NEUROSCIENCE

The Promise and Perils of Oxytocin

Is oxytocin the next revolution in psychiatric medicine—or an overhyped hormone that could make some patients worse?

Few substances produced by the human body have inspired as much hoopla as oxytocin. Recent newspaper articles have credited this hormone with promoting the kind of teamwork that wins World Cup soccer championships and suggested that supplements of the peptide could have prevented the dalliances and subsequent downfall of a certain high-ranking U.S intelligence official. Although the breathless media coverage often goes too far, it reflects a genuine and infectious excitement among many scientists about the hormone's role in social behavior. First studied by biologists for its role in childbirth and lactation, oxytocin has more recently captivated neuroscientists and psychologists who have found that it can promote trust and cooperation and make people more attuned to social cues.

Now psychiatrists have caught oxytocin fever. Dozens of clinical trials are under way, or will be soon, to investigate the hormone's potential benefits for a wide range of psychiatric disorders. The interest isn't hard to understand. Many psychiatric conditions have social symptoms, such as the characteristic lack of empathy in autism, the attachment anxiety of borderline personality disorder, and the paranoia of schizophrenia. Yet no drugs currently approved for psychiatric use directly target social behavior.

For autism in particular, hopes for oxytocin run high. A large trial of the hormone on 300 affected children is expected to begin this spring. Meanwhile, thousands of impatient parents of autistic children have persuaded physicians to prescribe oxytocin nasal spray, which can be obtained from compounding pharmacies.

At first glance, oxytocin might seem like just what the doctor should be ordering. But as researchers have continued to explore the hormone's effect on human behavior, a darker side has emerged. Oxytocin seems to promote aggression or other antisocial behavior in some circumstances. Its effects also appear to vary depending on a person's genetic makeup and psychological status. And no one knows what long-term oxytocin treatment does to the developing human brain. Disconcertingly, one recent study found that male voles treated for several weeks with oxytocin nasal spray around the time of adolescence later exhibited impaired social bonding with females. "The more we know, the more complicated it's getting," says Sue Carter, a behavioral neuroendocrinologist and a pioneer of research on oxytocin's role in social behavior now based at RTI International in Research Triangle Park, North Carolina.

> "What worries me, and should worry others, is that so much of the basic background is missing."
>
> —SUE CARTER, RTI INTERNATIONAL

Carter is particularly worried about giving oxytocin to children before more is known about the hormone's developmental effects. "I think there probably is a place for oxytocin in several aspects of medicine," she says. "But what worries me, and should worry others, is that so much of the basic background is missing."

At the same time, those leading the trials say that the scientific rationale for using oxytocin is already strong enough, especially given the lack of better options. "This could be the first drug to address the core symptoms of autism," says Geraldine Dawson, a developmental and child clinical psychologist and chief science officer of Autism Speaks, which has funded some of the early pilot studies. At the heart of the debate is the tension between scientific caution and the desperation of patients and families living with disruptive disorders day in, day out.

From bonding to bedside

The hypothalamus, an evolutionarily ancient part of the mammalian brain, makes oxytocin. Released into the bloodstream by the nearby pituitary gland, it signals the uterus to contract during childbirth and stimulates the release of milk for nursing. The hormone was the first peptide to be synthesized in the laboratory, a feat that earned American biochemist Vincent du Vigneaud the 1955 Nobel Prize in chemistry.

Given the hormone's known roles, researchers soon wondered whether it also played a role in reproductive behavior. In the late 1970s and early 1980s, work with rats and sheep found that oxytocin enhances mother-infant bonding. In the '90s, Carter and others established its role in fostering pair bonding in prairie voles. Unlike most rodents, these furry inhabitants of the North American plains form lifelong bonds and share the work of raising offspring (although trysts are not uncommon). In 2000, Larry Young and colleagues at Emory University in Atlanta reported that genetically engineered mice lacking oxytocin are unable to recognize other individuals, pointing to an even broader role for the hormone in nonreproductive social behavior.

