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Effects of intranasal and peripheral oxytocin or gastrin-releasing peptide administration on social interaction and corticosterone levels in rats

Pamela Kent[a,b], Alisha Awadia[a,b], Leah Zhao[a], Donna Ensan[a,b], Dinuka Silva[a,b], Christian Cayer[a,b], Jonathan S. James[a,b], Hymie Anisman[d], Zul Merali[a,b,c,e,*]

[a] University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Ottawa, ON K1Z 7K4, Canada
[b] Department of Psychology, University of Ottawa, Ottawa, ON K1N 6N5, Canada
[c] Department of Psychiatry, University of Ottawa, Ottawa, ON K1N 6N5, Canada
[d] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON K1N 6N5, Canada
[e] Institute of Neuroscience, Carleton University, Ottawa, ON K1S 5B6, Canada

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ABSTRACT

The intranasal route of drug administration has gained increased popularity as it is thought to allow large molecules, such as peptide hormones, more direct access to the brain, while limiting systemic exposure. Several studies have investigated the effects of intranasal oxytocin administration in humans as this peptide is associated with prosocial behavior. There are, however, few preclinical studies investigating the effects of intranasal oxytocin administration in rodents. Oxytocin modulates hypothalamic-pituitary-adrenal (HPA) axis functioning and it has been suggested that oxytocin's ability to increase sociability may occur through a reduction in stress reactivity. Another peptide that appears to influence both social behavior and HPA axis activity is gastrin-releasing peptide (GRP), but it is not known if these GRP-induced effects are related. With this in mind, in the present study, we assessed the effects of intranasal and intraperitoneal oxytocin and GRP administration on social interaction and release of corticosterone in rats. Intranasal and intraperitoneal administration of 20, but not 5 μg, of oxytocin significantly increased social interaction, whereas intranasal and peripheral administration of GRP (20 but not 5 μg) significantly decreased levels of social interaction. In addition, while intranasal oxytocin (20 μg) had no effect on blood corticosterone levels, a marked increase in blood corticosterone levels was observed following intraperitoneal oxytocin administration. With GRP, intranasal (20 μg) but not peripheral administration increased corticosterone levels. These findings provide further evidence that intranasal peptide delivery can induce behavioral alterations in rodents which is consistent with findings from human studies. In addition, the peptide-induced changes in social interaction were not linked to fluctuations in corticosterone levels.

1. Introduction

The intranasal (IN) route of drug administration has garnered considerable interest in recent years, particularly with respect to peptide administration in humans. Unlike central injection which is impractical for human subjects, or systemic injection that is inefficient owing to the inability of large peptides to cross the blood-brain barrier (BBB), IN delivery is non-invasive and may potentially bypass the BBB, allowing compounds more direct access to the brain, while limiting systemic exposure (Graff and Pollack, 2005; Lochhead and Thorne, 2012; Meredith et al., 2015). Of the many peptides being investigated, oxytocin (OXT) is notably popular owing to its role in social cognition and affiliation (Lee et al., 2009; Lukas et al., 2011; Ramos et al., 2013; Veening and Olivier, 2013) and consequently, its therapeutic potential in the treatment of disorders characterized by social dysfunction.

Oxytocin is a nine amino acid neuropeptide produced by the paraventricular and supraoptic nuclei of the hypothalamus and acts on the OXT receptor, which is widely distributed throughout the brain (Barberis and Tribollet, 1996). In human studies, IN OXT administration increased trust (Baumgartner et al., 2008), positive communication (Ditzen et al., 2009), improved mind reading (Domes et al., 2007), and had a positive impact on social behaviors

* Corresponding author at: University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Ottawa, ON K1Z 7K4, Canada.
E-mail address: merali@uottawa.ca (Z. Merali).

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in both normal (Ebstein et al., 2009) and autistic individuals (Aoki et al., 2014; Watanabe et al., 2015).

In rodents, the effects of OXT on social behavior have typically been investigated using either systemic or central injection where acute OXT injection increased social or affiliative behavior (Holley et al., 2015; Lukas et al., 2011; Ramos et al., 2013) and social reward (Ramos et al., 2015), but diminished social avoidance (Lukas et al., 2011). Surprisingly, there are very few studies investigating effects of IN OXT administration on social behavior in rodents. In one study, IN OXT application elicited either no effects or sex-specific effects on social behavior (Huang et al., 2014), whereas in a second more recent study, IN OXT administration increased social exploration and decreased aggression (Calcagnoli et al., 2015).

It has been hypothesized that a possible mechanism for the increased prosocial behavior elicited by OXT is through a reduction in stress reactivity. In this regard, Taylor et al. (2000) suggested that OXT's ability to lower arousal levels may facilitate approach behavior in a social context. Supporting this contention are several reports in both animals and humans demonstrating that OXT can reduce the stress response reflected by altered hypothalamic-pituitary-adrenal (HPA) and sympathetic activation (Cardoso et al., 2014; Parker et al., 2005). However, as in the case of studies regarding the prosocial effects of OXT, human studies investigating stress-buffering effects of OXT have primarily utilized IN application, whereas rodent studies have only been conducted using either systemic or central OXT injection.

