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Oxytocin modulates behavioral and physiological responses to a stressor in marmoset monkeys

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ABSTRACT

Social isolation is a major source of stress and can lead to activation of the hypothalamic-pituitary-adrenal (HPA) axis. The presence of a close social partner can reduce the magnitude of the HPA-axis response during a stressor, a phenomenon known as social buffering. The oxytocin (OXT) system has been identified as one candidate for mediating social buffering due to its role in the facilitation of social bonding and the expression of prosocial behavior. The goal of the present study was to determine whether the OXT system contributes to social buffering of HPA-axis activity in response to stressor exposure in marmoset monkeys (*Callithrix jacchus*). Male and female marmosets experienced a standardized psychogenic stressor with and without their long-term mate under OXT-treatments (Pro[8]-OXT, Leu[8]-OXT, OXT antagonist, and saline); we assessed HPA-axis activity by measuring urinary cortisol across the stressor. We found that blocking, but not augmenting, the OXT system altered patterns of cortisol and proximity behavior in response to a stressor. We demonstrated that (1) the presence of a mate during a stressor significantly attenuated HPA-axis activity in female, but not male, marmosets; (2) male, but not female, marmosets treated with an OXT antagonist had significantly higher HPA-axis activity across the stressor than when they were treated with saline, suggesting that the OXT system may reduce the stressor-induced rise in cortisol levels; (3) male and female marmosets treated with an OXT antagonist spent significantly less time in close proximity to their mate during the first 30 min of the stressor than when they were treated with saline, suggesting that the OXT system may be important for the expression of partner-seeking behavior during a stressor. Thus, the OXT system and social context differentially influenced how the HPA-axis responded to a stressor in male and female marmosets, and may modulate HPA-axis activity by promoting the expression of proximity behavior with a close social partner.

1. Introduction

Social disruption, isolation, and neglect are major sources of stress and can negatively impact health and well-being (McEwen, 2008), as well as contribute to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Smith and Wang, 2012). Long-lasting social relationships and positive social interactions can serve as resilience factors against stressors. These relationships, including the bonds between parents and offspring, peer friendships, and adult male–female bonds provide critical social resources that operate as protective mechanisms against environmental challenges, including predation, inter- and intra-group aggression, disease, as well as psychogenic stressors (Ditzen and Heinrichs, 2014). The social support originating from these close social partnerships can help mitigate the deleterious consequences of social stress through HPA-axis attenuation (Ditzen et al., 2008; Smith et al., 1998), a phenomenon known as social buffering (Cohen and Willis, 1985). Thus, the formation and preservation of long-lasting, social relationships may be an adaptive behavioral strategy for maintaining physiological and psychological well-being and reducing the detrimental health consequences of psychogenic stress.

While there are a number of biological pathways that contribute to the stress-buffering effect of social support (Hostinar et al., 2014), the oxytocin (OXT) system has been identified as a leading candidate for the regulation of social buffering due to its role in the facilitation of social bonding and the expression of prosocial behavior (Johnson and Young, 2015). The HPA-axis activity reducing, and anxiolytic properties of OXT have been identified in a variety of model species, including rodents, humans, and non-human

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primates (Neumann and Landgraf, 2012). For instance, OXT-deficient mice displayed more anxiety-like behavior and had higher corticosterone levels than wild-type mice following a psychogenic stressor (Amico et al., 2004). In socially monogamous New World primates, social isolation increased HPA-axis activity and anxiety-like behaviors (Fernandez-Duque et al., 1997; Rukstalis and French, 2005; Smith et al., 1998), and it appears that OXT treatment can reduce the magnitude of the physiological stress response. In particular, chronic intranasal OXT administration reduced circulating adrenocorticotropic hormone (ACTH) following 90 min of social isolation (Parker et al., 2005). In humans, central and peripheral OXT release during social support from a long-term partner following a stressor facilitated the attenuation of the HPA-axis and anxiety-like behavior (Grewen et al., 2005; Heinrichs et al., 2003). When OXT was administered intranasally during conflict in marital couples, positive communication between partners increased and circulating cortisol levels decreased (Ditzen et al., 2009), relative to individuals that received a placebo. Furthermore, positive couple interactions have a stress buffering effect on total daily cortisol secretion (Ditzen et al., 2008). Thus, the salubrious effects of social support occur in large part as a result of the positive social interactions among close social partners, and it appears that OXT maybe be a key anxiolytic agent and HPA-axis modulator during stressors.

Marmosets (*Callithrix jacchus*) are a highly social, cooperatively-breeding New World primate that readily form and maintain long-term, male–female relationships (Digby, 1995; Schaffner et al., 1995). Marmosets employ several long-term mating behaviors, including expressing high levels of sociality with a pair-mate (Schaffner et al., 1995), a pronounced stress response to social disruption (Rukstalis and French, 2005), aversion to an opposite-sex stranger in the presence of a pair-mate (Inglett et al., 1990), and aggressive responses to potential same-sex rivals (Ross et al., 2004). In marmosets, a single nucleotide substitution in the coding region of the *OXT* gene leads to a unique OXT ligand (Pro^8-OXT), with distinct structural and physicochemical properties from consensus mammalian OXT (Leu^8-OXT; Lee et al., 2011; Ren et al., 2015; Vargas-Pinilla et al., 2015). Furthermore, this ligand variation is associated with significant changes in the marmoset oxytocin receptor (OXTR; Ren et al., 2015) and social phenotype (Cavanaugh et al., 2015, 2014; Mustoe et al., 2015; Taylor and French, 2015).