Although much of this work has been written into textbooks, the more recent oxytocin research in humans has frequently found its way into tabloids. In one of the first eye-catching studies, neuroeconomist Ernst Fehr of the University of Zurich in Switzerland and colleagues gave oxytocin nasal spray or a saline spray placebo to university students before a game in which they had to decide how much money to entrust to a stranger. (The more money a player entrusts, the larger the potential gains and potential losses.) Those who got oxytocin were more trusting, the researchers reported in *Nature* in 2005. A torrent of studies followed, suggesting that oxytocin not only increases trust and cooperation, but also boosts social perceptiveness, such as face recognition and the ability to read what's on someone's mind from the look in their eyes.

Online

sciencemag.org

Podcast interview with author Greg Miller (http://scim.ag/pod_6117).

These findings quickly led to speculation about clinical applications. The first published study in which oxytocin was given to autistic children appeared online in *Biological Psychiatry* in late 2009. In an experiment conducted by Adam Guastella, a clinical psychologist at the University of Sydney in Australia, and colleagues, 16 autistic boys between 12 and 19 years old received a single dose of oxytocin nasal spray or a placebo in one session, and the alternative in another. (Neither the boys nor the researchers evaluating them knew which time they'd gotten the hormone.) On oxytocin, the boys performed better on a common test of social cognition that involves looking at photographs of faces cropped to show just the eyes and reporting what emotion the person is most likely experiencing. The improvement was modest: from about 45% to 49% correct on average. People without autism typically get more than 70% correct.

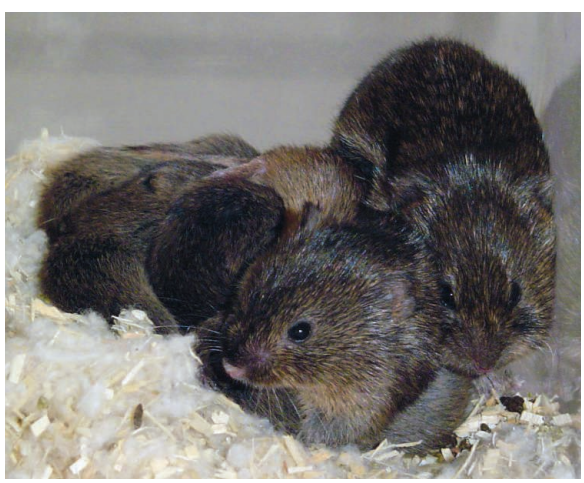
Studies in adults with autism have also demonstrated improvements on standard lab tests of social cognition. But the vast majority of published work on oxytocin to date has looked at the effects of a single dose over the course of an hour or so in the lab. The real question is whether the hormone can restore normal behavior in real life.

To find out, Guastella and others are conducting trials in which people with autism take daily sniffs of oxytocin for several weeks or months. These pilot studies are in various stages and several researchers told *Science* that it's too soon to talk about the findings in detail. "Interesting things are coming out of these studies," Guastella says of his group's work. "At the same time, we're not seeing a ginormous result that makes us think this is a cure for autism."

A far larger trial scheduled to get under way this spring should help clarify things. It will be led by psychiatrist Linmarie Sikich at the University of North Carolina (UNC), Chapel Hill, who received a $12.6 million Autism Centers of Excellence grant from the National Institutes of Health in September for this trial. Her team plans to enroll 300 autistic children between the ages of 3 and 17, half of whom will receive oxytocin nasal spray twice daily for 6 months in a placebo-controlled, double-blind trial, and all of whom will receive the hormone for 6 months in a subsequent open-label extension of the trial. Researchers will look for any adverse side effects and monitor the kids with various checklist measures of social behavior filled out by a clinician or parent.

Autism is hardly the only disease being investigated. Out of 44 neuropsychiatric trials of oxytocin listed on clinicaltrials.gov, roughly three-quarters are for other disorders. Pilot studies in people with schizophrenia, who often suffer from paranoia and difficulty reading social cues, suggest that oxytocin can reduce psychotic symptoms and improve social cognition. The benefits are modest, but encouraging, says Cort Pedersen, a psychiatrist and behavioral neurobiologist at UNC Chapel Hill.