Another peptide that appears to modulate both social behavior and the stress response is gastrin-releasing peptide (GRP). The 27 amino acid peptide, GRP, and a related smaller peptide, neuromedin B (NMB), are the mammalian analogs of the amphibian peptide bombesin (BB). Gastrin-releasing peptide binds to the BB2 receptor which is widely distributed throughout the brain with particular abundance in hypothalamic and limbic structures (Battey and Wada, 1991). Contrary to the prosocial and stress-reducing effects of OXT, GRP appears to have the opposite action. In this regard, mice lacking BB2 receptors displayed increased social behavior compared to wild-type mice (Wada et al., 1997) and microinjection of related NMB into the dorsal raphe nucleus decreased social interaction (Merali et al., 2006). Furthermore, central administration of GRP increased HPA activation reflected by elevated plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone (Garrido et al., 1998; Olsen et al., 1992). The behavioral or physiological effects of IN GRP administration have not yet been explored.

Given the lack of studies involving IN peptide administration in rodents, the primary objective of the present investigation was to examine the effects of IN OXT and GRP administration on social interaction and corticosterone release in rats and compare these effects with those elicited by peripheral (intraperitoneal [IP]) injection as both of these routes of administration have therapeutic relevance. A secondary objective was to determine whether an association exists between level of social interaction and HPA activity (reflected by levels of corticosterone) following peptide administration. It was hypothesized that both IN and IP administration of OXT would increase whereas IN and IP GRP would decrease social interaction and that these behavioral effects would be accompanied by either decreased or increased levels of corticosterone, respectively.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (200–250 g body mass on arrival; Charles River Laboratories Inc., St. Constant, Quebec) were used for all experiments. Rats were housed individually for one week prior to behavioral testing and maintained under standard animal room conditions (clear Plexiglas cages, 24 × 30 × 18 cm, 12 h light–dark cycle, 21 ± 1 °C, 60% humidity, Purina Lab Chow and tap water ad libitum). All experimental procedures were approved by the Research Ethics Committee of the University of Ottawa and met the guidelines set out by the Canadian Council on Animal Care (CCAC).

2.2. Drugs

OXT and GRP (Tocris Bioscience, Minneapolis, MN) were dissolved in 0.9% saline and administered IN at doses of both 5 μg/20 μl and 20 μg/20 μl. The same doses were used for the IP study; however, the injection volume was increased to 100 μl. Controls received equivalent volumes of saline. Dosages for OXT were chosen based on Neumann et al. (2013). Preliminary studies confirmed that similar dosages for GRP would be appropriate as well.

2.3. Intranasal administration

Intranasal administration was performed as described in Lukas and Neumann (2012). A minimum of three days prior to behavioral testing, the rats were habituated to IN administration. On day one, animals were restrained using the appropriate hold for IN administration. On day two, the animals were restrained and touched on the rhinarium (glaberous skin around the nostrils) with a pipette tip. On day three, the animals were restrained and received distilled water on the rhinarium using a pipette. This process was repeated daily until all rats displayed minimal resistance to handling and distilled water administration. When administering saline or drug, the animal was restrained by a trained experimenter and saline or drug was applied bilaterally to the highly innervated rhinarium with direct application to the nostrils avoided. Any displaced drops were replaced with the equivalent volume. The rat was then restrained for an additional 30 s to ensure complete diffusion into the rhinarium.

2.4. Social interaction

All social interaction tests were conducted in a relatively non-aversive, familiar, low-level illumination environment. The arena was a white Plexiglas square box (58 cm × 58 cm; 48.5 cm high walls) with a grid (15 × 15 cm) floor. The experiment was conducted over a period of three days: the first two days consisted of habituation and testing was conducted on the third day. All testing occurred between 1000 h and 1400 h. Unfamiliar rats were paired based on body weight (less than 10% difference between their weights). On Day 1, rats along with their test day partner (both receiving same treatment) were placed in the arena for 4 min. On Day 2, rats were individually placed in the arena for a period of 4 min. On the test day (day 3), rats (n = 8/group) received IN administration or IP injection of OXT or GRP (0, 5 or 20 μg), 40 min (IN experiment) or 20 min (IP experiment) prior to being placed together in the arena for a 10 min period. The timing of injections was based on Neumann et al. (2013) showing peak brain levels of OXT within 60 or 30 min post IN or IP injection of 20 μg OXT, respectively. Between trials, the arena was cleaned with 70% ethanol. A video camera located directly above the arena permitted monitoring and scoring of behavior. Total time spent engaged in active social interaction (including sniffing, crawling over and under each other, allogrooming [grooming partner], following and play fighting) was recorded. Finally, locomotor activity in the arena was assessed by counting the number of squares crossed by the rat.