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Serotonin May Hold Key to Hyperactivity Disorder

Much concern has been raised over prescribing Ritalin® or other stimulants to control hyperactivity disorders in children. Relatively little is known about the long-term effects of these stimulants or how they alter brain chemistry.

Now researchers at the Howard Hughes Medical Institute at Duke University have discovered that Ritalin® and other stimulants exert their paradoxical calming effects by boosting serotonin levels in the brain. Elevating serotonin appears to restore the delicate balance between the brain chemicals dopamine and serotonin and calms hyperactivity, says HHMI investigator Marc Caron at Duke University Medical Center. Caron is an author of the study published in the January 15, 1999, issue of the journal *Science*.

Attention deficit hyperactivity disorder (ADHD) affects three to six percent of school-aged children. Symptoms include restlessness, impulsiveness, and difficulty concentrating. Stimulants commonly used to treat ADHD are so effective that "researchers haven't really taken the time to investigate how they work," says Caron.

Previous dogma, says Caron, held that the calming action of Ritalin® works through the neurotransmitter dopamine. Specifically, researchers believed that Ritalin® and other stimulants interact with the dopamine transporter protein (DAT), a housekeeper of sorts for nerve pathways. After a nerve impulse moves from one neuron to another, DAT removes residual dopamine from the synaptic cleft—the space between two neurons—and repackages it for future use.

Caron's team suspected that dopamine wasn't the only key to understanding ADHD, so they turned to mice in which they had "knocked out" the gene that codes for DAT. Since there is no DAT to "mop up" dopamine from the synaptic cleft, the brains of the mice are flooded with dopamine. The excess dopamine causes restlessness and hyperactivity, behaviors that are strikingly similar to those exhibited by children with ADHD.

When placed in a maze that normal mice negotiate in less than three minutes, the knockout mice became distracted—performing extraneous activities such as sniffing and rearing—and they failed to finish in less than five minutes. The

knockout mice also seemed unable to suppress inappropriate impulses-another hallmark of ADHD.

Surprisingly, the knockout mice were still calmed by Ritalin®, Dexedrine® and other stimulants even though they lacked the protein target on which Ritalin® and Dexedrine® were thought to act. "That caused us to look for other systems that these stimulants might affect," says Caron.

To test whether the stimulants interact with dopamine through another mechanism, the researchers administered Ritalin® to the normal and knockout mice and monitored their brain levels of dopamine. Ritalin® boosted dopamine levels in the normal mice, but it did not alter dopamine levels in knockout mice. That result implied that "Ritalin® could not be acting on dopamine," says Caron.

Next, the researchers gave the knockout mice a drug that inactivates the norepinephrine transport protein. With transport disabled, norepinephrine levels increased as expected, but the boost in norepinephrine did not ameliorate the symptoms of ADHD as it should. This suggested to Caron's team that Ritalin® exerted its effects through another neurotransmitter.

They then studied whether the stimulants altered levels of the neurotransmitter serotonin. The scientists administered Prozac®-a well-known inhibitor of serotonin reuptake-to the knockout mice. After ingesting Prozac®, the knockout mice showed dramatic declines in hyperactivity.

"This suggests that rather than acting directly on dopamine, the stimulants create a calming effect by increase serotonin levels," Caron says.

"Our experiments imply that proper balance between dopamine and serotonin are key," says Raul Gainetdinov, a member of Caron's research team. "Hyperactivity may develop when the relationship between dopamine and serotonin is thrown off balance."

The brain has 15 types of receptors that bind to serotonin, and Gainetdinov is now trying to determine which specific serotonin receptors mediate the effects of Ritalin®.

The hope, says Caron, "is that we can replace Ritalin® with a very specific compound that targets a single subset of receptors." While Prozac® calmed hyperactivity in the knockout mice, Gainetdinov says that "Prozac® isn't the best, because it isn't very selective." Caron and Gainetdinov are optimistic that a new generation of compounds that interact more specifically with the serotonin system will prove to be safer and more effective for treatments for ADHD.