

**'Cuddle chemical' could treat mental illness**[Click to Print](#)

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Maia Szalavitz

IT has been called the love hormone, the cuddle chemical and liquid trust. It peaks with orgasm, makes a loving touch magically melt away stress and increases generosity when given as a drug. Oxytocin is the essence of affection itself, the brain chemical that warmly bonds parent to child, lover to lover, friend to friend, and it could soon be unleashing its loved-up powers far and wide.

Oxytocin has long been used to induce labour and assist the let-down of milk in breastfeeding. Now there is growing interest in its potential as a therapy for mental illnesses characterised by "people problems" - autism, personality disorders, depression, social phobia, psychosis and even impotence. Some tout it as an elixir that makes you more likeable, trustworthy and attractive. Decoding its mysteries could even lead to the development of a powerful new recreational drug that makes ecstasy look like a mild dose of cheerfulness.

Oxytocin was discovered in 1909, when British pharmacologist Henry Dale found that a substance extracted from the human brain could cause contractions in pregnant cats. He named it using the Greek for "quick birth", and for decades it was known only for its role as a pregnancy hormone, promoting contractions and aiding breastfeeding.

In the 1970s it started to become clear that oxytocin was more than just a hormone - it was also a neurotransmitter. Released from a brain region called the hypothalamus during social interactions and sex, oxytocin is detected by receptors throughout the brain's emotional centre, the limbic system. This discovery prompted scientific interest that has mushroomed ever since, with oxytocin now one of the hottest topics in neuroscience.

The groundbreaking work on oxytocin's role in the brain was done by C. Sue Carter, then at the University of Maryland in College Park. She studied two closely related species of vole - prairie voles (*Microtus ochrogaster*) and montane voles (*Microtus montanus*) - which differ primarily in their reproductive behaviour. Prairie voles form long-lasting pair bonds to rear young whereas montane voles mate promiscuously and fathers do not contribute to parenting.

Carter discovered that the key to the different behaviours was oxytocin. Female prairie voles have many oxytocin receptors in their brains' pleasure centres, while the males have lots of receptors for both oxytocin and a closely related hormone, vasopressin. In montane voles, however, there are far fewer receptors for oxytocin and vasopressin. When these receptors are blocked in prairie voles the animals do not form the usual pair bonds. Carter concluded that oxytocin released in the brain during mating bonds prairie voles to one other, making further contact with that partner pleasurable and separation stressful (*Psychoneuroendocrinology*, vol 23, p 779).

**Bonding and friendship**

It also turns out that oxytocin plays a central role in bonding mothers to their offspring and in social behaviour generally. If oxytocin is blocked in rats and mice, for example, they stop nurturing their young and lose their ability to recognise familiar members of their species. "Animals without oxytocin have social amnesia," says Larry Young of Emory University in Atlanta, Georgia.

Overall, oxytocin's role in the brain appears to be to link social contact with pleasure. Without it, social species could not function. This, of course, includes humans. Evidence is emerging that oxytocin plays a

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central role in many aspects of human life, including romantic and social interactions and parenting. "It's the glue of society, so simple yet so profound," says Paul Zak, director of the Center for Neuroeconomics Studies in Claremont, California. As an example of its far-reaching effects, Zak and his colleagues have found that people given oxytocin become substantially more generous and trusting in tasks that involve sharing money with strangers (*Nature*, vol 435, p 673).

So how does oxytocin exert its soothing touch? Recent research has revealed one way: by reducing stress and fear. Markus Heinrichs of the University of Zurich, Switzerland, carried out brain-imaging studies in humans showing that oxytocin damps down activity in the right side of the amygdala, a part of the brain that processes emotional responses (*Biological Psychiatry*, vol 62, p 1187). When subjects were given oxytocin, exposure to pictures of frightened and angry faces produced a weaker amygdala response. "It's taking over parts of the nervous system and putting information into them about a sense of safety and trust," Carter says.

The chemical also appears to work through the brain's reward system: drugs that block dopamine and opioids - the reward-centre neurotransmitters that signal the anticipation of reward and satiation - also negate some of the effects of oxytocin, even though they do not block the oxytocin receptors themselves. For example, blocking dopamine can prevent the long-lasting pair bonding of prairie voles. Similarly, opioid blockers negate the stress-relieving effects of human petting on rats. In contrast, both opioids and oxytocin powerfully relieve the separation distress felt by young animals kept away from their mothers.

Oxytocin's ability to connect social contact with feelings of pleasure and well-being has got researchers excited about potential therapeutic uses, since so many mental illnesses involve disorders of sociability or empathy. An obvious starting point is autism, which is marked by difficulty understanding the minds of others, aversion to human contact, and repetitive behaviours such as rocking.

