Scientists Probe Oxytocin Therapy for Social Deficits in Autism, Schizophrenia

Bridget M. Kuehn

EMERGING EVIDENCE INDICATES THAT oxytocin plays an important role in human social interactions, and preliminary clinical studies suggest the hormone may help improve social functioning in individuals with autism or schizophrenia. But experts caution that much remains to be learned about oxytocin and its physiological effects before it is ready for clinical use.

Oxytocin has long been known to help facilitate mother and infant bonding. Research on the socially monogamous prairie vole has demonstrated that the hormone plays a much wider role in helping to establish social bonds among animals. The animal findings have led to studies in humans to assess how exposure to the hormone affects human interactions, including early clinical studies in individuals with social impairments related to such disorders as autism and schizophrenia.

Still, a host of questions remain about the hormone's wider physiological effects on humans, which range from aiding lactation to potentially promoting healing, noted Sue Carter, PhD, professor of psychiatry and co-director of the Brain-Body Center at the University of Illinois, in Chicago. In addition, data on the safety and effects of chronic use of oxytocin are limited because many human studies have involved only a single intranasal dose or several weeks of administration.

"Oxytocin research is exciting and promising, but how the information should be applied is not clear," Carter said in an interview. "What we have now are fragments of knowledge, and we can't yet see the full picture."

INCREASING SALIENCE

In the past several years, scientists have learned that oxytocin plays an important reinforcing role in social interactions that goes far beyond the previously documented effects of the hormone in female reproduction.

Oxytocin has long been known as a key factor in bonding between a mother and infant. It also has important physiological effects on pregnant women during and after delivery. A synthetic version of oxytocin is widely used to induce or augment labor. Intranasal oxytocin has also been used to promote the release of breast milk.

Now, basic research on an unusual animal model has allowed scientists to understand the wider physiological effects of oxytocin.

Carter began working with prairie voles with a field biologist and colleague, Lowell Getz, PhD, at the University of Illinois, in Urbana-Champaign, who was studying them in the wild. Field evidence on the voles suggested they live in lifelong pairs, and Carter brought them into the laboratory to study the physiology behind this behavior, hoping to gain insights that might be relevant to human relationships. Other groups also began working with the animals, which became a laboratory model for understanding the endocrinology behind sociality, according to Carter.

The voles are one of the few species besides humans with a complex family structure, according to Larry J. Young, PhD, director of the Center for Translational Social Neuroscience at Emory University, in Atlanta, who summarized this area of research at the Society for Neuroscience annual meeting in San Diego in November. In an interview, he explained that while strong bonds between mother and offspring are common in many species, few species form lasting bonds between the mother and father.

"The male and female prairie voles work as a team [to raise their offspring], as humans do," Young said.

Carter's group was able to demonstrate that giving oxytocin to a female vole promotes bonding with her mate,

Todd Ahern, PhD/Emory University

Studying the social interactions of prairie voles has led scientists to believe that oxytocin plays an important role in mediating social bonds. Preliminary clinical studies suggest the hormone might benefit individuals with disorders that involve social deficits.

and that blocking the oxytocin receptors in females prevents them from forming bonds with their mates (Carter CS et al. *Prog Brain Res*. 2008;170:331-336). Such work led some to refer to oxytocin as "the love hormone," but both Young and Carter say that is a misnomer because the hormone actually has a much broader role in social interaction.

In studies of mice without oxytocin receptors, Young and his team found that oxytocin enables mice to recognize one another. The mice without the receptors could not recognize mice they had previously met—a state Young called "social amnesia." Other work has verified that oxytocin helps mice to focus on social signals.

"We realized that oxytocin isn't just a bonding hormone," he said. "Oxytocin tunes the brain in to social cues."

Human studies have solidified oxytocin's role in social interactions (Ross HE and Young LJ. *Front Neuroendocrinol*. 2009;30[4]:534-547). Humans exposed to intranasal oxytocin make more eye contact (which is essential to reading social cues), feel increased trust in social interactions, and are better able to infer emotions from other people's facial expressions.

"All of this is telling us that oxytocin increases the saliency of social stimuli," Young said.

