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Do delivery routes of intranasally administered oxytocin account for observed effects on social cognition and behavior? A two-level model

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ABSTRACT

Accumulating evidence demonstrates the important role of oxytocin (OT) in the modulation of social cognition and behavior. This has led many to suggest that the intranasal administration of OT may benefit psychiatric disorders characterized by social dysfunction, such as autism spectrum disorders and schizophrenia. Here, we review nasal anatomy and OT pathways to central and peripheral destinations, along with the impact of OT delivery to these destinations on social behavior and cognition. The primary goal of this review is to describe how these identified pathways may contribute to mechanisms of OT action on social cognition and behavior (that is, modulation of social information processing, anxiolytic effects, increases in approach-behaviors). We propose a two-level model involving three pathways to account for responses observed in both social cognition and behavior after intranasal OT administration and suggest avenues for future research to advance this research field.

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1. Introduction

An accumulating body of evidence demonstrates the crucial role of the neuropeptide hormone oxytocin (OT) in the modulation of social cognition and behavior (between 20 and 40 IU; Guastella and MacLeod, 2012; Young and Wang, 2004). For instance, intranasal oxytocin (IN-OT) increases gaze to the eye-region (Guastella et al., 2008) and improves social cognition performance in healthy

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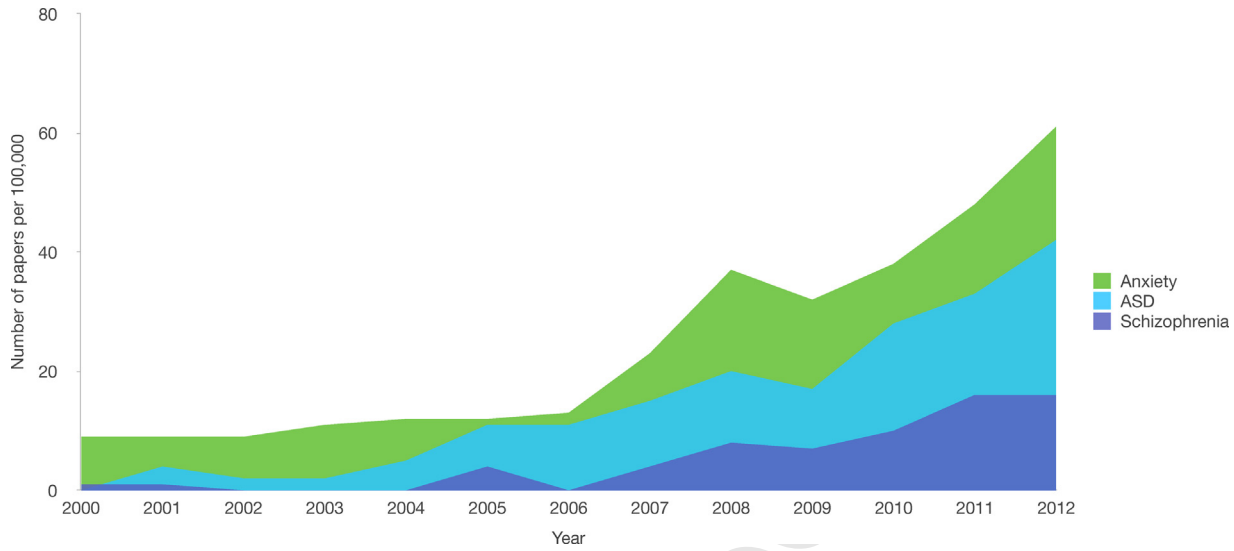

Fig. 1. Publications in PubMed with the keyword "oxytocin" paired with "anxiety", "autism", or "schizophrenia".

controls (Domes et al., 2007b), autism spectrum disorders (ASD; Guastella et al., 2010), and schizophrenia (Gumley et al., 2014). Functional imaging research has also shown that IN-OT increases brain activity in regions involved in social cognition (Bethlehem et al., 2013; Gordon et al., 2013) and modulates functional connectivity between these regions (Kirsch et al., 2005; Riem et al., 2013; Wittfoth-Schardt et al., 2012). Such research has led many to propose that IN-OT, through its effects on social behavior and cognition, may benefit a wide variety of psychiatric illnesses characterized by poor social functioning, such as ASDs (Modi and Young, 2012) and schizophrenia (MacDonald and Feifel, 2012). Reflecting the interest in OT's role in modulating social cognition and behavior, a search in PubMed using the terms "oxytocin" paired with "autism", "anxiety", and "schizophrenia", demonstrates a steady increase in publications since the year 2000 (Fig. 1).

