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## Knockout Mice Reveal Mechanism of Dopamine Regulation



**Image Title:** - Chris Hildreth/Duke University

Mice living in the Duke University lab of Howard Hughes Medical Institute investigator Marc G. Caron act crazed. They race about their cages. They eat too little. They die young. In fact, these mice act as though they were permanently high on drugs. And that's the idea. Caron and colleagues engineered the mice to mimic drug addicts by knocking out their gene for a brain protein called a "dopamine transporter." Normally, the protein regulates levels of the neurotransmitter dopamine—a potent chemical implicated in addiction, schizophrenia and Parkinson's disease.

In the February 15, 1996 issue of the journal *Nature*, Caron and colleagues reported that these knockout mice show just how essential the dopamine transporter is. The transporter works by mopping up circulating dopamine that has already stimulated brain cells. When the transporter is missing, dopamine lingers outside cells, stimulating them "100 to 300 times longer" than normal, Caron said. Hyperactivity and other drug-related behavior result.

In the body, dopamine exerts some control over locomotion, cognition and certain social behavior, Caron said, noting that locomotion is the easiest to

assess in lab animals. His knockout mice are five to six times more active than normal mice.

As the first animal model of a system flooded with too much dopamine—a condition called hyperdopaminergia—the mice offer a way to study the basic mechanisms of addiction. "The thinking is that addiction, craving, [and] even pleasure comes from the modulation of the dopamine system," Caron said. "Nicotine, alcohol, marijuana, even caffeine—which act on different targets— may all have common reward or reinforcing effects through the dopamine system." Caron next plans to see if his knockout mice will self-administer addictive substances. In the end, he hopes to better understand the scope of dopamine's power over these rodents—and over us.