Brain mechanism linked to relapse after cocaine withdrawal

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Addictive drugs are known to induce changes in the brain's reward circuits that may underlie drug craving and relapse after long periods of abstinence. Now, new research, published by Cell Press in the September 9 issue of the journal *Neuron,* uncovers a specific neural mechanism that may be linked to persistent drug-seeking behavior and could help to guide strategies for development of new therapies for cocaine addiction.

Previous research has shown that the ventral tegmental area (VTA) is a brain region that is activated when cocaine users experience a craving for cocaine after being exposed to cocaine-associated cues. The medial prefrontal cortex (mPFC), which receives input from the VTA via circuits that use the "reward" neurotransmitter dopamine, has also been implicated in drug craving after cocaine withdrawal. Further, increases in the level of brain-derived neurotrophic factor (BDNF) have been observed in the VTA and mPFC in rats after withdrawal from repeated cocaine exposure.

"BDNF plays a key role in modulating the structure and function of synapses, the sites of communication between neurons. Therefore, increased BDNF after cocaine withdrawal may drive synaptic changes that contribute to compulsive drug seeking behavior," explains senior author, Dr. Mu-ming Poo from the University of California, Berkeley. "It has been shown that increased BDNF in the VTA after cocaine withdrawal in rats promotes the drug-dependent motivational state. However, nothing is known about the potential BDNF effect on synaptic function and plasticity in mPFC neurons after cocaine withdrawal."

Dr. Poo and colleagues designed a study to examine how BDNF and the mPFC might contribute to relapse after cocaine addiction. The researchers found that the gradual increase in BDNF expression in the rat mPFC after terminating repeated cocaine exposure significantly enhanced the activity-induced potentiation of specific synapses. Dr. Poo's group went on to uncover the specific cellular mechanism linking increased BDNF with enhanced synaptic plasticity and demonstrated that interference with the key molecule in the BDNF signaling process reduced behavioral sensitivity after cocaine withdrawal in rats.

"In short, our results demonstrate that elevated BDNF expression after cocaine withdrawal sensitizes the excitatory synapses in the mPFC to undergo activity-induced persistent potentiation that may contribute to cue-induced drug cravings and drug-seeking behavior," concludes Dr. Poo. Although a clear correlation between rat and human behaviors of cocaine craving and relapse remains to be established, the cellular mechanism uncovered in this study does appear to have behavioral relevance and may represent a direct brain sensitization that is involved in triggering relapse.

Provided by Cell Press