



Pay Attention: Ritalin Acts Much Like Cocaine

Brian Vastag

WASHINGTON—Advanced imaging research has answered a 40-year-old question about methylphenidate (Ritalin), which is taken daily by 4 million to 6 million children in the United States: how does it work? The answer may unsettle many parents, because the drug acts much like cocaine, albeit cocaine dripped through molasses (*J Neurosci.* 2001;21:RC121).

Taken orally in pill form, methylphenidate rarely produces a high and has not been reported to be addictive. However, injected as a liquid it sends a jolt that “addicts like very much,” said Nora Volkow, MD, psychiatrist and imaging expert at Brookhaven National Laboratory, Upton, NY. “They say it’s like cocaine.”

Acknowledged as leaders in the field of brain imaging of drug effects, Volkow and colleagues have spent several years tracing the effects on the brain of drugs of addiction, using positron emission tomography (PET) and other advanced techniques. Among their long list of findings, they’ve identified the brain’s dopamine system as a major player in compulsive behavior, including drug taking and overeating.

A PRAGMATIC PARADOX

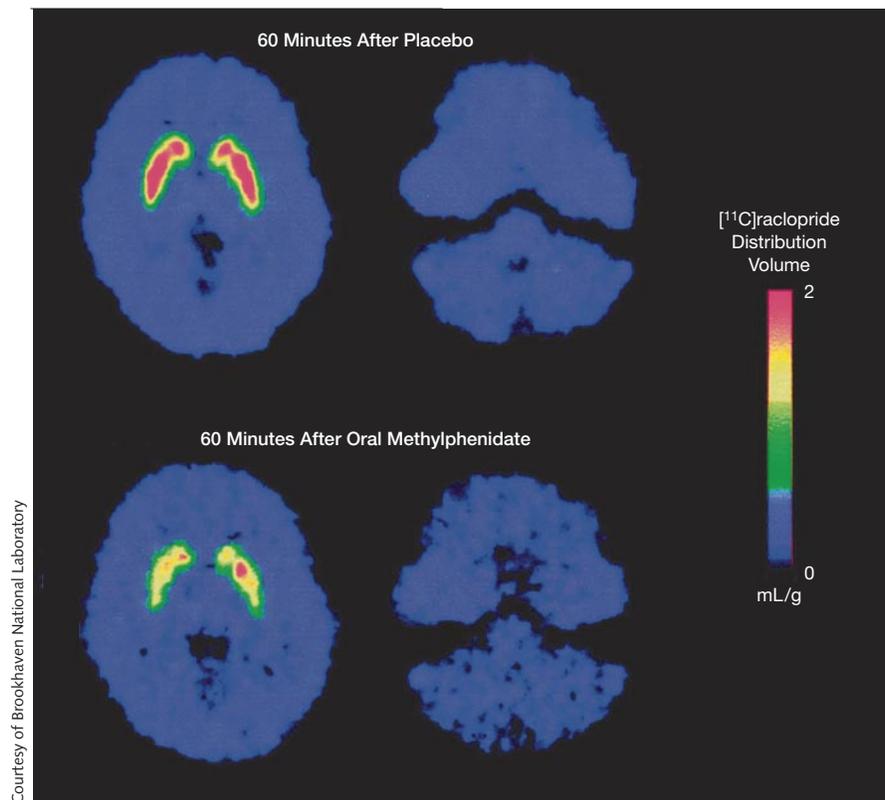
Building on that base, Volkow, associate laboratory director for life sciences at Brookhaven, hit the trail of a legal stimulant. Although they have used it to treat attention-deficit/hyperactivity disorder (ADHD) for 40 years, psychiatrists and pharmacologists have never known how or why it worked. Chemically similar to cocaine and other stimulants, methylphenidate presents a pragmatic paradox: it decreases activity and increases the ability to concentrate in

people with ADHD, but in studies, about half of those without ADHD find it unpleasant, like drinking too much coffee.

“I’ve almost been obsessed about trying to understand [methylphenidate] with imaging,” said Volkow at a recent media conference. “As a psychiatrist, sometimes I feel embarrassed [about the lack of knowledge] because this is, by far, the drug we prescribe most frequently to children.”

So the team went to work with PET scans to examine the dopamine system, which stimulates reward and mo-

tivation circuits during pleasurable experiences—eating, having sex, learning. To pick one of many pleasures, tasting chocolate ice cream will trigger cells in the basal ganglia to release dopamine molecules. These float across the synapse to neurons in a reward circuit. Receptors on these cells sop up the dopamine, activating signals that translate to “this experience is worth paying attention to.” Too much signal and the experience feels unpleasant, overstimulating. Too little, and the experience elicits a yawn; no pleasure, only boredom and distraction.



