Cocaine addiction linked to voluntary drug use and cellular memory

30 July 2008

Rats that voluntarily use cocaine show a persistent cellular memory in the brain's reward center even after several months of abstinence from the drug, while their involuntary counterparts had no such memory, according to a new study by researchers at the University of California, San Francisco.

The researchers conclude that the pharmacologic effects of cocaine alone are not enough to cause long-lasting cellular memories in the brain's reward circuit. The discovery by neuroscientists at UCSF's Ernest Gallo Clinic and Research Center appears in the July 31 issue of the journal "*Neuron*."

The study opens a window onto the significance of active choice in using cocaine and extends our understanding that addiction is caused by more than the pharmacological effects of a given drug, according to Antonello Bonci, MD, senior author of the paper, UCSF associate professor of neurology, Howard J. Weinberger Chair in Addiction Research and principal investigator at the Gallo Center.

"We know that environmental cues are significant in many addictions, including tobacco and alcohol, and contribute to relapses," Bonci said. "This study identifies the specific neuronal process involved and helps explain relapse even after rehabilitative therapy or long-term abstinence."

The researchers trained rats to self-administer cocaine, food or sucrose using a lever-pressing procedure. A separate group of rats also received passive researcher-administered cocaine. Neural activity was compared in brain tissue samples from the four groups and with samples from rats that had not experienced any rewards or training.

The study found that rats that learned to self-administer cocaine showed an increase in communication to dopamine neurons, which form the brain's key natural reward and motivational circuit, known as the ventral tegmental area (VTA).

In rats that self-administered cocaine, the increase in neuronal communication – called long-term synaptic potentiation (LTP) – was similar to those that had self-administered food or sucrose, but with a critical distinction. The increase in LTP due to cocaine persisted for up to three months of abstinence, but the increase in response to natural rewards dissipated after only three weeks. One striking finding, according to the research team, was that rats given passive cocaine infusions did not show LTP in the VTA dopamine neurons.

One subset of rats in the active group also underwent behavioral extinction. In extinction training, depression of the lever was no longer accompanied by cocaine leading to the cessation of drug-seeking behavior. Despite the absence of the behavior, LTP remained just as high as in rats that had not received the extinction training, indicating that the cellular memory produced by cocaine-seeking behavior remained intact, according to Billy T. Chen, PhD, a postdoctoral fellow at the Gallo Center and lead author of the study.

"These potentiated synapses are persistent, regardless of what your new behavior is, and because the memory is still maintained, it could trigger relapse when the conditions are repeated," Chen said. "This is a clear validation that drug addiction is a life-long disease. Three months for a rat could equal several years in a human. Although drug-taking behaviors may be absent, the 'memory' makes relapse not only possible, but likely."

Source: University of California - San Francisco