BOOSTING SOCIAL BEHAVIOR

Oxytocin's role in enhancing social interaction led researchers to wonder whether it might be a useful therapy for individuals with disorders that involve social deficits. For example, patients with autism spectrum disorders often fail to pick up on social cues, Young noted.

Preliminary evidence suggests the hormone may benefit such patients. For example, one study compared social behaviors in 13 adult patients with Asperger syndrome or high-functioning autism receiving intranasal oxytocin or a placebo with such behaviors in 13 matched healthy controls (Andari E et al. *Proc Natl Acad Sci U S A*. 2010;107[9]:4389-4394). The researchers found that while playing a game in which some players are cooperative and others are less so, the patients treated with oxytocin were more likely than untreated patients to exhibit preferential treatment toward helpful players. In another task, treated patients spent more time gazing at human faces, especially the eyes, than untreated patients. However, the treated patients still spent less time looking at the faces than healthy controls. Another randomized, blinded controlled trial of 16 male patients aged 12 to 19 years with an autism spectrum disorder found that intranasal oxytocin improved patients' performance on the Reading the Mind in the Eyes Task, a test of patients' ability to recognize emotion in people's faces (Guastella AJ et al. *Biol Psychiatry*. 2010;67[7]:692-694).

Eric Hollander, MD, clinical professor of psychiatry at Albert Einstein College of Medicine and director of the Compulsive, Impulsive, and Autism Spectrum Disorder Program at the Montefiore Medical Center, in Bronx, NY, reviewed studies of oxytocin in patients with autism spectrum disorders (Green JJ and Hollander E. *Neurotherapeutics*. 2010;7[3]:250-257). He noted that studies have found that oxytocin may also have beneficial effects on the irritability and repetitive behaviors seen in patients with autism. "The findings are very consistent," he said in an interview.

Other studies have suggested that both intranasal oxytocin and endogenous oxytocin may improve some symptoms of schizophrenia. In a study of 23 women and 27 men with schizophrenia, a team led by Leah H. Rubin, PhD, a research assistant professor at the University of Illinois at Chicago, found that higher levels of endogenous oxytocin were associated with less severe positive symptoms and reduced psychopathology (based on the Positive and Negative Syndrome Scale [PANSS]) in female patients, while higher endogenous oxytocin levels were associated with more desirable social behaviors in both sexes (Rubin LH et al. *Schizophr Res*. 2010;124[1-3]:13-21). A recent randomized controlled crossover trial of oxytocin as an adjunct to antipsychotic medications in 19 patients with schizophrenia found that, based on PANSS scores and Clinical Global Impression-Improvement Scale scores, oxytocin reduced symptoms compared with placebo after 3 weeks of treatment but not at earlier time points (Feifel D et al. *Biol Psychiatry*. 2010;68[7]:678-680).

Despite these promising effects, Hollander cautioned that further study is necessary. He noted that so far, data from trials and clinical use of oxytocin suggest that it is well tolerated, but large-scale safety and efficacy studies are needed for specific indications. Additionally, scientists must develop and validate outcome measures that can be used to study the effects of oxytocin on social cognition.

"This is new territory because there are not treatments for things like social cognition," he said.

But given the promising results so far, particularly in older patients, Hollander was optimistic about the therapeutic potential of oxytocin in patients with autism spectrum disorders. "It could be used in older individuals to target core symptoms, or in younger individuals to enhance development. If such treatment improved social interaction, it might have positive effects on the overall trajectory," he said.

Young, too, was optimistic about the potential therapeutic benefit of oxytocin in autism, but he noted it is unlikely to correct symptoms associated with autism other than social deficits. Additionally, he suggested that its use might be most beneficial in specific settings.

"I think it will be most effective when paired with socially reinforced behavioral therapies," he said. For example, oxytocin might be administered shortly

before a therapy session so that a patient receives the benefit of the drug in interpreting social cues from the therapist, such as eye contact.