Courtesy of Brookhaven National Laboratory

Representative distribution volume PET images of the radiotracer [¹¹C]raclopride from one of the study participants show that radiotracer binding is reduced at the level of the striatum (bottom left) after oral administration of 60 mg of methylphenidate. Reduced radiotracer binding indicates decreased availability of open dopamine receptors after methylphenidate-induced increases in extracellular dopamine. Cocaine produces a similar effect in those who take it.



Volkow wanted to know how methylphenidate affects this signal. But instead of focusing on dopamine receptors, she tracked another part of the system. After the pleasure signal is sent on its way, dopamine molecules recycle back to the neurons that produced them. There, transporters—also called autoreceptors—act as vacuum cleaners, scouring the synapse for another go-around.

Earlier research had shown that cocaine blocks about 50% of these transporters, leading to a surfeit of dopamine in the synapse and a hit of pleasure. Because of methylphenidate's chemical similarities to cocaine, pharmacologists thought that it might work in the same way, only less potently, blocking fewer transporters. Animal studies with high doses of methylphenidate indicated that this could be the case.

STARTLING RESULTS

Using a radiotracer, [¹¹C]raclopride, that labels dopamine transporters, the team scanned 11 healthy men who took various doses of oral methylphenidate. The results were shocking.

"We were surprised as hell," said Volkow. "We didn't expect this." Instead of being a less potent transport inhibitor than cocaine, methylphenidate was more potent. A typical dose given to children, 0.5 mg/kg, blocked 70% of dopamine transporters. "The data clearly show that the notion that Ritalin is a weak stimulant is completely incorrect," Volkow said.

More pondering led the team to consider two theories. Methylphenidate could be blocking the recycling of dopamine exactly as cocaine does, leading to strong signals that would yield a high and lead to addiction. But this did not jibe with four decades of clinical experience.

So they considered another possibility. Perhaps methylphenidate seeps into the brain slowly, and as one by one the drug molecules block the transporters, dopamine cells shift gears. Like a union foreman yelling to an assembly line to slow down, the

cell interprets the transporter congestion as a signal that too much dopamine is being produced. The neuron cranks down production, sending less dopamine into the synapse, suppressing the reward signal.

The two theories opposed each other. But Volkow was unfazed. "We had to let the data speak for itself," she said.

That meant measuring the amount of dopamine floating in the synapses. Fortunately, the investigators had at hand another radioactive label that binds only to open dopamine receptors. A weak PET signal would mean low numbers of open receptors, which in turn would mean that large amounts of dopamine occupied the synapse.

After combining data from the volunteers, the team got its second surprise. Those who took methylphenidate displayed high levels of extracellular dopamine—just like people using cocaine. But if methylphenidate works like cocaine, why aren't millions of US children getting high and becoming addicted?

CAPTURING THE ANSWER

The answer came after Volkow combined her results with those from another research team. In 1999, Darin Dougherty, MD, and colleagues at Massachusetts General Hospital and Harvard University Medical School reported that people with ADHD have many more dopamine transporters than those without the condition (*Lancet*. 1999;354:2132-2133). This surplus increases the collective cleaning power of each cell; as dopamine fires into the synapse it is quickly sucked back, before it can home in on reward circuit receptors. "There isn't enough time for it to produce a signal," said Volkow.

It finally started to make sense. Children with ADHD produce weak dopamine signals, meaning that usually interesting activities provide fewer rewards. In effect, their attention circuitry is underfed. At the same time, they experience a related effect: random, distracting neuron firing. Or, as Volkow put it, more noise and less signal. This background hum interferes

with concentration, making the child more distractible.

Methylphenidate flips the relationship, upping the signal and reducing the noise. After someone swallows methylphenidate, it enters the bloodstream and eventually finds the brain, where it blocks dopamine transporters and increases attention signaling. Again, cocaine acts the same way. But the two drugs differ in a significant way: methylphenidate takes about an hour to raise dopamine levels, whereas inhaled or injected cocaine hits the brain in seconds. "It is the speed at which you increase dopamine that appears to be a key element of the addiction process," said Volkow.

While the team is unclear on why this speed factor is so important, future research will focus on it. They also plan to map dopamine levels in volunteers who have ADHD when they are at rest or while concentrating. Other research will search for molecular tools to screen children for dopamine transporter levels; those with high levels could be identified early and encouraged with behavioral solutions before methylphenidate is prescribed. "We know that social interactions can increase dopamine receptors," said Volkow, but whether better interplay also affects transporter levels is unknown.

