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Review article

Oxytocin effects in schizophrenia: Reconciling mixed findings and moving forward

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ABSTRACT

Schizophrenia is a severe mental illness that causes major functional impairment. Current pharmacologic treatments are inadequate, particularly for addressing negative and cognitive symptoms of the disorder. Oxytocin, a neuropeptide known to moderate social behaviors, has been investigated as a potential therapeutic for schizophrenia in recent years. Results have been decidedly mixed, leading to controversy regarding oxytocin's utility. In this review, we outline several considerations for interpreting the extant literature and propose a focused agenda for future work that builds on the most compelling findings regarding oxytocin effects in schizophrenia to date. Specifically, we examine underlying causes of heterogeneity in randomized clinical trials (RCTs) conducted thus far and highlight the complexity of the human oxytocin system. We then review evidence of oxytocin's effects on specific deficits in schizophrenia, arguing for further study using objective, precise outcome measures in order to determine whether oxytocin has the potential to improve functional impairment in schizophrenia.

1. Introduction

Schizophrenia is a severe neurodevelopmental disorder that affects nearly 1% of the population worldwide (McGrath et al., 2008) and results in marked functional impairment. In recent years, the neuropeptide oxytocin, known to play a key role in bonding and social behavior, has been heralded as an important player in the etiology, symptom severity, and possible treatment of schizophrenia. Interest in this area of research stems from numerous studies suggesting pro-social effects of intranasal oxytocin in both non-clinical and clinical human populations. However, initial enthusiasm about oxytocin has now given way to doubt and controversy. Mounting evidence suggests that the oxytocin system is highly complex and has multifaceted influences on behavior. The human oxytocin literature is limited by small sample sizes, failures to replicate (Nave et al., 2015), disputed statistical approaches (Conlisk, 2011; Walum et al., 2015), incomplete understanding of pharmacodynamics (Leng and Ludwig, 2016), possible publication bias (Lane et al., 2016), and variable study design. The subset of this literature focused on schizophrenia is limited by the same challenges (Oya et al., 2015). As a result, understanding of oxytocin's role in schizophrenia remains insufficient and we continue to lack consensus regarding its place, if any, in future treatment protocols.

Others have already published thorough and excellent reviews regarding oxytocin and schizophrenia (Bartholomeusz et al., 2015; Feifel et al., 2015; Macdonald and Feifel, 2012; Meyer-Lindenberg et al., 2011). In this review, we aim to contribute to the existing body of work in a few specific ways. First, we summarize the literature on oxytocin effects on positive and negative symptoms of schizophrenia and explore potential causes of heterogeneity in these studies, including study design factors as well as individual-level factors such as antipsychotic dosage. Second, we review evidence of oxytocin effects on social cognition and other deficits in schizophrenia, arguing that these areas warrant further study. Specifically, we highlight promising early findings regarding oxytocin's effects on mentalizing, as well as on non-social cognition, facial expressivity, and olfaction. Finally, we propose an agenda for future research, emphasizing the importance of more objective, precise outcome measures in order to rigorously characterize oxytocin's role in schizophrenia and explore its utility as a treatment.

2. Functional impairment in schizophrenia

Schizophrenia is characterized by three symptom domains: positive, negative, and cognitive (American Psychiatric Association, 2013). Positive symptoms include disorganized behavior, delusions, and perceptual aberrations such as auditory hallucinations. Negative symptoms are a multi-dimensional construct, referring to a cluster of deficits that affect motivation (asociality, avolition, anhedonia) and emotional expressivity (alogia, blunted affect) (Blanchard and Cohen, 2006).

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Cognitive deficits span multiple areas, affecting both social (Green et al., 2015) and non-social (Green and Harvey, 2014) domains. Together, these symptoms make schizophrenia a particularly devastating illness that ranks among the top 25 leading causes of disability worldwide (Chong et al., 2016) and costs over $60 billion annually in the U.S. alone (Marcus and Olfson, 2008). Affected individuals suffer from high levels of unemployment, limited ability to function independently, and social isolation (World Health Organization, 2008). These impairments lead to productivity losses that are the greatest contributor to the overall societal cost of schizophrenia (Wu et al., 2005).

Unfortunately, the functional impairment associated with schizophrenia has changed little over the past several decades (Hegarty et al., 1994; Jääskeläinen et al., 2013). Although there is widespread use of antipsychotic medications to treat the illness, these medications typically only ameliorate positive symptoms and fail to improve negative or cognitive symptoms (Carpenter and Koenig, 2008; Fusar-Poli et al., 2015; Kirkpatrick, 2000). Developing treatments to improve negative and cognitive symptoms in schizophrenia is essential, as severity of impairment in these domains is consistently associated with quality of life and functional outcomes (Mancuso et al., 2011; McGlashan and Fenton, 1992; Rabinowitz et al., 2012). Given that the costs associated with psychiatric illness continue to escalate (Bloom et al., 2012) while development of new therapeutics in the field has slowed (Hyman, 2012; Miller, 2010), investigating novel potentially effective treatments is a critical task to reduce morbidity.

