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Commentary

Can Understanding Social Preferences in Rodents Lead to Novel Pharmacotherapies for Social Anxiety and Avoidance in Psychiatric Disorders?

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Social creatures, including us, are naturally drawn to social stimuli. We are more attracted to biological motion, faces, and other social cues than we are to trees, rocks, or other inanimate objects. Social interactions are critical for our well-being. However, individuals with autism spectrum disorder or schizophrenia display diminished interest in social stimuli and may be socially withdrawn. In addition, social phobias and social anxiety can have devastating impacts on the development of healthy social relationships. A study published in this issue by Lukas *et al* (2011) from Inga Neumann's group in Regensburg, Germany, used rats and mice to explore the role of the neuropeptide, oxytocin, on the preference for social stimuli and a form of social anxiety induced by social defeat. These preclinical studies in animals have important implications for developing novel pharmacotherapies for psychiatric disorders with muted social interest and elevated social withdrawal.

Oxytocin has had a prominent spotlight in biology for over a century (Burbach *et al*, 2006), and is now experiencing a renaissance in neuropsychopharmacology. In 1906, Sir Henry Dale found that the constituents in the pituitary potently stimulate uterine contractions, an activity that he dubbed as 'oxytocin,' from the Greek meaning 'quick birth'. Oxytocin also stimulates milk ejection during nursing, making it the quintessential maternal hormone. Oxytocin was the very first peptide to have its structure defined and synthesized, leading to a Nobel Prize in Chemistry for Vincent du Vigneaud in 1955.

The first evidence that oxytocin influences behavior came in the 1980s, when Cort Pedersen and colleagues reported that oxytocin induces the onset of maternal behavior in virgin rats (Pedersen and Prange, 1979), and Kendrick *et al* (1997) showed that oxytocin stimulates the mother–infant bond in sheep. A series of papers published in the 1990s using monogamous prairie voles as subjects showed that oxytocin also stimulates pair bonding (reviewed in Ross and Young, 2009). More recent studies in rats and mutant mice now suggest that oxytocin is more than just a maternal, or a bonding hormone, but it also enhances various aspects of social cognition and promotes social affiliation (Ross and Young, 2009). In these early years of oxytocin research few, if any, investigators were aware of the translational implications of their work.

However, today there are many studies, inspired by the basic biology elucidated in animal models, showing that intranasally delivered oxytocin enhances trust, empathy, and attention to social cues and various other aspects of social cognition (Bos *et al*, 2011). In fact, there is a remarkable congruence between the effects of oxytocin on social behavior in animals and social cognition in man. This congruence provides some level of confidence that preclinical studies in rodents can inform pharmacotherapies for social disorders in humans.

Lukas *et al* (2011) used rats and mice to demonstrate for the first time that endogenous oxytocin is involved in the preference for social stimuli over non-social stimuli. As expected, control rats and mice spent more time exploring a novel stimulus animal in a wire cage than in an empty wire cage. However, infusion of a selective oxytocin receptor antagonist prevents this preference. In a sense, they became socially aloof. Similar results were found if the rats were tested in their home cage and the stimulus rat was a freely moving juvenile.

The authors further showed that oxytocin infusion could overcome the social anxiety induced by social defeat, a rodent version of bullying. Male rats that have been defeated by another male continue to show a social preference as long as the stimulus animal is not the bully. But when presented with the bully male in a wire cage, the experimental male spends no more time exploring the wire cage with the bully than exploring an empty cage, presumably reflecting an experimentally induced social anxiety and social avoidance. However, an infusion of OT

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reinstates the social preference, even toward the bully! This is reminiscent of a study showing that intranasal OT increases trust even toward individuals who have betrayed the subject (Baumgartner *et al*, 2008).

The mechanisms by which oxytocin enhances social preference and decreases social anxiety are unknown. The studies performed by Lukas *et al* (2011) suggest that brain areas other than the amygdala, are involved, and the effect is not likely to be explained by the anxiolytic effects of oxytocin.

These data have important translational implications, and combined with the larger oxytocin literature, provide a strong rational for establishing clinical trials to determine whether intranasal oxytocin might reduce social anxiety and social phobias in clinical populations. Indeed, it has already been shown that intranasal oxytocin increases attention to social cues such as eyes in subjects with autism spectrum disorder (Andari *et al*, 2010).

Although these results are promising, there are major challenges in translating the findings of acute preclinical studies into pharmacotherapy strategies in a clinical setting. Intranasal delivery of oxytocin in humans has given some promising results, but the rise in CNS oxytocin is likely transient, and nearly all of those studies examined the acute effect effects of the treatment. There are no small molecule oxytocin agonists approved for human use. Drugs that stimulate endogenous oxytocin release may be a viable strategy. But what would be the optimal treatment paradigm for targeting the oxytocin system for treating social anxiety or social phobia? Should the oxytocin stimulation be chronic, or should it be in the context of a controlled therapeutic session? These are some questions that must be addressed empirically.

Many psychopharmacotherapies used in psychiatry today do not have a firm foundation in biology. Now the oxytocin system is an exciting potential pharmacological target with a tremendous body of basic science supporting its role in regulating social cognition. Although the early years of oxytocin research were driven by a basic science curiosity of how the brain controls behavior, increasingly, studies like those presented by Lukas *et al* (2011) are motivated by translational implications. Indeed, our knowledge of the biology of the social brain, as determined by animal studies, will likely be the foundation of novel pharmacotherapies to treat a host of disorders with deficits in the social domain.

DISCLOSURE

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