Review

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A Review of Oxytocin's Effects on the Positive, Negative, and Cognitive Domains of Schizophrenia

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ABSTRACT

Schizophrenia is a disabling, heterogeneous disorder with clinical features that can be parsed into three domains: positive symptoms, negative symptoms, and cognitive deficits. Current antipsychotic drugs produce fairly robust clinical benefit against positive symptoms but typically have minimal therapeutic effects on negative symptoms and cognitive deficits. Oxytocin (OT) is a nonapeptide that, in addition to its role as a hormone regulating peripheral reproductive-relevant functions, acts as a neurotransmitter in the brain. Several lines of preclinical and clinical research suggest that the OT system may play a role in regulating the expression of schizophrenia spectrum disorders and that targeting the central OT system may yield novel treatments to address these symptoms. In this review, we summarize the extant preclinical and clinical evidence relevant to the role of OT in schizophrenia with particular emphasis on its putative therapeutic effects on each of the three above-mentioned clinical domains.

Keywords: Antipsychotic, Cognitive deficits, Negative symptoms, Oxytocin, Positive symptoms, Schizophrenia

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Schizophrenia (SCZ) is a disabling, heterogeneous disorder whose symptoms can be parsed into three domains: positive symptoms, negative symptoms, and cognitive deficits. Positive symptoms include the presence of perceptual aberrations (auditory and visual hallucinations), delusions (fixed, false beliefs), and disorganized behavior or speech. Negative symptoms include deficits in motivation (avolition), experiencing pleasure (anhedonia), seeking social interaction (asociality), verbal communication (alogia), and emotional expression. In addition to these impairments, most people with SCZ also have deficient cognitive processing that further impairs their ability to function. The National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative identified seven specific domains of cognitive impairment in patients with SCZ: visual and verbal learning and memory, attention/vigilance, working memory, reasoning and problem solving, information processing speed, and social cognition (1). Although currently subsumed under a single diagnostic label, in reality there is substantial clinical heterogeneity among patients meeting the criteria for SCZ (2).

Established antipsychotic drugs (APDs) exert their most robust and consistent clinical benefit on the positive symptoms of SCZ, a therapeutic effect associated primarily with their ability to bind mesolimbic dopamine D2 receptors. Whereas inhibition of mesolimbic D2 neurotransmission is the sole mechanism of action for first generation APDs (FGAs), e.g., haloperidol, second generation APDs (SGAs), e.g., clozapine, have additional pharmacologic mechanisms, most notably binding and blockade of serotonin 2A receptors (3,4) while producing minimal extrapyramidal side effects. As the negative symptoms and cognitive deficits are major contributors to poor functioning in patients with SCZ, it is highly unfortunate that APDs have, at best, modest therapeutic effects on these domains of the disorder (5,6). It follows that developing novel, effective treatments for negative symptoms and cognitive deficits is a pressing therapeutic priority.

One promising molecule in addressing this need is oxytocin (OT), a nonapeptide neurohormone with well-known peripheral reproduction-related functions, including induction of uterine contractions and milk letdown. OT also acts as a neurotransmitter in the brain and is now widely recognized to regulate social cognition/affiliation, stress, learning, and memory (7).

Evidence from animal studies and several recent small randomized, double-blind, placebo-controlled clinical trials in humans suggests that the OT system is a promising therapeutic target for all three of the abovementioned symptom domains of SCZ. In this review, we summarize these data, and address the potential for OT or

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OT-mimetics[1] to provide broad-spectrum benefit in multiple domains of this devastating disorder.

POSITIVE SYMPTOMS

Positive symptoms are a sine qua non of SCZ, as according to the diagnostic criteria of DSM-5, at least one positive symptom must be present to confer this diagnosis. Pathophysiologically, increased (or dysregulated) dopaminergic transmission in the mesolimbic pathway from the ventral tegmental area to the nucleus accumbens is thought to play a crucial role in the generation of positive symptoms (13,14).

PRECLINICAL STUDIES OF THE EFFECTS OF OT ON POSITIVE-LIKE SYMPTOMS

Animal models of relevance for positive symptoms of SCZ, although fraught with translational challenges, are valuable tools to screen putative novel APDs and to gain a better understanding of their mechanisms of therapeutic action (2). Since there is currently no reliable way to induce and measure hallmark positive symptoms (e.g., auditory hallucinations, delusional thinking) in animals, investigators seeking to model these symptoms have mostly attempted to reproduce the neurochemical perturbations that are thought to underlie their manifestation (2,15). In this regard, psychostimulants such as amphetamine and cocaine produce mesolimbic hyperdopaminergia, which in turn produces behavioral changes (e.g., hyperactivity). Though hyperactivity is not a characteristic feature of SCZ, in the psychostimulant model it functions as a behavioral surrogate for the underlying abnormality, mesolimbic hyperdopaminergia. Notably, FGAs and SGAs attenuate the hyperactivity associated with the drug-induced hyperdopaminergia (16,17), suggesting predictive validity of this model for drugs with antipsychotic efficacy.

