Receptor limits the rewarding effects of food and cocaine

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(Medical Xpress) -- Researchers have long known that dopamine, a brain chemical that plays important roles in the control of normal movement, and in pleasure, reward and motivation, also plays a central role in substance abuse and addiction. In a new study conducted in animals, scientists found that a specific dopamine receptor, called D2, on dopamine-containing neurons controls an organism's activity level and contributes to motivation for reward-seeking as well as the rewarding effects of cocaine.

A report of the findings, by researchers at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of the National Institutes of Health, and colleagues at the Institute for Research on Genetic Engineering and Molecular Biology in Argentina and the University of Michigan Medical School, Ann Arbor, appears online in *Nature Neuroscience*.

"These important findings enhance our understanding of the roles of dopamine and the D2 receptor in neuronal function," says NIAAA Scientific Director George Kunos, M.D., Ph.D. "The findings will likely inform our understanding of the actions of drugs of abuse, and could have important implications for treatment."

"Research in humans and other species has shown that increased vulnerability to drug addiction correlates with reduced availability of D2 dopamine receptors in a brain region called the striatum," explains study coauthor David M. Lovinger, Ph.D., chief of NIAAA's Laboratory for Integrative Neuroscience. "Furthermore, healthy non-drug-abusing humans that have low levels of the D2 dopamine receptor report more pleasant experiences when taking drugs of abuse."

Efforts to investigate dopamine's role in addiction and normal biological processes have been complicated by the fact that the nervous system contains multiple kinds of receptor molecules for dopamine as well as different types of nerve cells that use dopamine.

In the current study, scientists in Dr. Lovinger's lab worked with Argentinean researchers led by senior author Marcelo Rubinstein, Ph.D., to develop genetically engineered mice in which expression of D2 receptors was selectively prevented in nerve cells that use dopamine as their neurotransmitter. These nerve cells are present in the midbrain region and connect to other neurons in the striatum. The receptors normally present on these cells are known as D2 autoreceptors.

The researchers found that loss of D2 autoreceptors in the mice prevented the normal feedback effect by which dopamine already present in brain synapses reduces subsequent activity of dopamine-containing neurons and dopamine release. This crucial control system prevents the neurotransmitter from reaching concentrations that produce excessive levels of movement and other behaviors. Mice that lacked D2 autoreceptors were more active than mice with normal autoreceptor levels. When investigators examined behaviors related to brain mechanisms of reward and addiction, they found that mice lacking D2 autoreceptors worked longer and harder to obtain food, and showed increased sensitivity to the rewarding effects of cocaine, compared to normal mice. Cocaine increases activity in mice, and the mice lacking D2 autoreceptors were also more sensitive to this effect of the drug.

"Our findings indicate that, among the many dopamine receptors, D2 receptors on the dopamine neurons themselves appear to play crucial roles in dampening dopamine levels in brain," says Dr. Lovinger. "Through this function the D2 autoreceptors help to prevent production of excessive behaviors and limit the rewarding effects of food and cocaine. Our observations might help to explain why altered levels of D2 receptors in human midbrain and striatum are associated with

susceptibility to addiction."

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