NEUROBIOLOGY

New Clues to Brain Dopamine Control, Cocaine Addiction

Maintaining normal brain function, like many things in life, requires a delicate balancing act: Too much neuronal activity can be just as bad as too little. Researchers have long known that the chemical dopamine—one of the neurotransmitters that relay signals between nerve cells—is essential in such functions as movement, cognition, and emotion. But how the brain keeps its dopamine levels in equilibrium has been the subject of intense inquiry. Now, a research team led by Marc Caron of the Howard Hughes Medical Institute lab at Duke University has shed new light not only on this balancing act, but also on the mechanisms by which drugs, including cocaine and amphetamine, cause addiction.

The team reports in the 15 February issue of *Nature* the creation of a strain of "knockout" mice in which the gene for a protein known as the dopamine transporter has been eliminated. Previous evidence suggested that the transporter, which mops up the dopamine that nerve cells release when they fire, helps regulate dopamine signaling. Many experts also believe that cocaine, and perhaps amphetamines, cause their addictive highs by raising brain dopamine, possibly by acting through the transporter. But Caron and his Duke colleagues Bruno Giros, Mohamed Jaber, and Sara Jones, and collaborator Mark Wightman of the University of North Carolina have shown that the transporter is even more important than once thought.

They found that the knockout mice, which are unable to clear dopamine from the synapses between nerve cells, become markedly hyperactive, despite heroic attempts by the animals' nervous systems to turn down their dopamine-signaling pathways. Caron and his colleagues conclude that the transporter is the key factor controlling dopamine levels. And this conclusion is buttressed by their finding that the animals are completely unaffected by administration of cocaine and amphetamines, which suggests that these drugs exert most of their effects through the transporter. "We have demonstrated for the first time the really primordial role it plays," Caron says.

Other experts agree. "This is a wonderful paper," says Michael Kuhar, a neuropharmacologist at the Yerkes Regional Primate Research Center at Emory University in Atlanta. "It's going to be a classic in the field." And Alan Leshner, director of the U.S. National Institute on Drug Abuse (NIDA), says the new mouse is "a fantastic tool" to help understand addiction, because "every drug of abuse works through the dopamine system" to a significant extent. Indeed, the work may help in the design of new drugs for treating drug addiction, and perhaps also for Parkinson's disease, which is caused by a sharp fall in brain dopamine concentrations.

Evidence that the transporter is important in regulating dopamine has been building for some time. Researchers had found, for example, that it captures the dopamine released into synapses and then pumps it back into the nerve cell, where it is repackaged in storage vesicles. But because the transporter is only one of several elements of the dopamine system, Caron's group used the knockout approach to see just how key the transporter's role is.

The results were dramatic: Mice lacking the transporter were five to six times more active than "wild-type" mice who have the gene, as measured by the number of times they passed through photocell beams in an "activity box." By itself, this hyperactivity was not surprising: Without the transporter, dopamine was expected to accumulate in the synapse and continue to activate nerve firing. However, the researchers were surprised to find much less dopamine was produced in the knockout's brains compared to normal mouse brains.

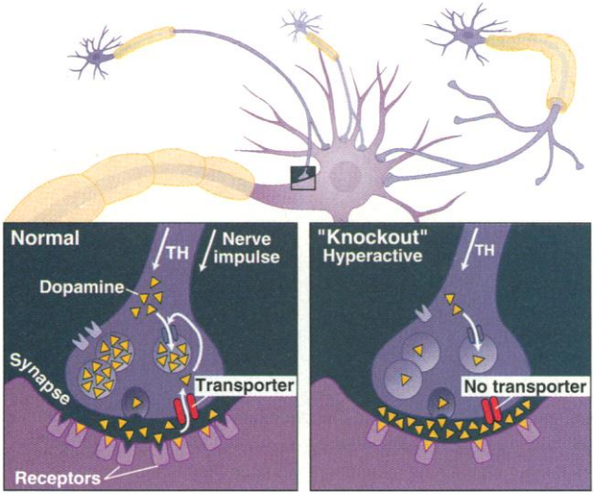
To explain this seeming inconsistency, the Duke team demonstrated that the animals try to compensate for the lack of the transporter by "down-regulating" the entire dopamine system. Not only did their brain neurons release less dopamine when stimulated, but they also made less of a key enzyme involved in dopamine synthesis. And at the other side of the synapse, there was a dramatic decrease in the number of the receptors through which dopamine exerts its effects. "The animals are doing everything possible to dampen the signal generated by absence of dopamine reuptake," Caron says. But these efforts weren't enough: In the knockout mice, dopamine remains in the synapse 100 times longer than in wild-type mice, producing an enhanced effect despite the much lower concentrations.

The group's finding that the knockout mice lost their sensitivity to cocaine and amphetamines is consistent with recent work indicating that cocaine raises dopamine concentrations in synapses by binding to the transporter near the site where the neurotransmitter itself binds, thus blocking dopamine reuptake. But, says NIDA's Leshner, "we've never had a technique like this, where you can see just how necessary the transporter is to the psychostimulatory effect." As for amphetamines, earlier studies had suggested that these drugs acted primarily by increasing dopamine release—a view that might now have to be modified. The Duke workers "show that the transporter is a mandatory component for dopamine release triggered by amphetamines, and that's a surprise," says neurobiologist Ann Graybiel of the Massachusetts Institute of Technology.

Caron's team is launching a new series of experiments to fine-tune their understanding of the dopamine transporter's role. For example, Giros, now at the French biomedical agency INSERM in Paris, will lead a study to see if the knockout mice self-administer cocaine and amphetamines, "That will be a key experiment," says Kuhar. If the Duke workers are right about the dopamine transporter, mice lacking this protein would be unlikely to derive any pleasure from these drugs and thus won't self-administer them.

If this prediction pans out, it might boost efforts to develop new therapies against drug addiction, particularly cocaine dependence, which Leshner says is a major NIDA priority. This might be done, he suggests, by designing drugs that prevent cocaine from binding to the transporter. And a greater appreciation of the role of the transporter could also lead to new medications for Parkinson's disease; the symptoms of low dopamine might be alleviated by blocking the transporter. "This paper shows you can do a lot with a little bit of dopamine, if you can just keep it in there," says Graybiel.

–Michael Balter



No exit. Transporter knockout mice are hyperactive because their neurons can't remove dopamine from synapses.

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