In a series of studies aimed at investigating OT's antiaddiction properties, Sarnyai *et al.* (18) reported that subcutaneous (SC) OT produced a dose-dependent attenuation of cocaine-induced hyperactivity (see Table 1 for a summary of OT preclinical studies with relevance to the positive symptoms of SCZ). A follow-up microdialysis study confirmed these findings were associated with OT's inhibition of the cocaine-induced increase in nucleus accumbens dopamine levels (19). Importantly, the nucleus accumbens is a brain region highly responsive to the dopamine elevating effects of stimulants and has been implicated in both the pathophysiology of SCZ (15) as well as the clinical effects of APDs (20). A subsequent, similar study by Qi *et al.* (21) showed that intracerebroventricular OT dose-dependently blocked methamphetamine-induced hyperactivity as well as the methamphetamine-induced increase in nucleus accumbens and striatal dopamine.

Feifel and Reza (22) conducted the first intentional investigation of OT's APD potential by examining its ability to reverse deficient prepulse inhibition (PPI) of the startle reflex. PPI is a measure of sensorimotor gating, a key process involved in the central nervous system's processing of information (23). Deficits in PPI have been consistently demonstrated in patients with SCZ and are thought to reflect an underlying abnormality in the brain's process of gating excessive environmental stimulus, thereby leaving patients with SCZ vulnerable to a chaotic internal representation of reality. Deficient PPI is thus considered an endophenotype of SCZ (24).

SCZ-like deficits in PPI can be modeled in animals in a number of ways, including the administration of psychotomimetic drugs, such as those that increase mesolimbic dopamine transmission. Importantly, the potency of the reversal of PPI deficits by APDs are predictive of their potency against positive symptoms (25). As all established APDs bind D2 receptors, they are able to block disruption of PPI by both direct (e.g., dopamine mimetics) and indirect dopamine agonists (which increase extracellular dopamine levels).

Feifel and Reza (22) demonstrated that SC administered OT reversed PPI deficits induced by the indirect dopamine agonist amphetamine but not by the direct dopamine agonist apomorphine, suggesting OT had the potential to attenuate mesolimbic hyperdopaminergia via presynaptic rather than postsynaptic mechanisms. These findings present the possibility that OT may have a mechanism of action that complements the postsynaptic inhibition of mesolimbic dopamine transmission produced by established APDs. Although it is thought that peptides such as OT do not effectively cross the blood-brain barrier, a recent study demonstrated that intraperitoneal administration of pharmacologic doses of OT in rodents produced a rapid, significant increase in brain OT levels (26). This effect may, in part, be due to stimulation of endogenous OT release in the brain.

In addition to mesolimbic hyperdopaminergia, reduced central glutamatergic function—particularly through the *N*-methyl-D-aspartate (NMDA) receptor complex—has also been implicated in positive symptoms (27). In kind, noncompetitive NMDA antagonists such as phencyclidine (PCP) and its analog, dizocilpine (MK801), produce PPI deficits in animals. Whereas both FGAs and SGAs reverse PPI deficits produced by dopamine agonists, only SGAs will reverse PPI deficits produced by noncompetitive NMDA antagonists (28). Furthermore, PPI deficits in patients with SCZ are consistently restored by treatment with SGAs (29). In their above mentioned study, Feifel and Reza (22) also found that SC OT restored PPI deficits induced by dizocilpine. This finding suggested that OT's APD-like profile involved more mechanisms than just dopamine inhibition and that it shared features with the multi-transmitter effects of SGAs.

[1]While OT exerts its primary actions by binding the single oxytocin receptor (OXTR), it also has significant affinity for vasopressin receptors, including the vasopressin-1A receptor (the arginine vasopressin receptor [AVPR] most abundant in the brain) (8). Experiments disambiguating the relative roles of OXTR versus vasopressin-1A receptor in mediating OT's central effects have, in fact, found that AVPRs often contribute to OT's effects (9) and sometimes are solely responsible (10,11). That said, the relative role of OXTR versus AVPRs has not been well elucidated in clinical or preclinical studies related to SCZ spectrum disorders. Thus, readers should keep in mind that the experimental effects of OT reviewed herein may be mediated by OXTR, one of the AVPRs, or both. Readers should also note that the structure, function, and physiology of the OT system are described in detail in other articles in this special edition and have previously been reviewed by Macdonald and Feifel (12).