The long-term dopamine effects of taking methylphenidate for years, as many do, are another unknown. The only two large epidemiological studies conflict. One reports more drug addiction in children with ADHD who took methylphenidate compared with children with ADHD who took no drug (*J Learn Disabil*. 1998;31:533-544); the other shows the opposite result (*Pediatrics*. 1999;104:e20).

Because people with low levels of dopamine receptors are at risk for drug addiction, Volkow said that researchers need to understand if methylphenidate can alter the whole dynamic of the dopamine pathway. "Could chronic use of Ritalin make you more vulnerable to decreased dopamine brain activity as cocaine does? It's a key question nobody has answered." □



New Advice for Women Patients About Hormone Therapy and the Heart

Mike Mitka

AFTER YEARS OF TAKING THE opposite tack, the American Heart Association (AHA) is recommending that hormone replacement therapy (HRT) should not be initiated for secondary prevention of cardiovascular disease (CVD) in postmenopausal women.

The recommendation follows results from clinical trials suggesting that no overall cardiovascular benefit results, and a possible early increased risk of CVD events occurs, when women with documented atherosclerosis begin to take HRT (estrogen typically combined with a progestin).

The AHA recommendations (*Circulation*. 2001;104:499-503; online at <http://circ.ahajournals.org/cgi/content/full/104/4/499>) are needed because physicians have asked for clarification of the data surrounding HRT, said Lori Mosca, MD, PhD, lead author of the AHA science advisory and director of preventive cardiology at New York Presbyterian Hospital in New York City.

"NOT SUFFICIENT EVIDENCE"

"For many years, cardiologists and other health care providers who take care of women have assumed that HRT protects the heart," Mosca said. "At this time there is not sufficient evidence to make that claim. Our purpose is to clarify the role of hormones in heart disease prevention."

The two key trials cited in the recommendation are the Heart and Estrogen/progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) Trial.

In HERS, researchers found that after an average of 4.1 years of follow-up, there was no difference in the pri-

mary outcome of nonfatal myocardial infarction and coronary death between the hormone and placebo arms (*JAMA*. 1998;280:605-613). In fact, a post hoc time-trend analysis found a 52% increase in cardiovascular events in the first year in the HRT group compared with the placebo group.

The ERA trial, the first randomized angiographic end-point study to test the effect of estrogen replacement therapy (ERT) and HRT on the progression of atherosclerosis in postmenopausal women with documented coronary stenosis, showed no benefit from either one (*N Engl J Med*. 2000;343:522-529).

Physicians who are treating women with CVD who are already taking HRT, said the association, should decide to continue or stop long-term therapy based on established noncoronary benefits and risks and patient preference. It also recommended that if a woman with CVD who is undergoing HRT develops an acute event, such as myocardial infarction, or is immobilized, it is prudent to consider discontinuing HRT or to consider anticoagulant prophylaxis while she is hospitalized to minimize the risk of developing a thromboembolism.

Whether or not to restart HRT should then be based on established noncoronary benefits and risks, as well as patient preference.

USE FOR PRIMARY PREVENTION

As for primary prevention of CVD, the AHA cited a meta-analysis showing an approximate 35% reduction in CHD events among uses of ERT and of HRT (*Annu Rev Public Health*. 1998;19:55-72). But the AHA said data are insufficient to suggest that HRT should be initiated only for primary prevention of CVD, and that it would withhold firm clinical recommendations for

use of HRT for primary prevention until results are published from ongoing randomized clinical trials.

WOMEN'S HEALTH INITIATIVE DATA

Last year, investigators informed participants in one of these ongoing trials—the Women's Health Initiative, begun in 1997—that during the study's first 24 months there was a small increase in the number of myocardial infarctions, strokes, and thromboembolism in women taking HRT or ERT compared with those taking placebo. This June, the investigators informed participants that the data through February 28, 2001, still showed that a small number, less than one half of 1% per year, continue to have acute cardiovascular events.

Mosca said the established benefits of HRT for treatment of menopausal symptoms must be weighed against its risks.

HRT AND "THE EQUATION"

"The new guidelines recommend essentially taking HRT out of the risk-benefit equation for women who have already had a heart attack or stroke," Mosca said. "For postmenopausal women without heart disease, we do not suggest that HRT be taken completely out of the equation. We state that heart disease prevention should not be used as the sole purpose of therapy. It can weigh into the decision; it just shouldn't drive the decisions for women without heart disease."

