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Schizophrenia and alcohol dependence: Diverse clinical effects of oxytocin and their evolutionary origins

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ABSTRACT

Beginning in 1979 with the first report that central administration of oxytocin stimulates maternal behavior in virgin rats, decades of animal research and more recent human studies have demonstrated that oxytocin has many pro-social effects. These many findings suggest that oxytocin may be an effective treatment for social deficits that are hallmark features of disorders such as autism and schizophrenia. Effects in preclinical animal models also imply that oxytocin may be an efficacious pharmacotherapy in a wide range of psychiatric disorders including psychoses and addictions. To date, 3 small clinical trials found that daily intranasal oxytocin treatment for 2–8 weeks significantly reduced psychotic symptoms in schizophrenia. Two of these trials also found improvement in social cognition or neurocognition, areas in which patients have significant deficiencies that do not respond to conventional antipsychotic treatment and contribute to disability. In another small trial, intranasal oxytocin potently blocked alcohol withdrawal. After reviewing the rationale for these trials, they are described in more detail. Questions are then asked followed by discussions of the large gaps in our knowledge about brain oxytocin systems in humans. The hope is to highlight important directions for future investigations of the role of oxytocin in the pathophysiology of psychotic disorders and addictions and to extend clinical research in these areas. Heretofore unrecognized roles for which oxytocin may have been selected during the evolution of placental mammalian maternal–infant and other social attachments are considered as possible origins of oxytocin antipsychotic and antiaddiction effects.

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1. Evolutionary prologue

Chapter 2 (in this volume) discusses the evolution of oxytocin (OT) and its central roles in unique aspects of placental mammalian reproduction. These include milk ejection, which is essential for the success of lactation, and stimulation of uterine contractions, which facilitates parturition following fetal development within the uterus. Chapter 2 also emphasizes that OT was selected to activate avid and sustained maternal behavior in parturient females, another novel

Abbreviations: OT, oxytocin

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reproductive strategy that was essential for the successful evolution of placental mammals. It was hypothesized that the much higher quality maternal behavior exhibited by placental mammals required the evolution of new brain systems that could initiate and maintain a highly motivated social behavioral state, systems that OT activates at parturition. OT (as well as vasopressin) appears to have been selected to initiate other social attachments that evolved in placental mammals, such as monogamous pair-bonding. Evidence was reviewed that OT may also have been selected to regulate other social and emotion behavior control systems that emerged during placental mammalian evolution to enhance reproductive success. For example, OT has been strongly implicated in reducing anxiety and fear responses during parturition and lactation which enabled successful activation of offspring caretaking in parturient mothers, especially primiparous mothers in whom the novelty of parturition and newborns could produce aggression toward or avoidance of offspring. As is reviewed by MacDonald (in this volume), OT anxiolysis is not restricted to reproductively relevant states in animals, has been demonstrated in human subjects, and may be therapeutically beneficial in human anxiety disorders. Later in placental mammalian reproductive, central OT systems evolved to facilitate the formation of selective maternal–infant bonds by enabling mothers to learn the unique odors of their offspring.

Chapter 2 also speculates that the evolution of avid and sustained maternal behavior, as well as lactation and *in utero* fetal development, enabled, in multiple ways, the subsequent evolution of higher intelligence. The many recent reports that intranasal OT administration facilitates social cognition in human subjects (see Evans et al. (in this volume) as well as the review of these findings later in this chapter) suggest that OT may have been centrally involved in advances in cognitive ability, especially social intelligence, during the evolution of placental mammals.

The primary goal of this article is to review evidence that OT is a promising new treatment for schizophrenia and alcohol dependence. A secondary but still key aim is to propose that the seemingly unrelated antipsychotic and antiaddiction effects of OT may provide new insights into other OT mechanisms that may have been selected during placental mammalian evolution to facilitate the formation of social bonds. This argument is summarized here and restated at the end of the article. As is discussed in more detail below, the antipsychotic efficacy of OT may be based on enhancement of sensory-motor gating, *i.e.*, the ability to rapidly process the significance of sensory input and initiate appropriate behavioral responses. Successful evolution of avid and sustained maternal behavior in placental mammals may have required a considerable up-grade in sensory-motor gating ability. Effective mothering requires accurate perception of diverse sensory cues from offspring and swift mobilization of appropriate caretaking behaviors. The antiaddiction effects of OT appear to be based on inhibition of tolerance formation to addictive substances. The evolution of the ability to form lasting social attachments may have required selection of brain mechanisms that prevent habituation to the highly rewarding stimuli from reproductively important conspecifics such as offspring or pair-bonded mates. OT could have been selected to play this role. As a by-product, OT may block tolerance formation to other strong activators of reward pathways including addictive drugs.

2. Introduction

Three recent clinical trials have rapidly propelled OT into the forefront of schizophrenia research. All 3 trials found that twice daily intranasal administration of OT for 2–8 weeks as an adjunct to antipsychotic medication significantly reduced positive, negative and general symptoms in patients with schizophrenia (Feifel et al., 2010; Pedersen et al., 2011; Modabbernia et al., 2013). Furthermore, OT treatment but not placebo improved performance on tests of social cognition in the Pedersen et al. (2011) study and improved verbal learning but not working memory (Feifel et al., 2012). Patients with schizophrenia have deficits in these cognitive domains that profoundly impair their function and which do not respond to currently available antipsychotic medications (Harvey et al., 2006; Sergi et al., 2007; Penn et al., 2009). A recent preliminary trial suggests that OT may have efficacy in treating a quite different clinical disorder-addiction. Pedersen et al. (2013) discovered that twice daily intranasal OT for 3 days was markedly more effective than placebo in reducing withdrawal symptoms and the amount of benzodiazepine required for successful medical detoxification of alcohol dependent patients. This is the first evidence in human subjects that OT has therapeutic efficacy in a substance dependence disorder. Remarkably, intranasal OT treatment produced no increased side effects or adverse events in these clinical trials or other studies (MacDonald et al., 2011).

The sections below begin with reviews of animal and human studies that led investigators to test OT as a treatment for schizophrenia and alcohol withdrawal. The clinical trials are then described as well as relevant studies that have been published more recently. Questions are then posed about the large gaps in our current knowledge about OT systems in the human brain. These are discussed to highlight important areas for future research that will advance our understanding of OT in schizophrenia, alcohol dependence and other addictive disorders as well as other types of psychopathology (see Macdonald and Feifel (2013) for a comprehensive overview of unresolved issues relevant to the development of OT pharmacotherapeutics). Finally, roles for which OT may have been selected during the evolution of placental mammalian maternal behavior are considered as possible origins for OT efficacy in treating disorders as diverse as schizophrenia and alcohol dependence.

3. Oxytocin and schizophrenia

MacDonald and Feifel (2012) thoroughly reviewed evidence for therapeutic effects of OT in schizophrenia. We will briefly summarize and update that evidence and elaborate further on OT as a treatment for social cognition and function deficits in schizophrenia.