Reward-stress link points to new targets for treating addiction

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Rewarding and stressful signals don't seem to have much in common. But researchers studying diseases ranging from drug addiction to anxiety disorders are finding that the brain's reward and stress signaling circuits are intertwined in complex ways.

Vanderbilt University Medical Center investigators have now discovered a functional link between reward and stress. They found that dopamine – the brain's chief reward signal – works through corticotrophin-releasing factor (CRF) – the brain's main stress signal – to increase the activity of a brain region involved in addiction relapse.

The findings, reported Dec. 17 in *The Journal of Neuroscience*, point to new potential targets for treating alcohol and drug abuse – particularly the problem of relapse.

It is widely accepted that stress is a key signal in prompting alcohol and drug abuse relapse.

"Even after long periods of abstinence, an individual is at risk for relapse, and stress is what's most frequently cited as initiating that relapse," said Danny Winder, Ph.D., associate professor of Molecular Physiology & Biophysics and an investigator in the Center for Molecular Neuroscience and the Vanderbilt Kennedy Center.

Studies in animal models had suggested that a brain region called the extended amygdala – an area that extends anatomically between reward and stress centers – and CRF within this region were involved in stress-induced reinstatement (relapse) behavior.

It was also known that alcohol and drugs of abuse increase dopamine levels, not just in the "classical" reward circuitry in the brain, but also in the extended amygdala. It was not clear, however, what dopamine did in this region.

Thomas Kash, Ph.D., a research instructor in Winder's laboratory, decided to explore dopamine's actions in the extended amygdala. Using an in vitro brain slice system, he discovered that dopamine increased excitatory glutamate signaling in this brain region. Surprisingly, he found that dopamine required CRF signaling to increase glutamate signaling.

The researchers next looked for this mechanism in animals. William Nobis, an M.D./Ph.D. student, injected mice with cocaine and studied signaling in brain slices. His studies confirmed that in vivo administration of cocaine engaged the dopamine-CRF signaling cascade that the team had discovered in vitro.

"We think that when an individual takes a drug of abuse or alcohol, it causes a rise in dopamine levels in the extended amygdala, and that likely engages this CRF signaling cascade in this region," Winder said. "That's now activating portions of this brain structure, which then communicate with the core addiction reward circuitry. We believe the dopamine-CRF signaling may be a key initial step in promoting reinstatement behavior."

The findings suggest a new target to consider for therapeutics that might address stress-induced reinstatement, Winder said.

"If we can hone in on the mechanisms of this dopamine-CRF interaction, if we can identify the key population of CRF cells, then we could start to think of approaches to silence those cells."

Such a therapy would be extremely valuable, Winder noted.

"Essentially all of the pharmacotherapies for addiction to date help people get through the withdrawal phase," he said. "There's really nothing available to reduce the likelihood of relapse."

The studies add to a growing number of research findings that point to the interwoven nature of the brain's reward and stress circuitry. Investigators need to be looking beyond dopamine and the classical reward circuitry – long considered the "common target" of drugs of abuse – to understand mechanisms underlying addiction-related behaviors, Winder said.

"The recruitment of CRF signaling may be another common feature of drugs of abuse."

Source: Vanderbilt University Medical Center