could be used in combination with cognitive behavioral therapies as part of a cocaine abuse treatment strategy," said Dr. Schmeichel.

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* (2017). DOI: 10.1016/j.biopsych.2016.06.010

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