While initial results seem promising, subsequent studies have reported failures to replicate, inconsistent results, or findings that are only significant when individual differences are taken into account. Recent efforts have been taken to interpret these inconsistencies. For instance, the social salience (or "optimizing") model proposes that rather than increasing the expression of prosocial emotions (Meyer-Lindenberg, 2008), OT increases the salience of social cues (Shamay-Tsoory et al., 2009). This model first emerged following a series of studies that demonstrated group based findings highlighting the role of oxytocin in enhancing social cognition and behavior (for a review see Guastella and MacLeod, 2012). However, the critical importance of this interpretation was highlighted after findings suggested that OT increased reactions of envy and gloating in a social context, which were considered non-prosocial behaviors (Shamay-Tsoory, 2010; Shamay-Tsoory et al., 2009). Alternatively, the "interactionist" model suggests that individual (e.g., presence of psychiatric illness; Perez-Rodriguez et al., 2014a,b) and situational features can constrain or amplify the observed effects of OT administration. These situational factors include experimental task characteristics (e.g., emotional valence) and task difficulty. Indeed, opposite results have been observed with similar tasks performed by different populations (e.g., brain activity in males and females after OT administration; Domes et al., 2010; Kirsch et al., 2005), illustrating how both the individual and experimental context contributes to the observed effects of OT administration.

Despite such endeavors, however, remarkably little work has explicitly addressed how OT reaches key targets in the body and brain to cause its documented impact. Almost all studies exploring the impact of OT on social behavior and cognition have used intranasal delivery (cf. Hollander et al., 2007, 2003 for notable exceptions using intravenous OT delivery). Nasal delivery provides a means to deliver molecules to the central nervous system (CNS) when other modes of delivery would display poor bioavailability along with the ability to bypass the blood brain barrier (BBB). Unlike the gastrointestinal (GI) target of many orally administered drugs, which will almost always reach the targeted area of uptake due to esophageal peristalsis and the large surface area of GI epithelia, the body's absorption of nasally administered drugs requires more direct delivery to specific regions of the nasal cavity in order to reach CNS targets. Such necessity for targeted delivery highlights the importance of understanding delivery in OT research. An improved understanding of IN-OT delivery pathways can take the field forward by firstly, enhancing the delivery of OT to optimum targets in the nasal cavity, and secondly, by helping interpret prior research in the field. As we have highlighted previously (Guastella et al., 2013), important targets for OT delivery in the nasal cavity lie beyond the nasal valve. However, only half of the OT dose actually reaches this area when administered with commonly used hand-actuated pumps (Djupesland et al., 2006). Working towards the therapeutic use of OT, the control of dosing will also become increasingly important. Optimizing OT delivery, based on nasal anatomy and physiology, will have substantial implications for the therapeutic and clinical applications of such work. For example, a recent study (Cacciotti-Saija et al., 2014) specifically showed that the amount of spray used by participants significantly correlated with clinical effect as shown by a reduction in negative symptoms of psychosis. This suggests that improving the delivery of spray is likely to lead to better outcomes for clinical trials. Furthermore, there is a need to identify how these delivery pathways interact with neural circuitry underlying OT's impressive effects on social behavior and cognition. Finally, a better understanding of these delivery pathways and their behavioral endpoints will help to show if the observed effects of exogenous OT are due to an anxiolytic effect (MacDonald and Feifel, 2014), increases in approach-related behavior (Kemp and Guastella, 2011), heightened social salience (Bartz et al., 2011; Shamay-Tsoory et al., 2009), or a combination of all three processes.

We recently reviewed (Guastella et al., 2013) and proposed four routes of IN-OT administration that included; (1) oral mucosa into the gastroenteral and respiratory systems; (2) nasal vasculature

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