Young noted that studies are needed to determine if direct administration of oxytocin is the best approach or whether treatments that increase endogenous oxytocin levels would be better. He added that research is also needed to determine whether chronic administration of oxytocin might lead to a decrease in oxytocin receptors. Until such issues are worked out, he cautioned against the use of oxytocin by individuals without physician supervision. Some web sites claim to market oxytocin for use in boosting trust in relationships. "It's important for [individuals] to realize it's not the time for them to start taking these drugs without a physician," he said. "We don't know the safety issues." □

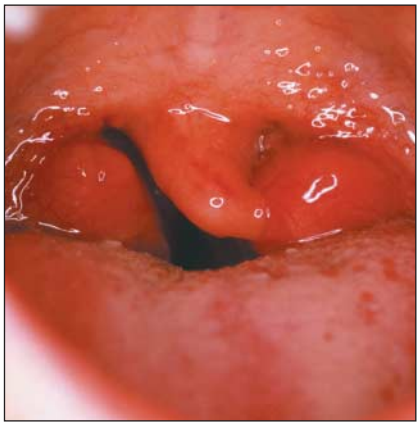
Guideline Cites Appropriateness Criteria for Performing Tonsillectomy in Children

Mike Mitka

PROMPTED BY A LACK OF CONSENSUS on surgical indications and perioperative management for tonsillectomy in children in the United States, the American Academy of Otolaryngology–Head and Neck Surgery has issued the first-ever guideline on the topic.

The clinical practice guideline, released January 3, provides evidence-based guidance in identifying children who may benefit from tonsillectomy and offers recommendations intended to optimize the perioperative management of children undergoing the procedure (Baugh RF et al. *Otolaryngol Head Neck Surg*. 2011; 144[1][suppl]:S1-S30). The document also provides guidance on how to improve counseling and education of parents of children who may be candidates for tonsillectomy and suggests ways to reduce inappropriate or unnecessary variations in care.

Tonsillectomy is the third most common surgery in US children younger than 15 years, with more than 530 000 performed annually, primarily for recurrent throat infections and sleep-disordered breathing. Evidence gathered by the guideline authors suggests that tonsillectomy may be overused as a treatment for throat infections and underused for sleep-disordered breathing, said Richard M. Rosenfeld, MD, MPH, a coauthor of the document and chair of otolaryngology at the Long Island College Hospital in Brooklyn, NY. "The big surprise is seeing how many kids with frequent throat infections get better on their own without surgery, showing us how high the bar should be set to get a worthwhile benefit for tonsillectomy," Rosenfeld said.



P. Marazzi, MD/www.sciencesource.com

The first-ever guideline for tonsillectomy in children addresses a variety of topics, such as considering removal of enlarged tonsils when certain comorbid conditions are present.

The guideline authors set the bar for considering tonsillectomy at at least 7 episodes of documented sore throat in the preceding year, at least 5 episodes over each of the proceeding 2 years, or at least 3 episodes in each of the previous 3 years. In addition, either a temperature exceeding 38.3°C, cervical lymphadenopathy, tonsillar exudate, or a positive culture for group A β-hemolytic streptococcus should be documented with each episode. For children who do not meet that standard, "tonsillectomy seems to offer little benefit over watchful waiting," Rosenfeld said. And there are possible harms and adverse events associated with tonsillectomy, including hospitalization, the risks of anesthesia, prolonged throat pain, bleeding, and financial costs.

In commenting on the guideline, Scott R. Schoem, MD, chair of the American Academy of Pediatrics section on otolaryngology–head and neck surgery, said that clinicians who refer children who do not meet the criteria to an otolaryngologist for tonsillectomy may be missing opportunities to successfully treat those children. Specialists who see children referred to them "after just 3 streps in a row will not do anything except say that if it continues, then tonsillectomy will be considered," explained Schoem, director of pediatric otolaryngology at Connecticut Children's Medical Center in Hartford.

As for sleep-disordered breathing, the guideline states that if the condition coexists with tonsil hypertrophy and there are comorbid conditions such as growth retardation, poor school performance, enuresis, and behavioral problems, tonsillectomy may be appropriate. Performing tonsillectomy for sleep-disordered breathing is increasing because the condition's prevalence is on the rise due to its association with obesity—a condition that is also increas-