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Oxytocin and the Social Brain

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In the first poem of *The Lichtenberg Figures*, the contemporary poet Ben Lerner (son of psychotherapist Harriet Lerner) captures the dynamics of a volatile romance. He opens with the hopeful line, “Did you mean ‘this could go on forever’ in a good way?” only to conclude, three stanzas later, “The chicken is a little dry and/or you’ve ruined my life.”

We may laugh (or cringe) at this absurd juxtaposition. But we can all relate, in some way, to the challenge it speaks to: relationships are complicated if not fraught. This is a core part of human experience (and thus why so much of art reflects relationship intricacies). For some individuals, difficulty navigating social attachment may cause distress or impairment in function to the point of pathology. While psychotherapists have been trying to understand the complicated mechanisms of attachment for many years, it is only relatively recently that scientists have begun to understand the neurobiological systems responsible for social behavior.

Seminal research in this field was conducted by Tom Insel and colleagues, beginning in the late 1980s. Insel’s group sought to understand the biological basis of a peculiar observation of animal behavior: female prairie and pine voles establish monogamous partner preference, whereas the closely related montane and meadow voles do not (1). A series of elaborate experiments ultimately showed that the hormone oxytocin played a critical role in this behavior. Only prairie/pine voles have oxytocin receptors in the brain regions needed to promote social attachment. These studies helped launch an entire field of research exploring the role of oxytocin in social cognition.

Oxytocin is produced in the hypothalamus and stored in the posterior pituitary. It acts both through direct projections to other brain regions and through release into the bloodstream (1,2). Its function was first described in sexual intercourse and parturition: it is released with vaginal and cervical stimulation, induces contractions during labor, and induces first onset of maternal behavior. While oxytocin itself is specific to mammals, oxytocin-like signaling has been observed via homologous genes in worms (2).

Other circuits (see Figure 1) through which oxytocin appears to play a key role in social functioning include the following:

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Sensory systems: In rodents, social learning is mediated by olfactory cues (with signals passing from the olfactory epithelium to the olfactory bulb and on to the olfactory cortex). The processing of socially relevant data involves both bottom-up sensory signals and also top-down modulation from the cerebral cortex. A key mechanism by which oxytocin affects social signaling may be by modulating the excitatory/inhibitory balance in this circuit (2). Oxytocin enhances top-down signals to olfactory bulb interneurons, thereby increasing overall inhibitory tone and improving signal-to-noise ratio for olfactory signaling of social information (2,3). This activity is important for both learning and recall of social information. The action of oxytocin in the regulation of excitatory/inhibitory balance is likely also important in other brain regions (auditory cortex, hippocampus) and in neurodevelopment.

Limbic circuits: Oxytocin also has the ability to modulate aspects of limbic circuitry, though the effects are complicated and appear to vary in sex- and illness-specific ways. In healthy rats, oxytocin activity in the amygdala diminishes fear behaviors [(4), reviewed in (2)]. The pathway through which this occurs is worth highlighting: oxytocin-producing cells in the hypothalamus (paraventricular and supraoptic nuclei) project onto gamma-aminobutyric acidergic inhibitory interneurons in the central amygdala; these interneurons then decrease output from the amygdala to the brainstem, thus decreasing fear behaviors such as freezing.

Oxytocin modulation of the amygdala may also enhance social recognition, decrease attention to negative and threatening social cues, and promote social learning in healthy people [though, again, these effects seem to differ by sex and psychopathology; cf. (5)]. In this issue of *Biological Psychiatry*, Takayanagi *et al.* build on this literature (6). They explore the role of a separate peptide hormone, secretin, that is also thought to be involved in social functioning. Their work shows that secretin acts on cell bodies in the supraoptic nucleus of the hypothalamus. This leads to increased oxytocin production and, ultimately, increased oxytocin release in the medial amygdala, thereby leading to improvements in social recognition.

Social learning: Oxytocin also plays a key role in modulating learning from social interactions. One important mechanism seems to be a complex interaction between oxytocin and serotonergic projections from the dorsal raphe to the nucleus accumbens.