Eric Hollander of Mount Sinai School of Medicine in New York is studying what happens when you give oxytocin to autistic adults. He has found that it improves their ability to recognise emotions like happiness and anger in people's tone of voice, something autistic people struggle with. A single intravenous infusion produced improvements that lasted two weeks (*Biological Psychiatry*, vol 61, p 498).

Hollander has also found that oxytocin increases his volunteers' ability to recognise faces and interpret emotional expressions. Prior studies have already shown that when autistic people see faces, they activate brain areas normally used to recognise inanimate objects. Hollander says his preliminary results show that when given oxytocin intravenously, autistic people are more able to recruit the normal face-recognition area, the fusiform gyrus. Oxytocin also reduced their repetitive behaviours.

Hollander is not the first researcher to connect autism to oxytocin. A 1998 study detected lower levels of oxytocin in the blood plasma of severely socially-averse autistic children (*Biological Psychiatry*, vol 43, p 270), and more recently variants in the oxytocin receptor gene have been linked to the risk of developing autism (*Biological Psychiatry*, vol 58, p 74).

Until now, Hollander has only dispensed oxytocin to consenting adults, but he believes that its effects in children might be even stronger, and he's not alone. "I'm absolutely convinced that we should study administering oxytocin when there is an early diagnosis of autism," says Heinrichs, "but it's difficult to get permission to administer to children."

One argument for starting oxytocin treatment early in a child's life is that it appears to play a crucial role in brain development during infancy, helping babies learn to associate social contact with calmness and pleasure. For example, rats that receive more grooming from their mothers are better able to manage social stress. "In rats which get lots of attention from mom, there is a higher level of oxytocin in certain parts of the brain than in those that get less. These are systems shaped by early life experience," says Young.

Zak adds: "We find in animal studies that if the mother neglects the baby, the number of oxytocin receptors atrophies." Similarly, studies of monkeys raised without mothers find that they have lower oxytocin levels than monkeys reared normally.

The influence of oxytocin on mother-infant attachment can be seen in humans, too. Children who suffer severe early neglect - for example, raised without individual attention in a bare orphanage - often have symptoms indistinguishable from those of autism. A 2005 study found that children who had spent the first few months or years of their lives in a Romanian orphanage had lower than normal oxytocin responses to contact with their adoptive mothers (*Proceedings of the National Academy of Sciences*, vol 102, p 17237).

As a result of such work, Hollander is interested to see whether oxytocin can help alleviate disorders associated with early neglect. One of these is borderline personality disorder, which is overwhelmingly associated with childhood trauma. People with this disorder have severe relationship problems, find

social stress difficult to cope with and rejection unbearable.

If oxytocin can help treat borderline personality disorder, then it could help rescue abused and neglected children from a lifetime of mental health problems. These children are at higher risk of developing virtually every psychiatric illness, from post-traumatic stress disorder to addiction, depression, anxiety disorders, antisocial personality disorder and schizophrenia.

The list of potential applications for oxytocin doesn't stop there. Heinrichs is studying oxytocin as a therapy for social phobia, an anxiety disorder characterised by crippling self-consciousness. Ziad Nahas at the Medical University of South Carolina in Charleston is looking at oxytocin as a treatment for depression, which is also marked by social withdrawal. A team at the National Institute of Mental Health in Bethesda, Maryland, is even investigating its use in treating psychosis, which can be seen as an extreme fear of others.

Oxytocin may also help a different type of social interaction problem: erectile dysfunction. Zak notes that about 25 per cent of male volunteers given oxytocin in his trust experiments get erections, while Meyer Jackson of the University of Wisconsin-Madison has found that Viagra affects oxytocin levels, making neurons that are already releasing it churn out even more (*Journal of Physiology*, vol 584, p 137). As yet oxytocin's role in erection isn't known, but it's an interesting avenue for future research.

### **Climactic events**

The link between Viagra and oxytocin also hints at why the little blue pill has a reputation as an enhancer of sex, rather than simply a facilitator. Since large amounts of oxytocin are released as both men and women reach climax, it's possible that Viagra potentiates and enhances orgasm. "There are lots of anecdotes and nonscientific chatter about Viagra enhancing sex, but now that there is a plausible mechanism, it would be worthwhile performing a definitive study," says Jackson. He has also suggested giving Viagra to women to help during childbirth (see "Labour of love").