3. The promise of oxytocin and current challenges

Oxytocin, a highly conserved neuropeptide produced in the hypothalamus, is widely recognized as a moderator of affiliation, stress, memory, and learning in animals and humans (Caldwell, 2012; Churchland and Winkielman, 2012; Sarnyai and Kovács, 2014). Research involving administration of oxytocin has increased dramatically over the last decade, and studies in non-human primates demonstrating that intranasal oxytocin can elevate oxytocin concentrations in the cerebrospinal fluid (CSF) (Chang et al., 2012; Dal Monte et al., 2014; Modi et al., 2014a) have supported the widespread adoption of intranasal administration in human populations. Administration of a single dose of oxytocin to healthy individuals has been shown to improve retention of social information (Guastella et al., 2012), reduce anxiety associated with social threat (Meyer-Lindenberg et al., 2011), facilitate interpretation of faces expressing complex mental states and social emotions (Domes et al., 2007; Leknes et al., 2013), and promote trust during interpersonal economic transactions with human (versus computer) partners (Kosfeld et al., 2005). Neuroimaging studies have implicated oxytocin in a variety of social brain processes and shown that the amygdala, medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), insula, and temporal regions are modulated by exogenous oxytocin (Adolphs, 2009; Bethlehem et al., 2013; Wigton et al., 2015a). Oxytocin has also been linked with non-social cognitive processes, such as spatial and episodic memory and cognitive flexibility (Chini et al., 2014). These promising findings have generated enthusiasm for oxytocin's potential as a therapeutic in multiple psychiatric disorders.

A dramatic rise in the number of oxytocin studies in clinical populations over the past decade reflects this enthusiasm (Quintana et al., 2015b). In addition to targeting deficits in schizophrenia, oxytocin has been investigated as a treatment for deficits in autism (Alvares et al., 2016; Ooi et al., 2017; Guastella and Hickie, 2016), alexithymia (Luminet et al., 2011), Prader-Willi Syndrome (Einfeld et al., 2014; Tauber et al., 2011) and social anxiety (Guastella et al., 2009; Labuschagne et al., 2010; Tabak et al., 2016). Results of these clinical studies have been notably inconsistent, however. A growing body of evidence now suggests that oxytocin's effects are more complex than previously thought: rather than being simply "pro-social," it appears to modulate social interaction in a context-specific manner (Bartz et al., 2011) that is impacted by individual differences (Macdonald and Feifel, 2012; Tabak, 2013). In addition, there is debate about intranasal oxytocin's ability to consistently reach neural targets, lack of clarity about its pharmacodynamics (Bakermans-Kranenburg and van I Jzendoorn, 2013; Leng and Ludwig, 2016; Quintana and Woolley, 2015), and incomplete understanding of oxytocin receptor distribution in the human brain (Freeman and Young, 2016). Perhaps not surprisingly, there have been recent failures to replicate some of the early oxytocin findings in healthy humans (Nave et al., 2015). These issues present major challenges to investigating oxytocin's effects in schizophrenia, and have tempered the excitement that followed early work. Still, given oxytocin's critical role in socialization and the marked impairment that results from schizophrenia-associated deficits, tackling such challenges may prove to be a worthwhile effort.

4. Oxytocin and the pathophysiology of schizophrenia

Evidence from animal and human models suggests that oxytocin system dysregulation may play a role in the pathophysiology of schizophrenia. Results from rodent studies suggest that oxytocin could influence both positive (Caldwell et al., 2009; Feifel and Reza, 1999) and negative symptomatology (Meziane et al., 2015; Peñagarikano et al., 2015) (for a review see Feifel at al. (2015)). One neurofunctional model posits that abnormal oxytocinergic and dopaminergic signaling in the amygdala influences emotional salience processing, potentially leading to some of the social cognitive deficits observed in schizophrenia (Rosenfeld et al., 2010). Neuroimaging studies have shown that the amygdala and other social brain regions such as the PFC as well as the temporal gyri and sulci are modulated by exogenous oxytocin in healthy individuals (for a review see Bartholomeusz et al. (2015)). Taken together, these findings suggest a relationship between the oxytocin system and social brain function that may have important implications for treatment of schizophrenia.

Understanding of the link between impairments in schizophrenia and endogenous oxytocin system functioning, however, remains limited. Multiple studies have examined central and peripheral oxytocin levels in individuals with schizophrenia, with mixed results. CSF oxytocin levels correlated with negative symptoms in one study (Sasayama et al., 2012), but another found no difference in levels between individuals with and without schizophrenia (Glovinsky et al., 1994). Others have observed correlations between plasma oxytocin levels and facial affect identification (Goldman et al., 2008; Rubin et al., 2011), perception of emotion in dynamic body expressions (Strauss et al., 2015b), and less severe negative symptoms (Kéri et al., 2009) in schizophrenia. However, elevated plasma oxytocin levels in individuals with schizophrenia have also been associated with more severe positive symptoms (Rubin et al., 2014; Walss-Bass et al., 2013) and social cognitive impairment (Walss-Bass et al., 2013). Moreover, the utility of peripheral oxytocin measurement has been called into question: it is unclear whether plasma levels consistently reflect levels in the brain (Carson et al., 2014; Kagerbauer et al., 2013; Takagi et al., 1985). Thus, though the oxytocin system may play an important role in terms of etiology and symptom severity, its relationship with the deficits associated with schizophrenia is far from clear.

5. Oxytocin effects on positive and negative symptoms of schizophrenia

Despite this lack of clarity, a number of studies have investigated oxytocin's ability to treat symptoms of schizophrenia (see Table 1). The majority of RCTs conducted thus far have assessed the effects of intranasal oxytocin on positive and negative symptoms, with mixed results. In a within-subject cross-over study of 15 outpatients, Feifel et al. (2010) found improvement in both positive and negative symptoms after three weeks of twice daily 40 IU doses of oxytocin. Pedersen et al. (2011a,b) found significant within-subject improvement in positive symptoms, paranoia, and general psychopathology in the