Pedersen's work in the 1970s established the role of oxytocin in mother-infant bonding, but more recently his interest has turned to the hormone's clinical potential. "One of the real deficits in psychiatry research is a complete lack of appreciation of evolution," Pedersen says. "The human brain evolved to evaluate and maneuver in very complex social environments." Pedersen argues that the role of the brain's social circuitry in psychopathology is too often ignored. And that's what makes oxytocin so exciting in his view. "One of the really cool things about oxytocin is that it probably plays a central role in the social brain," he says.



Caring family. Prairie vole parents share the work of raising offspring, but a recent study suggests long-term oxytocin treatment can disrupt bonding between partners.

CREDIT: KAREN BALES/UNIVERSITY OF CALIFORNIA, DAVIS

Cause for concern

The explosion of clinical trials with oxytocin, particularly those in children, troubles Karen Bales, a behavioral neuroscientist at the University of California, Davis. "There's been this quick leap from looking at a single dose of oxytocin in healthy adults to trying to give it to children with autism whose brains are still developing," she says. Bales says that she looked and couldn't find a single published study on the long-term behavioral effects of multiple doses of oxytocin in developing animals. "It seemed to me that we were really skipping a step."

From work she did as a postdoctoral fellow with Carter, Bales knew that even a single dose of oxytocin can have long-lasting effects. In a series of studies published in the 2000s, they found that prairie vole pups treated with oxytocin on the day of birth exhibited abnormal pair bonding and parental behavior as adults. The effects were messy—treated animals grew up to be more social or less social than normal, depending on their sex and the dose they received. "The clearest message was that any exposure to oxytocin can cause long-term behavioral and neuroendocrine effects," Bales says. In one study, Bales found that males given a single dose of oxytocin at birth had reproductive difficulties as adults: They deposited sperm in the female reproductive tract in only 50% of mating attempts, for example.

More recently, Bales and colleagues tried to better mimic the type of oxytocin treatment now in clinical trials for autism, giving young prairie voles daily squirts of oxytocin in the nose for 3 weeks. In developmental terms, Bales says that the voles were roughly equivalent to 12- to 17-year-old children, the target group for several trials. In the short term, oxytocin made the voles more social, as expected: After a dose, they spent more time in close contact with a cage mate. As adults, however, treated males had abnormal relationships with their partners, the researchers reported online on 15 October 2012 in *Biological Psychiatry*.

The standard test of pair bonding in voles, Bales explains, is to put a male in an empty chamber connected to two other chambers: one containing his mate, and another containing an unfamiliar female. "A normal male prairie vole will run around and check everything out and then go hang out with his partner," Bales says. But males that had gotten a daily dose of oxytocin comparable to that being given to autistic children—or an even lower dose—were more likely to spurn their partner in favor of the stranger. To Bales, the findings raise the troubling possibility that repeated use of oxytocin nasal spray may cause long-term changes in the brain that negate or even reverse the hormone's benefits, perhaps by tricking the brain into making less oxytocin of its own.

Other signs that there's more to oxytocin than cuddles and hugs have emerged from human experiments. In 2010, psychologist Carsten De Dreu and colleagues at the University of Amsterdam gave oxytocin nasal

spray to men before they played a computer game in which small teams competed for money. Compared with men who got a saline spray, those who sniffed oxytocin behaved more altruistically to members of their own team—but at the same time, they were more likely to preemptively punish competitors, the team reported in *Science.* In a 2011 study in the *Proceedings of the National Academy of Sciences*, De Dreu's team found that oxytocin increased favoritism toward subjects' own ethnic group (native Dutch men) on a series of tasks and thought experiments done on a computer, and in some situations the treated men exhibited more prejudice against other groups (Germans and Middle Easterners, in this case).

