HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Biol Psychiatry. 2016 February 1; 79(3): 150–152. doi:10.1016/j.biopsych.2015.10.014.

Understanding the Oxytocin System and Its Relevance to Psychiatry

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Oxytocin research has experienced a remarkable resurgence over the past decade, particularly with respect to its role in regulating social cognition and its prospects for treating psychiatric disorders. The oxytocin system has long been the focus of rigorous scientific investigation as a model of neurosecretion from the pituitary and for its role in regulating uterine contractions during labor and milk ejection during nursing. Beginning in the mid-1960s, oxytocin became the focus of behavioral studies with an early emphasis on its influence on learning and memory (1). By the late 1970s, pioneering studies in rats and sheep revealed that oxytocin not only leads to birth and successful nursing but also transforms the mother's brain so that she is motivated to nurture the infant and develops selective mother-infant bonds (2–5); this area of research continues to evolve today (6). Subsequent research in monogamous prairie voles revealed a central role in the formation of pair bonds between mates (7). With the development of oxytocin mutant mice, the more subtle role of oxytocin in facilitating social recognition and social information processing became apparent (8). The role of oxytocin in regulating social relationships has been extended to facilitate the bond between dogs and their owners (9). More recent exquisite molecular and cellular studies have begun to reveal the precise mechanisms by which oxytocin modulates signal to noise in neural circuits to facilitate information processing (10). Collectively, these studies in animals have led to the hypothesis that oxytocin increases the salience and reinforcing value of social cues, a process that could be useful to manipulate clinically (11).

A seminal study published in *Nature* in 2005 suggesting that intranasal administration of oxytocin increases trust in humans was a game changer for human oxytocin research (12). A surge of intranasal oxytocin studies ensued, with most emphasizing a role for oxytocin in increasing positive prosocial behaviors such as trust, altruism, affiliation, empathy, and romantic relationships. These new findings provided new perspectives on oxytocin and have created a scientific as well as a popular interest in this peptide that is unprecedented. A quick Google search for "oxytocin" reveals popular media references to oxytocin as the "love

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Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

drug" or the "cuddle hormone," monikers that make some veterans in the field shudder. It might appear at first glance that oxytocin is the elixir of the social brain.

Building on the solid foundation of animal research, the studies in healthy human subjects subsequently laid the groundwork for translational studies that examine the effectiveness of using intranasal oxytocin to ameliorate symptoms of social dysfunctions in various psychiatric conditions, including schizophrenia, autism, psychopathy, borderline personality disorder, and social anxiety. Complementary evidence from studies on plasma or urinary oxytocin concentrations and polymorphisms in oxytocin-related genes has linked oxytocin to affiliation and prosocial behavior in healthy and disease states. Nonetheless, in recent years, it is increasingly acknowledged that the effects of oxytocin are not monolithic and are more complex than previously believed. Furthermore, criticisms of the methodologies commonly used in oxytocin research are beginning to emerge, reflecting the beginning of scientific maturity in the field.

This special issue of *Biological Psychiatry* is focused on understanding the various complex facets of oxytocin and oxytocin research. This issue presents several frameworks or models that attempt to reconcile the conflicting reports of the effects of oxytocin on social behavior and anxiety and examines how the effects of oxytocin may be harnessed to treat psychiatric disorders. Critically, the current issue is inclusive of a diversity of viewpoints, including provocative perspectives on methodologic and statistical limitations that may have been overlooked in the rapidly growing field.

There are three major components to this issue of *Biological Psychiatry*: 1) conceptualization of new psychological models that explain the various effects of oxytocin and the analysis of the neurobehavioral foundation of the core processes affected by oxytocin (13–18); 2) understanding the role of oxytocin in the etiology and treatment of psychiatric disorders (19–21); and 3) critical views on methodologic, statistical, and translational issues of human oxytocin research (22–24).

The issue begins with a commentary by Insel (22) that addresses the overwhelming challenges of translational research with oxytocin. From the perspective of the National Institute of Mental Health, it is critical that clinical trials be conducted to demonstrate target engagement with a range of doses to identify the clinically relevant dose so that studies will be informative regardless of whether the results are positive or negative. Few studies have done this, but more and more studies are relating behavioral outcomes with brain network activity.

Grinevich *et al*. (13) discuss the evolutionary, ontogenetic, and neuroanatomic aspects of the oxytocin system and the mechanisms of endogenous oxytocin delivery to as well as oxytocin signaling in brain regions involved in behavioral processes. This review also discusses the complex relationship between peripheral and central oxytocin release. The authors propose that alterations in endogenous oxytocin delivery from the site of synthesis to the target regions as well as in oxytocin receptor expression may contribute to psychiatric disorders that involve social dysfunction.

The review by Neumann and Slattery (19) focuses on animal and human studies that point to the central role of oxytocin in anxiety-related psychopathologies. The authors propose a theoretical framework in which an imbalance of endogenous oxytocin is involved in the etiology of anxiety disorders that revolve around social behavior, indicating that oxytocinergic treatments may be particularly beneficial for treatment of social anxiety disorder.

Maroun and Wagner (18) present a model of oxytocin function that is based on its modulation of emotional memories in rodents. Specifically, this review discusses the role of oxytocin in regulating social recognition and fear memories, with a particular focus on the amygdala. The authors propose that oxytocin regulates a balance between two distinct amygdala-prefrontal networks during social behavior, and an imbalance of these networks may account for social dysfunctions observed in psychiatric disorders.