Perhaps unsurprisingly for a chemical that is intimately associated with sex, love and pleasure, there is much speculation about oxytocin's potential as a recreational drug. However, the question of whether oxytocin is pleasurable - and if so, under what conditions - has been maddeningly difficult to resolve. What little evidence there is suggests that oxytocin won't be the next OxyContin - a prescription painkiller that was abused recreationally in the late 1990s, resulting in thousands of people being admitted to hospital.

"We spent a lot of time asking, 'Will oxytocin be desirable if it is injected into the brain?'," says Jaak Panksepp of Washington State University in Pullman, a long-time oxytocin researcher. He expected that it would be, so he tried to find out.

A standard test for whether a drug is likely to be misused is to give it to rats and see whether they develop a preference for the location where they received it, as they do with cocaine and heroin. Panksepp tried this with oxytocin but saw no reaction. "Over and over, we never saw a very clear place preference," he says.

So what effect would oxytocin have if taken recreationally in humans? Panksepp has tried taking it and says he felt only a mild effect. "I seemed to be in a more relaxed 'in the moment' mood, with a greater confidence and appreciation of my connectedness to other people and nature," he says. Most people, however, cannot tell whether they've been given oxytocin or a placebo. Women seem slightly more likely to report subjective effects like calmness, according to Panksepp. Hollander, meanwhile, says his subjects experience "no rush, high or euphoria".

Anecdotal evidence also suggests that the abuse potential of oxytocin is low. Oxytocin is sold freely in many countries in the form of a nasal spray to help stimulate breastfeeding. If it had abuse potential you can bet your bottom dollar that there would be a thriving underground market, yet there are no reports of people buying oxytocin for recreational use. That hasn't stopped some internet entrepreneurs from selling oxytocin as a "trust elixir" that, when sprayed on your clothes, will make people find you more congenial, attractive and trustworthy. Whether there's any truth in this claim has yet to be tested scientifically.

So why does a substance that seems so likely to be rewarding have so little subjective effect - or none at all? It could be that, early in life, oxytocin wires the connection between social contact and pleasure, but the pleasure itself comes from the reward regions, not oxytocin itself.

Alternatively, some researchers believe that the problem is not that oxytocin isn't pleasurable, but that current methods of administration don't get it into the brain in the right amount at the right time. Some estimate that only 10 per cent of intranasal oxytocin reaches the brain, while only a small proportion of intravenous doses cross the blood-brain barrier. What is more, Iain McGregor of the University of Sydney, Australia, notes that natural oxytocin release is rhythmic. This pulsing may be required for

oxytocin to have subjective effects.

McGregor suspects that oxytocin would be rewarding if administered in the right way. He has found that the club drug MDMA (the main active ingredient of ecstasy) raises oxytocin levels and thinks that oxytocin may contribute to MDMA's subjective effects, which often include a profound sense of joyful empathy (*Neuroscience*, vol 146, p 509). When he gave rats on MDMA an oxytocin-blocking drug, he found that it reduced, though didn't eliminate, MDMA's ability to make the rats more sociable. McGregor now plans to see whether rats on oxytocin-blockers will, like normal rats, work to get MDMA - another common test used to determine which drugs have abuse potential. If the rats don't bother, that would mean oxytocin is at least partly responsible for the MDMA high.

Another problem is that oxytocin's effects tend to be short-lived, and this could reduce both its potential as a therapy and appeal as a recreational drug. Pharmaceutical companies are eager to find a small molecule that would enter the brain more easily and switch on oxytocin receptors long-term. An "oxytocin agonist" is the ultimate prize, says Zak. So far, no one has announced such a discovery.

Ideally, such a substance would be beneficial but not prone to misuse. Yet given oxytocin's association with comfort, love and sex, such a molecule could turn out to be hugely pleasurable, or even make users fall in love. MDMA is often credited with unleashing the "second summer of love". Just imagine what the third could be like.

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### Labour of love

Though they don't realise it, millions of women have already taken artificial oxytocin. The drug Pitocin, used to induce or speed up labour, is a synthetic version of the hormone. It works because contractions are initiated by pulses of natural oxytocin, which stimulate newly sprouted receptors in the uterus.

Women given Pitocin tend to dislike it because it makes labour more painful. One reason for this is that oxytocin is released in waves during labour. Pitocin is not able to replicate this pattern and so causes persistent, sustained contractions.

Meyer Jackson of the University of Wisconsin-Madison has suggested a better way of accessing the oxytocin system in childbirth: Viagra. He recently showed that Viagra enhances the natural release of oxytocin. And because Viagra increases oxytocin levels only when it is already being released, it could intensify contractions without eliminating the breaks between them.

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