For primary prevention of CVD, the AHA recommends the tried-and-true approach: women should attempt to reduce their risk factors through such lifestyle modifications as smoking cessation, increased exercise, and weight loss, and, if needed, medications to improve cholesterol levels and lower elevated blood pressure. □



Genetic Research Features Murine Creatures

Joan Stephenson, PhD

BAR HARBOR, ME—With the sequence of the human genome largely in hand, scientists agree that the “real work”—understanding how the genes are regulated and the function of the proteins they encode—is largely uncharted territory.

Critical to the scientific pioneers exploring this new frontier are model organisms—fruit flies, yeast, zebrafish, rats, mice, and others—because studies revealing how their genes function can shed light on how homologous genes work in humans. The use of such animal models will “tremendously increase the pace” of discovery, said Kenneth Paigen, PhD, director of the Jackson Laboratory, at a press briefing here.

The work will provide insights into how certain genetic variants make people more susceptible to certain diseases—or more resistant. In the latter case, such information may point the way toward prevention or treatment of illnesses from infectious diseases to cancer.

MICE WITHOUT MAMMARY TUMORS

For example, researchers realized that one strain of mice developed in the 1920s appears to be protected from developing mammary gland tumors, a common malignancy in other strains. This strain of mighty mice, called I/LnJ, does not develop spontaneous tumors, nor do the animals develop mammary tumors when they are treated with potent carcinogens or exposed to a retrovirus that readily produces such tumors in susceptible mouse strains.

This observation suggested that the I/LnJ strain of mice has something unusual in its immune function, explained Tatyana Golovkina, PhD, an associate staff scientist at the Jackson Laboratory. She and colleagues found that the immune repertoire of I/LnJ mice includes a novel mechanism to resist retroviral infection, a discovery that might have implications for designing a candidate vaccine against HIV.

Mice can become infected with the retrovirus mouse mammary tumor virus (MMTV) when they suckle an infected mother whose mammary gland cells produce the virus. To cause tumors, the virus must become integrated into the mouse DNA next to the relevant protooncogene—the cancer gene-in-waiting. Because the infecting retrovirus is inserted randomly throughout the mouse DNA, it must re-infect mammary gland cells repeatedly until it is inserted in the right spot to have the oncogenic effect.



The Jackson Laboratory
Tatyana Golovkina, PhD

Golovkina and her colleagues found that when I/LnJ mice suckle an infected female from a susceptible strain, they become infected and also produce virus in their milk, but do not develop tumors. And when their own pups or pups from a susceptible strain suckled infected I/LnJ females, they did not become infected, nor did they develop tumors.

Subsequent experiments revealed that the I/LnJ mice were able to convert the MMTV into noninfectious virus by producing neutralizing antibodies to block the virus from re-infecting the mammary gland cells. This immune response is so potent and swift that it prevents selection of “escape” variants of the MMTV resistant to the effects of the antibodies.

FIRST EXAMPLE OF ITS KIND

It's the first known example of an immune response to a retrovirus being so profound and rapid that it blocks virus spread by preventing the viral replication necessary to allow the selection of escape variants, as occurs with HIV infection, said Golovkina, who found that the I/LnJ strain's retrovirus-fighting ability is conferred by a single recessive gene.

When the immune system responds to a threat, it first produces nonspecific IgM antibodies, then switches (under the direction of interferon- γ) to high-affinity IgG antibodies. There's evidence, said Golovkina, that I/LnJ mice are able to mount a swift and powerful immune response because, unlike most strains, they continuously produce IgG2a antibodies in response to the retrovirus infection, possibly owing to a chronic low level of interferon- γ .

Laboratory researchers have found that for a number of virus infections, including cytomegalovirus and adenovirus, IgG2a antibodies are the most potent in terms of neutralizing the virus as well as in stimulating the complement cascade.

The I/LnJ mouse's apparent ability to whip a retrovirus into submission provides some support for approaches to developing an HIV vaccine that entail giving HIV-specific antigens in conjunction with something to induce interferon- γ . Some researchers, for example, have found in animal studies that giving a DNA vaccine (containing HIV genes) with an adjuvant that stimulates interferon- γ and IgG2a or with plasmids that encode interferon- γ and interleukin 2 results in an enhanced immune response.

The little rodents also may prove to be a useful model for studying *Helicobacter* infection. Other mice can become infected with this organism, but I/LnJ mice are the only ones known to develop gastric ulcers and cancer, said Golovkina. □