Cocaine-induced synaptic plasticity linked to persistent addictive behaviors

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The persistent nature of addiction is its most devastating feature. Understanding the mechanism underlying this phenomenon is the key for designing efficient therapy. Two separate studies published by Cell Press is the August 14 issue of the journal *Neuron* identify specific cocaine-induced changes in dopamine (DA) neurons that play a pivotal role in behaviors associated with drug addiction.

DA neurons in an area of the brain called the mesolimbic system play a major role in both reward and motivation and are a primary target for abused drugs. However, exactly how drug-induced synaptic changes in DA neurons relate to the development of addictive behaviors remains a critical unresolved issue.

Plastic changes in excitatory glutamate synapses on DA neurons in the ventral tegmental area (VTA) have been implicated in the process of addiction. Previous research has linked cocaine-induced synaptic strengthening in DA neurons in the VTA with activation of a subtype of glutamate receptors, called NMDA receptors (NMDAR) and with changes in the subunit composition of another type of glutamate receptor, AMPA receptors (AMPAR).

In one study, Dr. Larry S. Zweifel, and colleagues, from the Howard Hughes Medical Institute and the Department of Biochemistry at the University of Washington in Seattle, examined the link between glutamate signaling in DA neurons and long-term changes associated with drug exposure by selectively inactivating NMDAR signaling in DA neurons and testing two widely used models of addiction in mice.

Dr. Zweifel and colleagues observed that while the stimulatory effects of cocaine on motor activity were unaltered and behavioral sensitization progressed normally, cue-evoked drug seeking and the enhancement of drug craving following withdrawal were significantly impaired in the mice lacking functional NMDAR in DA neurons. "Our findings support a role for NMDAR-dependent modulation of DA neurons in cue-induced relapse to drug seeking," says Dr. Zweifel.

In a separate study, Dr. Engblom and colleagues from German and Swiss research teams examined the relationship between glutamate signaling and drug-induced behavior using mice lacking the GluR1, GluR2, or NR1 glutamate receptor subunits selectively in DA neurons.

The mice with perturbed NMDAR signaling or AMPAR plasticity in DA neurons lacked cocaine-induced synaptic strengthening but exhibited normal basal and cocaine-induced DA release properties. However, the researches did observe two alterations in the persistence of drug-seeking behavior. Interference with NMDAR signaling in DA neurons abolished cocaine relapse behavior, and deletion of the GluR1 subunit in DA neurons resulted in a specific deficit in extinction of cocaine-induced reinforcement.

"Our findings link NMDAR signaling in DA neurons with relapse behavior and provide a new rationale in the treatment of cocaine addiction. Specifically, the selective activation of the GluR1 subunit could potentially improve the outcome of any given exposure therapy," concludes Dr. Engblom.

Findings from both studies support the hypothesis that cocaine-evoked synaptic plasticity does not mediate concurrent short-term behavior effects of the drug but may instead underlie long-term changes responsible for persistent drug-seeking behavior.

Source: Cell Press

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