Previous experimental work in marmosets has shown that the OXT system is involved in the expression of social behavior between pair-mates. Blocking endogenous OXT activity by administering an oral OXT antagonist (OXTA) significantly diminished sociality in newly-formed pairs (Smith et al., 2010). Additionally, administration of Pro^8-OXT, but not Leu^8-OXT, facilitated partner fidelity by reducing the time spent in close proximity with, and sociosexual behavior toward, an opposite-sex stranger (Cavanaugh et al., 2014), and reduced prosocial responses toward an opposite-sex stranger during an altruistic food-sharing task (Mustoe et al., 2015). However, we have also demonstrated that both the Pro^8 and Leu^8 variants of OXT influence social phenotype. Administration of Pro^8-OXT or Leu^8-OXT altered marmosets' stimulus properties in such a way as to enhance the social attractiveness of an OXT-treated individual during social interactions with their pair-mate (Cavanaugh et al., 2015). In a similar vein, intranasal administration of Leu^8-OXT subtly augmented sociality in newly formed marmoset pairs (Smith et al., 2010), and intracerebroventricular (icv) administration of Leu^8-OXT enhanced paternal tolerance for food sharing with offspring (Saito and Nakamura, 2011). Thus, the threshold for alteration of social behavior via OXT ligand administration may differ across measures of social behavior (i.e., offspring care, food sharing, partner preference, proximity, grooming). Furthermore, Pro^8-OXT and Leu^8-OXT likely produce differential binding affinity with the OXTR (Ren et al., 2015), and neural circuits underlying marmoset sociality may be differentially sensitive to the two forms of OXT. Thus, we sought to examine the influence of both Pro^8-OXT and Leu^8-OXT on social buffering in marmosets.

The current study examined the potential that the OXT system mediates the attenuation of the stress response from social support by measuring changes in HPA-axis activity, as well as affiliative and anxiety-like behavior, during stressor exposure in marmosets. If social relationships are an important mediator of social buffering, then excreted levels of cortisol and the expression of anxiety-like behavior should be reduced when an individual's pair-mate is present, relative to when an individual's pair-mate is absent, during a novel housing stressor. If the OXT system regulates these social buffering effects, then stressor-exposed marmosets treated with an OXTA should fail to display reductions in cortisol and anxiety-like behavior when their pair-mate is present, relative to when their pair-mate is absent. Treatment with an OXTA is also expected to reduce, while treatment with an OXT agonist is expected to enhance, measures of social behavior during a stressor when an individual's pair-mate is present. Furthermore, stressor-exposed marmosets treated with an OXT agonist should display reductions in cortisol and anxiety-like behavior regardless of whether their pair-mate is absent or present. If structural changes in the OXT ligand are biologically relevant, then marmosets treated with Pro^8-OXT, but not Leu^8-OXT, should display enhanced social behavior when their pair-mate is present and decreased cortisol secretion regardless of whether their pair-mate is absent or present.

2. Method

2.1. Subjects

Five adult male and five adult female white-tufted ear marmosets (*C. jacchus*), housed at the Callitrichid Research Center (CRC) at the University of Nebraska at Omaha, experienced a standardized novel housing stressor known to reliably elevate cortisol in adult marmosets (Rukstalis and French, 2005; Smith et al., 1998). Animals were 4.3 ± 0.2 (mean $\pm$ SEM) years of age at the start of the study, and had cohabitated with the same partner for 15 months in large indoor wire-mesh enclosures ($1.0 \times 2.5 \times 2.0$ m), equipped with a sleeping hammock, natural branches for climbing and various enrichment materials. Visual access was restricted between enclosures, but auditory and olfactory cues were not. Colony rooms at the CRC were maintained on a 12 h:12 h light:dark cycle and at a temperature range between 19 °C and 22 °C. For all dietary and husbandry protocols please refer to (Schaffner et al., 1995). The University of Nebraska at Omaha/University of Nebraska Medical Center Institutional Animal Care and Use Committee evaluated and approved all procedures: 12-099-12-FC.

2.2. Behavioral paradigm

Marmosets were exposed to a standardized novel housing stressor both with and without their long-term mate during four counterbalanced OXT-treatment conditions, over a series of eight treatment periods (2 contexts $\times$ 4 OXT-treatments). On the day of the stressor, the subject was removed from its home enclosure at 0830 h, administered an OXT-treatment, and transferred to a transport enclosure ($0.3 \times 0.3 \times 0.3$ m) located in a room some distance from the colony room that contained the pair's home enclosure. The marmoset was then transferred to a larger enclosure ($0.6 \times 0.6 \times 0.6$ m) at 0900 h and remained in this environment until 1600 h. Each member of a pair was treated separately during each treatment period, and treatments were administered in a counterbalanced order. Sequence of treatments within each individual was also counterbalanced. There was a 14–28 day washout period between drug treatments.