Brain's reaction to self-administered cocaine differs

30 July 2008

New research has uncovered a fundamental cellular mechanism that may drive pathological drug-seeking behavior. The study, published by Cell Press in the July 31 issue of the journal *Neuron,* examines the brain's reward circuitry and details strikingly distinct influences of self-administered cocaine compared to natural rewards or passive cocaine injection.

Dopamine (DA) neurons residing within the ventral tegmental area (VTA) of the brain are a key part of the brain's natural reward pathway and have been implicated in mediating many types of motivated behaviors. It is well established that the VTA DA neurons can express plasticity of excitatory glutamate synapses in the form of long-term potentiation (LTP), a widespread form of cellular plasticity thought to underlie learning and memory processes.

The VTA DA neurons have also been linked with drug addiction, but the cellular mechanisms underlying this phenomenon are not well understood. "While usurpation of learning and memory processes may support persistent seeking of abused drugs, common synaptic mechanisms of natural and drug reinforcement have not been demonstrated," says study author Dr. Antonello Bonci from the University of California, San Francisco.

Dr. Bonci and colleagues demonstrated that self-administration of cocaine produced a potentiation of VTA excitatory synapses that persisted for three months after abstinence and was still present after three weeks of extinction training. This finding may be relevant to relapse in humans as potentiation persisted even when drug-seeking behaviors were extinguished. In contrast to self-administration of cocaine, self-administration of natural rewards, such as food or sugar, induced a potentiation of VTA glutaminergic synapses that was equally potent but quite short-lived.

Interestingly, rats that received repeated passive injections of cocaine did not exhibit potentiation of VTA glutamatergic function, suggesting that cocaine-associated changes were due to an associative process and not just to the pharmacological effects of the drug. "We suggest that neuroadaptations induced specifically by drug self-administration may form a powerful 'memory' that can be activated by drug-associated cues," explains coauthor Dr. Billy T. Chen.

How self-administration of a drug but not a natural reward can elicit enduring changes within the brain remains a mystery. "Future studies are required to identify the exact mechanisms through which drugs of abuse alter neural circuitry that is normally accessed by naturally reinforcing events but is usurped by cocaine to persistently cement these synaptic adaptations, perhaps ultimately leading to pathological drug-seeking behavior," concludes Dr. Bonci.

Source: Cell Press