In a provocative review, Leng and Ludwig (23) question the value and interpretation of studies that use intranasal administration of oxytocin and studies that measure peripheral concentrations of oxytocin. They argue that most oxytocin administered intranasally enters the peripheral circulation, where activation of oxytocin receptors could have behavioral effects, and that peripheral oxytocin concentration is not related to central oxytocin activity. The authors emphasize the need for proper dose-response studies that control for peripheral action and for studies that use more selective pharmacologic agents that are currently not used in human research.

De Dreu and Kret (14) review evidence showing that oxytocin plays a major role in human group psychology. The authors propose that oxytocin motivates and enables humans to prefer in-group members, which may explain the development of intergroup conflict and deficits in understanding group relations in individuals with aberrant social behavior.

Walum *et al*. (24) extend the arguments presented by Leng and Ludwig regarding the mechanisms of intranasal oxytocin. These authors analyze statistical features of published intranasal oxytocin studies, including factors such as statistical power, prestudy odds, and potential bias; they conclude that many of the studies in the field are underpowered and suggest that some positive findings do not represent true effects. Conversely, many true findings may not replicate if the replication study is underpowered, adding to the confusion in the literature. The authors recommend improving the reliability of human oxytocin research by carrying out sufficiently powered replication studies, publishing negative results, and developing more efficient means of engaging the oxytocin system in human subjects.

Feldman *et al*. (15) review the associations between oxytocin-pathway genes and social behavior. In addition, they show how these associations may explain pathologic social behaviors observed in autism, depression, or schizophrenia. The authors suggest that although there is compelling evidence for the involvement of oxytocin-pathway genes in human social functions, cultural differences and early adversity may interact with genetic dispositions.

Hurlemann and Scheele (16) discuss the role of the oxytocin system in the context of social relationships and propose an integrative view in which oxytocin regulates interoceptive signals and self-referential processing. According to this view, oxytocin augments interoceptive prediction errors through top-down modulation in the context of passive perception and participates in interoceptive sensory attenuation in the context of self-generated action. Various social outcomes may result depending on outside context and the person's internal state. Specifically, the authors propose that disrupted oxytocin signaling owing to the loss of affectionate social bonds may result in emotional dysequilibrium, increasing the risk for stress-related disorders.

In an attempt to reconcile between the vast, often contradicting, social effects of oxytocin, Shamay-Tsoory and Abu-Akel (17) conceptualize the social salience hypothesis as an overarching framework for understanding the role of oxytocin in social behavior. By focusing on the interactions between oxytocin and dopaminergic systems, the authors suggest that the salience effect modulates attention orienting responses to external contextual social cues but is dependent on baseline individual differences.

Feifel *et al*. (20) address the involvement and therapeutic potential of oxytocin in regulating the expression of schizophrenia. Their review of the literature indicates that although the evidence from preclinical investigations and studies of the oxytocin system in patients with schizophrenia is not conclusive, it appears that oxytocin may diminish the positive and negative symptoms, including social dysfunctions, that are usually resistant to treatment. Despite the promising evidence, the authors discuss several limitations of clinical trials, among which are inadequate exploration of dose ranges, limited sample sizes, the nature of add-on trials, and inclusion and exclusion criteria.

Finally, Guastella and Hickie (21) focus on the involvement of oxytocin in autism spectrum disorders and its potential as a therapeutic agent for improving social functioning in autism. The authors note that although evidence shows that acute oxytocin administration improves numerous markers critical to social deficits, little is known about extended oxytocin treatment for autism. The authors stress the need for better methods of linking objective markers of response to oxytocin therapy with broader measures of therapeutic response and patient selection. The authors also highlight the overwhelming complexity of translating laboratory findings to clinical settings and the need for consistent and meaningful outcome measures across studies.

We hope that the views, concepts, and models presented in this special issue of *Biological Psychiatry* will be inspiring and thought provoking not only for psychiatrists conducting research involving oxytocin but for all readers with an interest in behavioral neuroscience, social neuroscience, psychology, and psychiatry. The growth in oxytocin research in the past decade has been tremendous, and the complexity of the findings can sometimes be bewildering. The field is in its adolescence. We believe that this issue can help funnel many of these findings into frameworks that will facilitate comprehension of the vast array of findings in the field. As with many fields that experience sudden growth spurts, some maturity in methodology and data interpretation is needed. Not all significant findings represent true effects or are biologically relevant. Mechanisms of action are not understood.

Optimal doses are unknown. However, taken together, the research in animal models and human subjects overwhelmingly demonstrates that the oxytocin system has a critical role in biological psychiatry.

What will the future bring? It is hoped that we will gain a better understanding of the neural mechanisms by which oxytocin regulates social cognition and anxiety-related behaviors. Localization of oxytocin receptors in the human brain and characterization of those neural systems is critical. We need better means of measuring target engagement after oxytocin manipulation. An understanding of the relationship between various measures (peripheral vs. central) of oxytocin function is needed. The future may bring more efficient means of manipulating the oxytocin system and more precise pharmacologic agents that will be useful in dissecting mechanisms of action. We need better strategies to translate laboratory studies into clinical outcomes. Our psychological frameworks of oxytocin action in the brain will continue to evolve as the field matures. Animal models and molecular genetic tools provide ever-increasing precision in the manipulations of the oxytocin system to increase our understanding of how oxytocin influences neural circuits.

In conclusion, triangulation of the results from animal and human studies, use of enhanced delivery systems and new pharmacologic agents, careful characterization of target engagement, and replication of findings with sufficiently powered studies will ultimately yield insight into the true nature of the oxytocinergic system as it relates to human nature and its potential as a pharmacologic target in psychiatry.

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