To some researchers, this suggests that oxytocin is a double-edged sword: promoting bonds with familiar individuals, but promoting unfriendly behavior toward strangers. "In the beginning, everyone thought it would have very robust prosocial effects, but it seems to depend on how you interpret the term prosocial," says René Hurlemann, a psychiatrist at the University of Bonn in Germany. In a study published on 14 November 2012 in *The Journal of Neuroscience*, his team reported that when men who reported being in a stable heterosexual relationship took oxytocin, they put a bit more distance between themselves and an attractive female experimenter who entered the room. To Hurlemann, these findings, like De Dreu's, suggest that oxytocin promotes bonding within an established pair (or group) at the expense of outsiders. That makes sense from an evolutionary perspective, he says, but may not be ideal for a prosocial drug. Though optimistic that oxytocin can help some people with psychiatric disorders, Hurlemann cautions that it might not have the same benefits for all patients.

An illustration of just that comes from work by Jennifer Bartz, a social psychologist at McGill University in Montreal, Canada. Encouraged by the reports that oxytocin increases trust, Bartz thought it might help people with borderline personality disorder (BPD), who are plagued by fears of abandonment and separation, and have profound difficulties with relationships as a result. But when she and colleagues gave a single dose of oxytocin nasal spray to people with BPD, they became less trusting and less likely to cooperate with a partner in a social dilemma game, the researchers reported in 2011 in *Social Cognitive and Affective Neuroscience*. This effect was strongest in those with BPD who scored highest on self-report measures of relationship anxiety and fear of rejection.

CREDIT: TONY GUTIERREZ/AP

Social studies. New clinical trials seek to determine if oxytocin can boost social behavior in children with autism.

One possibility, Bartz says, is that oxytocin increases the desire to connect and heightens attention to social cues. That may backfire in people with BPD, who are already hyperattentive and anxious in social situations. "The picture that's now emerging is that it's not this global social panacea," Bartz says. "In many cases it depends on the situation in which it's given or the person to whom it's given."

A risk worth taking?

Going forward, the success or failure of oxytocin as a psychiatric drug may hinge on figuring out which disorders and which people respond positively to the hormone—there's evidence that people with variants of the oxytocin receptor gene respond differently—and in what context. "In my view, the best benefit from stimulating the oxytocin system is going to be to combine it with a controlled behavioral therapy," Emory's Young says. He believes that oxytocin's main effect is to make people more sensitive to social cues. In a therapist's office, children could be assured of receiving positive, reinforcing social cues while under the hormone's sway. Not so if they simply take the hormone and went about their day. "Say you give it to a kid and then he goes to school and gets bullied. That's not going to have a positive impact, and it may even make things worse," Young says.

A better handle on the basic biology of intranasal oxytocin, such as how it enters the brain and which receptors it hits, might enable researchers to develop more effective drugs, Young adds. "If we want to move beyond this initial investigatory era and get more sophisticated and potent effects, we need to understand the mechanisms."

Despite the unknowns, Sikich and others insist that the clinical trials are justified. "A lot of people in this country, probably a few thousand, are going to compounding pharmacies and having them put together preparations of oxytocin," Sikich says. "We feel like it's really important, for something that's being used in this unregulated way, to get some data on how safe it is … and figure out does it work or does it not work."

For Dawson, the lack of better options is a powerful motivator. Only two drugs are currently approved for autism, she notes: Both are antipsychotic medications prescribed to cut down on tantrums, aggression, and self-injury. These drugs don't directly address the social deficits at the core of the disorder, and they have potentially dangerous side effects, not to mention unknown effects on brain development. Behavioral interventions such as the Early Start Denver Model, which Dawson co-developed, have proven successful in improving social behavior, but they require 25 hours or more a week of intensive one-on-one therapy and can cost $25,000 to $50,000 a year. In contrast, a year's supply of oxytocin, which is currently only available in a proprietary synthetic version, costs roughly $5000. And it could get much cheaper if a generic version becomes available.

Among parents of autistic kids, there's long been a willingness to try experimental treatments, even before they're fully vetted by researchers, Guastella says. A driving factor, he says, is frustration that science has let them down by moving too slowly. At the same time, researchers such as Carter and Bales hope that science won't let these families down again by rushing too quickly into clinical trials with a hormone whose effects aren't adequately understood. **–GREG MILLER**

Published by AAAS