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Research Report

Oxytocin and social cognition in rhesus macaques: Implications for understanding and treating human psychopathology

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ABSTRACT

Converging evidence from humans and non-human animals indicates that the neurohypophysial hormone oxytocin (OT) evolved to serve a specialized function in social behavior in mammals. Although OT-based therapies are currently being evaluated as remedies for social deficits in neuropsychiatric disorders, precisely how OT regulates complex social processes remains largely unknown. Here we describe how a non-human primate model can be used to understand the mechanisms by which OT regulates social cognition and thereby inform its clinical application in humans. We focus primarily on recent advances in our understanding of OT-mediated social cognition in rhesus macaques (*Macaca mulatta*), supplemented by discussion of recent work in humans, other primates, and rodents. Together, these studies endorse the hypothesis that OT promotes social exploration both by amplifying social motivation and by attenuating social vigilance.

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1. Introduction

Oxytocin (OT) is an evolutionarily conserved nonapeptide that mediates female sexual intercourse, parturition, lactation, as well as water regulation, and anxiolytic functions (Donaldson and Young, 2008). In highly social animals, these ancestral functions of OT have been co-opted to serve social functions, such as promoting maternal behavior (Champagne et al., 2001; Pedersen et al., 1982), fostering pair-bonding and affiliative behaviors (Cushing and Carter, 2000; Smith et al., 2010; Snowdon et al., 2010; Young and Wang, 2004), encouraging in-group bias (Dreu et al., 2010), reducing social vigilance

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(Ebitz et al., 2013; Heinrichs et al., 2003) and amplifying other-regarding behaviors (Barraza et al., 2011; Chang et al., 2012; Van IJzendoorn et al., 2011). Although there appears to be a large range of OT-mediated effects, one might argue that some functions of OT may be common to most, if not all, of OT-mediated social cognition. The anxiolytic, approach-promoting, and tolerance-enhancing roles of OT (Amico et al., 2004; Averbeck, 2010; Heinrichs et al., 2003; Kemp and Guastella, 2010; Neumann et al., 2000a; Riem et al., 2011; Ring et al., 2006; Uvnäs-Moberg et al., 1994; Waldherr and Neumann, 2007; Yoshida et al., 2009; Young, 2002) may serve as foundational substrates that promote social exploration and interaction while, typically, suppressing social avoidance.

A large number of studies have been conducted to probe the role of OT in regulating social behavior in both healthy and pathological states (Bartz et al., 2011; De Dreu, 2012; Guastella et al., 2012; Heinrichs and Domes, 2008; Insel, 2010; MacDonald and Feifel, 2013; Meyer-Lindenberg et al., 2011). Nevertheless, the neural mechanisms through which OT regulates social behavior and cognition—particularly in humans—remain poorly understood. Standard noninvasive neuroscientific techniques, such as functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS), used to study human brain and cognition are limited in their capacity to reveal the neuronal and circuit mechanisms that mediate the regulation of social behavior and cognition by OT. Conversely, rodent models permit exquisitely fine dissection of these neural pathways but lack the behavioral complexity of human social function.

Compared to other animals, primates, including humans, are unique in that they show remarkably complex social behavior in a society typically made up of many individuals. Adapting to increasing social complexity may have played a major role in primate brain evolution (Dunbar and Shultz, 2007). For example, across primate species, social complexity, as measured by group size, strongly predicts forebrain volume (after correcting for body size) (Dunbar, 1998). Although rodents offer the opportunity for exploitation of powerful molecular genetic techniques, their social behavior is not very similar to the social behavior of humans. While molecular genetic techniques are only beginning to be developed for use in non-human primates (Diester et al., 2011; Sasaki et al., 2009), their social behavior is much more similar to the social behavior of humans.

Here we argue that a rhesus macaque model (*Macaca mulatta*) can effectively bridge this gap. Rhesus macaques are Old World monkeys that live in large, hierarchical, and mixed-sex social groups, that last shared a common ancestor with humans some 25 million years ago (Smuts, 1987). Critically, rhesus macaques display basic aspects of complex social behaviors that are typically considered 'uniquely human' (Frith and Frith, 2007; Saxe, 2006). These include social imitation (Ferrari et al., 2006; Subiaul, 2004), prosocial behaviors (Chang et al., 2011; Masserman et al., 1964), as well as understanding others' perceptions (Flombaum and Santos, 2005; Santos et al., 2006). Mental capacities like these might be fundamental building blocks for empathy and theory of mind. Such similarities in social behaviors make rhesus macaques excellent models for studying neuropsychiatric conditions accompanied by complex social deficits, such as autism spectrum disorders (Watson and Platt, 2012). Although there are undoubtedly some differences between humans and rhesus monkeys (Byrne and Whiten, 1988), such as the strength of prosociality, rhesus macaques are outstanding models for studying the neural mechanisms underlying psychiatric disorders marked by social deficits. Due to their remarkably similar anatomy and physiology to humans, rhesus macaques have long served as the gold standard for electrophysiological, pharmacological, and lesion-based investigations into complex cognitive processes. In this review we highlight recent advances in understanding how OT influences social behavior in rhesus macaques, paving the way for future investigations into the neural mechanisms mediating these influences.

2. Inhaling OT increases its concentration in the brain

Numerous human studies have demonstrated that intranasally administered OT can modulate complex social cognition. One of the most exciting findings from recent OT studies is that the peptide appears to rescue some social deficits in individuals with psychopathological conditions (for a review, see: Insel, 2010; Meyer-Lindenberg et al., 2011). The clinical and basic science communities are currently working together to translate basic OT research into useful and safe OT therapies for social disorders (Miller, 2013). Nevertheless, whether or not intranasal administration of OT actually translocates the peptide into the central nervous system (CNS) remained unknown until recently. In humans, the closest demonstration was for arginine vasopressin (AVP), another neurohypophysial hormone with social functions closely related to OT and differing in only two amino acids. Intranasally administered AVP effectively increases CNS AVP concentration for a long duration (>80 min.) in a dose-dependent manner (Born et al., 2002). More recently, data from rhesus macaques demonstrated that aerosolized OT using a nebulizer system (Fig. 1A) effectively reaches the brain. Using a pediatric nebulizer, we recently showed that inhaled oronasal administration of OT increases its concentration in the cerebrospinal fluid (CSF), measured at 30 min post-delivery (Chang et al., 2012) (Fig. 1B). A recent microdialysis study in rats and mice has demonstrated that nasal administration of OT increases levels in the central nervous system (sampled from the amygdala and hippocampus), peaking 30–60 min from the time of nasal delivery (Neumann et al., 2013). Subsequent work in primates from another laboratory reported that the inhaled administration of aerosolized OT effectively elevates OT levels in the CSF in rhesus macaques, but the application of intranasal spray, which has been the standard method in studies in humans, does not (Modi et al., in press).

Anecdotally, monkeys readily accept and tolerate nebulization (e.g., training takes less than a week), a technique that is routinely used in babies and young children to administer drugs like albuterol to alleviate breathing difficulties, suggesting that this method may prove both effective and acceptable in young patients with neuropsychiatric disorders. This tolerability is particularly desired for an early OT intervention in young children or even infants. Further research will be