'Love hormone' oxytocin may play wider role in social interaction than previously thought

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Researchers at the Stanford University School of Medicine have shown that oxytocin - often referred to as "the love hormone" because of its importance in the formation and maintenance of strong mother-child and sexual attachments - is involved in a broader range of social interactions

than previously understood.

The discovery may have implications for neurological disorders such as autism, as well as for scientific conceptions of our evolutionary heritage.

Scientists estimate that the advent of social living preceded the emergence of pair living by 35 million years. The new study suggests that oxytocin's role in one-on-one bonding probably evolved from an existing, broader affinity for group living.

Oxytocin is the focus of intense scrutiny for its apparent roles in establishing trust between people, and has been administered to children with autism spectrum disorders in clinical trials. The new study, to be published Sept. 12 in *Nature*, pinpoints a unique way in which oxytocin alters activity in a part of the brain that is crucial to experiencing the pleasant sensation neuroscientists call "reward." The findings not only provide validity for ongoing trials of oxytocin in autistic patients, but also suggest possible new treatments for neuropsychiatric conditions in which social activity is impaired.

"People with autism-spectrum disorders may not experience the normal reward the rest of us all get from being with our friends," said Robert Malenka, MD, PhD, the study's senior author. "For them, social interactions can be downright painful. So we asked, what in the brain makes you enjoy hanging out with your buddies?"

Some genetic evidence suggests the awkward social interaction that is a hallmark of autism-spectrum disorders may be at least in part oxytocin-related. Certain variations in the gene that encodes the oxytocin receptor - a cell-surface protein that senses the substance's presence - are associated with increased autism risk.

Malenka, the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, has spent the better part of two decades studying the reward system - a network of interconnected brain regions responsible for our sensation of pleasure in response to a variety of activities such as finding or eating food when we're hungry, sleeping when we're tired, having sex or acquiring a mate, or, in a pathological twist, taking addictive drugs. The reward system has evolved to reinforce behaviors that promote our survival, he said.

For this study, Malenka and lead author Gül Dölen, MD, PhD, a postdoctoral scholar in his group with over 10 years of autism-research expertise, teamed up to untangle the complicated neurophysiological underpinnings of oxytocin's role in social interactions. They focused on biochemical events taking place in a brain region called the nucleus accumbens, known for its centrality to the reward system.

In the 1970s, biologists learned that in prairie voles, which mate for life, the nucleus accumbens is replete with oxytocin receptors. Disrupting the binding of oxytocin to these receptors impaired prairie voles' monogamous behavior. In many other species that are not monogamous by nature, such as mountain voles and common mice, the nucleus accumbens appeared to lack those receptors.

"From this observation sprang a dogma that pair bonding is a special type of social behavior tied to the presence of oxytocin receptors in the nucleus accumbens. But what's driving the more common group behaviors that all mammals engage in - cooperation, altruism or just playing around - remained mysterious, since these oxytocin receptors were supposedly absent in the nucleus accumbens of most social animals," said Dölen.

The new discovery shows that mice do indeed have oxytocin receptors at a key location in the nucleus accumbens and, importantly, that blocking

oxytocin's activity there significantly diminishes these animals' appetite for socializing. Dölen, Malenka and their Stanford colleagues also identified, for the first time, the nerve tract that secretes oxytocin in the region, and they pinpointed the effects of oxytocin release on other nerve tracts projecting to this area.

Mice can squeak, but they can't talk, Malenka noted. "You can't ask a mouse, 'Hey, did hanging out with your buddies a while ago make you happier?'" So, to explore the social-interaction effects of oxytocin activity in the nucleus accumbens, the investigators used a standard measure called the conditioned place preference test.

"It's very simple," Malenka said. "You like to hang out in places where you had fun, and avoid places where you didn't. We give the mice a 'house' made of two rooms separated by a door they can walk through at any time. But first, we let them spend 24 hours in one room with their littermates, followed by 24 hours in the other room all by themselves. On the third day we put the two rooms together to make the house, give them complete freedom to go back and forth through the door and log the amount of time they spend in each room."

Mice normally prefer to spend time in the room that reminds them of the good times they enjoyed in the company of their buddies. But that preference vanished when oxytocin activity in their nucleus accumbens was blocked. Interestingly, only social activity appeared to be affected. There was no difference, for example, in the mice's general propensity to move around. And when the researchers trained the mice to prefer one room over the other by giving them cocaine (which mice love) only when they went into one room, blocking oxytocin activity didn't stop the mice from picking the cocaine den.

In an extensive series of sophisticated, highly technical experiments, Dölen, Malenka and their teammates located the oxytocin receptors in

the murine nucleus accumbens. These receptors lie not on nucleus accumbens nerve cells that carry signals forward to numerous other reward-system nodes but, instead, at the tips of nerve cells forming a tract from a brain region called the dorsal Raphe, which projects to the nucleus accumbens. The dorsal Raphe secretes another important substance, serotonin, triggering changes in nucleus accumbens activity. In fact, popular antidepressants such as Prozac, Paxil and Zoloft belong to a class of drugs called serotonin-reuptake inhibitors that increase available amounts of serotonin in brain regions, including the nucleus accumbens.

As the Stanford team found, oxytocin acting at the nucleus accumbens wasn't simply squirted into general circulation, as hormones typically are, but was secreted at this spot by another nerve tract originating in the hypothalamus, a multifunction midbrain structure. Oxytocin released by this tract binds to receptors on the dorsal Raphe projections to the nucleus accumbens, in turn liberating serotonin in this key node of the brain's reward circuitry. The serotonin causes changes in the activity of yet other nerve tracts terminating at the nucleus accumbens, ultimately resulting in altered nucleus accumbens activity - and a happy feeling.

"There are at least 14 different subtypes of serotonin receptor," said Dölen. "We've identified one in particular as being important for social reward. Drugs that selectively act on this receptor aren't clinically available yet, but our study may encourage researchers to start looking at drugs that target it for the treatment of diseases such as autism, where social interactions are impaired."

Malenka and Dölen said they think their findings in mice are highly likely to generalize to humans because the brain's reward circuitry has been so carefully conserved over the course of hundreds of millions of years of evolution. This extensive cross-species similarity probably stems from pleasure's absolutely essential role in reinforcing behavior likely to

boost an individual's chance of survival and procreation.

More information: Paper: dx.doi.org/10.1038/nature12518

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