Because of its role in so many aspects of social functioning, researchers have considered the oxytocinergic system to be a prime target for treating diseases that involve aberrant social behavior. Two of the most studied examples are individuals with autism spectrum disorder and individuals with borderline personality disorder [though note that additional research suggests oxytocin may play a prominent role in other disorders, including schizophrenia (7), posttraumatic stress disorder (4), and anxiety disorders (8)].

Autism

Social cognitive deficits are a core feature of autism spectrum disorder, and the growing data about the role of oxytocin in social functioning have led to intense interest among autism

researchers, clinicians, and families. The hypothesis is obvious: if oxytocinergic signaling subserves social cognition, perhaps treatment with oxytocin (or some other agent that would facilitate this pathway) could counter the deficit seen in these individuals. Promising data have emerged from mouse models of autism. However, evidence from studies with human subjects is limited and inconsistent—it is unclear what dose, route, or administration schedule would be most effective (if any) (9).

Borderline Personality Disorder

Borderline personality disorder is a mental illness in which individuals experience a broad range of difficulties in social functioning. As in autism, there was hope that some of these symptoms could be ameliorated by treatment with oxytocin. Only a few small studies have tried this so far, and results are mixed (5). One article reported that oxytocin attenuated stress following a trigger (based on both self-report and cortisol levels) and another found that oxytocin reduced amygdala response to social threat. But two other groups found that trust and cooperation were decreased in an investment game with a partner. Further work to define symptom markers and biomarkers of subtypes will be helpful to explain these conflicting results (5).

Another interesting aspect of the literature on borderline personality disorder is that these individuals are known to have decreased pain sensitivity and self-injury is common. This is of special note given oxytocin's known interactions with the cannabinoid and opiate systems, both of which modulate pain (5). A proposed mechanism is that hypothalamic (parvocellular) oxytocin-positive neurons project directly to the brainstem and, in conjunction with modulatory signals from peripherally released oxytocin, may suppress physical and psychic pain (2).

Obesity

Of interest, across diagnostic categories individuals with psychiatric illness are known to be at elevated risk for various medical conditions and to also have lower overall life expectancy. One particularly common area of medical comorbidity is metabolic syndrome. While the reason for the disproportionate frequency of obesity among psychiatric patients is complex and multifaceted, a fascinating line of evidence suggests a possible mechanistic connection between feeding behavior and dysfunctional social behavior.

Recent studies showed that laboratory mice fed a fat-rich diet experienced a change in gut microbiome. This change was causally linked both to having decreased oxytocin cells in the paraventricular nucleus and also to altered social behaviors. The researchers were able to rescue both cellular and behavioral phenotypes with fecal transplant or reintroduction of gut bacteria (2). Future work will be important to elucidate interactions between oxytocin signaling and the gut microbiome in individuals with obesity and control subjects.

In conclusion, extensive data over the past 30 years increasingly point to the central role that oxytocin plays in a range of social behaviors. Oxytocin appears key to establishing and maintaining social bonds, both in adulthood and during formative periods of early life. It may regulate amygdala activity by facilitating inhibition through gamma-aminobutyric

acidergic interneurons, thereby altering fear response and the interpretation of social cues. It also has complex interactions with social reward circuitry, endogenous opioid and endocannabinoid systems, and the microbiome. Research to date suggest multiple partially elucidated factors contribute to the ultimate effects of oxytocin, including sex, psychiatric condition, and early life experience. Additional studies are also exploring the role of vasopressin, a closely related peptide hormone, in modulating a range of social and other functions (e.g., with recent clinical trials investigating vasopressin 1b receptor antagonists). While there is considerable excitement about the translational value of this research, trials to date have not yet lived up to the hype. Hope remains strong, however, that further research will identify oxytocinergic approaches that may help attenuate the significant morbidity relating to dysregulated social behavior.

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Pathways Through Which Oxytocin May Regulate Social Functioning

Figure 1.

Key pathways through which oxytocin affects social functioning, including top-down modulation of sensory input (in rodent models, via the olfactory system); social learning, through a complex interaction with serotonergic systems in the nucleus accumbens; modulation of the amygdala and other aspects of limbic activity; and direct action on brainstem nuclei.