could be given signaling molecules called cytokines to prompt immune system cells to divide. But whether these measures are warranted depends on discovering what HIV is actually doing to the immune system. The new methods, researchers say, are an important step in that direction. Says McLean: "We may now have a technique that can eventually bring the jury in." –MICHAEL BALTER

NEUROBIOLOGY

How Stimulant Drugs May Calm Hyperactivity

To calm down children diagnosed as hyperactive, pediatricians give them small doses of stimulants—drugs such as the widely prescribed Ritalin. It seems paradoxical. And the paradox is even more vivid to neuroscientists, who know that high doses of these drugs raise brain levels of dopamine, a neurotransmitter that promotes activity. New results from a research team at Duke University Medical Center in Durham, North Carolina, now point to a surprising explanation for the drugs' puzzling effectiveness: Rather than working through dopamine, low doses may instead raise the concentrations of another neurotransmitter, serotonin, known to have calming effects.

This conclusion comes out of a series of experiments that the Duke team, led by neurobiologists Raul Gainetdinov and Marc Caron, performed on a strain of genetically altered mice that have behavioral symptoms similar to those of children with attention-deficit hyperactivity disorder (ADHD). As the team reports on page 397, treatment with psychostimulant drugs, including methylphenidate (Ritalin), relieves the symptoms in the mice, apparently without affecting brain dopamine concentrations. Compounds that boost serotonin in the brain have similar effects, a result suggesting that this neurotransmitter is instead the one that tones down the animals' hyperactivity.

ADHD expert Russell Barkley of the University of Massachusetts Medical Center in Worcester describes the work as "an impressive series of studies, done very carefully." Many ADHD researchers are not convinced, however, that the mouse results apply to human patients. They think that in humans the stimulants probably work through dopamine in some way—perhaps by raising levels so high that neurons become inured to it. But if humans do respond in the same way as the mice, researchers might be able to design new ADHD therapies that work by mimicking serotonin's effects.

The new experiments use a mouse strain that Caron and his colleagues created 3 years ago by inactivating the gene for a protein called the dopamine transporter (*Science*, 16 February 1996, p. 909). The transporter, DAT for short, has the job of picking up dopamine released by nerve activity and transporting it back into the neurons that produced it. Because extracellular dopamine concentrations remain high in the brains of the knockout animals, they are much more active than normal mice. "They're hyperactive for a good reason," Caron says. "They have lots of dopamine."

Indeed, there is some reason to think that a DAT abnormality could contribute to ADHD. At least three genetic linkage studies have picked up an association between a particular variant of the gene that encodes DAT and the condition. And Gainetdinov, Caron, and their colleagues now have evidence that their knockout mice closely mimic the symptoms of hyperactive children. Novel environments, for example, can exacerbate the symptoms of ADHD in children. Similarly, the knockout mice were some 12 times more active than normal mice when first placed in new surroundings, and their high activity levels persisted for the entire 4-hour observation period.

Climbing the walls. The time-lapse photography shows the hyperactivity of the mouse at right, which has no DAT gene.

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Hyperactivity in children is also associated with an attention deficit. So the team tested the mice for a similar problem by putting them in a maze consisting of eight arms radiating from a central area, each of which is baited with food. The mice are supposed to learn to proceed from one arm to the next without backtracking—a task the normal animals learn within a half-dozen or so test sessions. "But the DAT knockouts don't ever learn," Caron says. Instead, they become distracted, returning to arms they've already visited, or rearing up and looking around the maze.

But methylphenidate and the other psychostimulant drugs tested had a dramatic effect on the knockout mice. The drugs calmed their hyperactivity in the novel environment. And they did this without measurable effects on brain dopamine concentrations. "This means that [the drugs] hit some other system" in the brain, Caron says.

Further tests pointed to the serotonin system. Although the researchers didn't measure brain serotonin levels, they found that giving the animals a serotonin mimic had effects similar to those of the psychostimulants. So did giving them an inhibitor of the serotonin transporter, the drug Prozac, or administering other treatments designed to raise brain serotonin levels, such as injecting the animals with compounds, such as 5-hydroxytryptophan or L-tryptophan, that are converted to the neurotransmitter in the brain. These results indicate, Caron says, that the psychostimulants calm the hyperactive mice by raising serotonin concentrations to balance the animals' high brain dopamine levels.

The next goal, he says, is to try to identify which of the 15 or so different receptors through which serotonin exerts its effects in the brain might be involved in the response to the psychoactive drugs. It might then be possible to design drugs for treating ADHD children that act on just that receptor. Such drugs might have fewer of the drawbacks of the psychoactive drugs, such as reduced appetite and possible drug dependence.

Other researchers who work on the condition caution, however, that although methylphenidate may work by raising serotonin levels in the DAT knockouts, the mouse model may not reflect what is happening in humans. Not everyone has been able to confirm the linkage between the variant DAT gene and ADHD, and even if the linkage does hold up, a defective DAT gene won't be the whole explanation for ADHD, which most researchers, including the authors of the paper, believe is caused by defects in several different genes.

What's more, any DAT defect in humans will likely be far less severe than that in a complete knockout. "A mouse that's never had a dopamine transporter is a very unusual creature," says Xavier Castellanos, who studies ADHD at the National Institute of Mental Health. "I'd be cautious about extrapolating to the idea that Prozac will help [ADHD children]." Indeed, some researchers have tried Prozac in ADHD children with what Barkley describes as "not very impressive" results.

Still, Barkley says, the Caron team's results raise the "very tantalizing hypothesis" that there might be a subtype of ADHD due to an altered DAT, which might respond to Prozac or other compounds that raise brain serotonin levels. The work is spawning fresh ideas about the disorder and how to treat it, agrees James Swanson of the University of California, Davis. "This is exactly what animal models are for." –JEAN MARX