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Aerosolized oxytocin increases cerebrospinal fluid oxytocin in rhesus macaques

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Summary Intranasal (IN) administration is a widely used method for examining the effect of oxytocin (OT) on social behavior and cognition in healthy subjects and psychiatric populations. IN-OT in humans enhances trust, emotional perception, and empathetic behavior and is under investigation as a potential pharmacotherapy to enhance social functioning in a variety of neuropsychiatric disorders, including autism spectrum disorders (ASD). Nonhuman primates (NHP) are an important model for understanding the effect of OT on social cognition, its neural mechanisms, and the development of IN-OT as a pharmacotherapy for treating social deficits in humans. However, NHP and even some human populations, such as very young infants and children, cannot easily follow the detailed self-administration protocol used in the majority of human IN-OT studies. Therefore, we evaluated the efficacy of several OT-administration routes for elevating central OT concentrations in rhesus macaques. First, we examined the effect of IN and intravenous (IV) routes of OT administration on concentrations of OT and vasopressin (AVP) in plasma and lumbar CSF. Second, we examined these same measures in monkeys after an aerosolized (AE) OT delivery route. All three administration routes significantly increased plasma OT concentrations, but only the AE-OT route significantly increased concentrations of CSF OT. No route affected concentrations of AVP in plasma or CSF. This study confirms that the AE route is the most effective method for increasing central OT concentrations in monkeys, and may also be an effective route, alternative to IN, for administering OT to some human populations.

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1. Introduction

The neuropeptide oxytocin (OT) has been shown to modulate social cognition and social behavior in a wide range of mammalian species, including humans. For example, in animals OT enhances social information processing, social recognition, maternal care, and social attachment through actions on central OT receptors (Ross and Young, 2009). Because of its enhancing effect on prosocial behavior and social cognition, research on the potential for OT's use as a pharmacotherapy to treat the social deficits associated with a number of psychiatric disorders, most notably autism, has dramatically increased (Young and Flanagan-Cato, 2012). However, OT is a large peptide molecule and resultantly fails to cross the blood brain barrier efficiently. In fact, peripheral administration of OT results in the entry of less than 1% of the exogenous neuropeptide into brain areas protected by the blood–brain barrier (BBB; Ermisch et al., 1985). This impermeability of the BBB endogenously allows for independent regulation of central and peripheral neuropeptide concentrations, resulting in its discrete behavioral and physiological functions (Landgraf and Neumann, 2004). In the periphery, for example, OT is essential for regulating a variety of female reproductive functions including uterine contraction during labor and milk stimulation during nursing, but it is thought that it is its central function in the brain that leads to the reported prosocial effects (Churchland and Winkielman, 2011). Thus, the failure of peripheral OT to readily penetrate the BBB has necessitated the development of alternative methods to effectively administer OT to the brain and further characterize its prosocial behavioral effects.

One such method involves the nasal administration of peptides, which is presumed to enable passage across the BBB at the level of the nasal epithelium. It is hypothesized that the rapid turnover of cells in the nasal epithelium leads to the loosening of tight junctions facilitating the transport of large molecules into the lamina propria (Altner and Altner-Kolnberger, 1974). Once in the lamina propria the molecules can either be absorbed into blood vessels and enter peripheral circulation or diffuse into perineural or perivascular spaces and gain access to the CNS (Lochhead and Thorne, 2011). In 2002, Born and colleagues reported that an intranasally sprayed administration of arginine vasopressin (AVP), a peptide that is structurally related to OT, effectively elevated levels of AVP in the CSF of humans (Born et al., 2002). Based on these encouraging findings, researchers have now almost exclusively adopted the intranasal (IN) spray administration method to examine the effects of OT on human social cognition (Guastella and MacLeod, 2012). These studies report numerous effects of IN-OT on human social cognition, including enhanced eye gaze, increased trust, better recognition of facial emotions, improved face memory, and empathy (Domes et al., 2010; Guastella and MacLeod, 2012; Guastella et al., 2008; Kosfeld et al., 2005; Rimmele et al., 2009; Savaskan et al., 2008). Moreover, several independent studies have now demonstrated the ability of IN-OT to enhance social congition in ASD (Anagnostou et al., 2012; Andari et al., 2010; Bartz and Hollander, 2008; Guastella et al., 2010; Tachibana et al., 2013). Given the promising therapeutic potential of IN-OT, and other drugs that target the oxytocinergic system, in promoting social functioning (Modi and Young, 2012), it is critical to develop a clear understanding of the mechanisms by which OT influences social cognition including its site of action.

Preliminary evidence in humans supports the assertion that IN administration provides some access to the central compartment. Nasal delivery of several peptides in humans, including insulin, α-melanocyte stimulating hormone, and AVP results in their increased concentrations in cerebrospinal fluid (CSF) over baseline levels (Born et al., 2002). Similarly, CSF OT concentrations are higher in humans who received IN-OT spray compared to those who received a vehicle treatment (Striepens et al., 2013). A more thorough characterization of the pharmacokinetic/pharmacodynamic profile of OT after IN administration, though, is limited due to the invasiveness of measuring central peptide concentrations in humans. Nor would humans be ideally suited for mechanistic studies using novel OT agonists/antagonists, microdialysis or in vivo electrophysiology to investigate the role of the oxytocinergic system in modulating social cognition. Animal models, therefore, are critically needed to elucidate the precise neural mechanisms of OT efficacy, including the development of pharmacokinetic/pharmacodynamic profiles for therapeutic doses, and characterizing the effects of repeated administration on social behavior and brain function over longer time scales.

Both rodents and NHP have been employed to assess the efficacy of IN administration in permeating the BBB and the behavioral consequences. In rat, nasally administered OT has been shown to increase extracellular concentrations of OT in limbic brain regions using microdialysis (Neumann et al., 2013). NHP, however, present several advantages over rodent models for evaluating the potential efficacy of administration routes in humans, including similar nasal architecture, greater homology in the OT receptor system, and more complex social behavioral repertoires (Donaldson and Young, 2008; Harkema, 1990; Klein et al., 2009). Moreover, the neuroanatomical distribution of OT receptors in rhesus macaques have recently been described, providing insights into the sites of OT action in the brain in this nonhuman primate (NHP) model organisms (Freeman et al., 2014).

Here, we performed two separate studies to evaluate the efficacy of several administration routes for delivering OT to the central nervous system in rhesus monkeys. The first study compared the two primary routes utilized in the majority of human studies, IN spray and intravenous (IV) injection. Six rhesus monkeys were administered OT using these two methods under anesthesia and the resulting concentrations of OT and AVP in plasma and lumbar cerebrospinal fluid (CSF) were measured. Since OT in the hypothalamus can modulate central AVP release, AVP concentrations were also measured as an indicator of potential feed-forward modulation of the neurohypophyseal system (Neumann et al., 2006).

In the second study, a passive nasal administration route using aerosolized OT (AE) was evaluated. This route has been shown to elicit effects on social behavior and perception in monkeys in three separate studies (Chang et al., 2012; Ebitz et al., 2013; Parr et al., 2013). Chang and colleagues (2012) were the first to show preliminary evidence that the AE route could be effective in elevating central concentrations of OT in two rhesus monkeys. The results of the present study will be important not only in identifying effective administration