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Plasma oxytocin is related to lower cardiovascular and sympathetic reactivity to stress

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ABSTRACT

In addition to known reproductive and social affiliation functions, oxytocin (OT) has been identified as a cardiovascular hormone. OT synthesis and receptors are found in cardiac and vascular tissue. Animal studies suggest that OT activates an 'anti-stress' response that reduces cardiovascular and neuroendocrine stress reactivity. We tested 28 early postpartum mothers, obtaining multiple blood samples for OT, the sympathetic marker, norepinephrine (NE), and the lactation hormone, prolactin, while monitoring their cardiovascular responses to two stressors: public speaking and forehead cold pressor. Although plasma OT did not increase reliably from pre-stress levels during stressors, greater overall OT level was related to greater vasodilation and cardiac stroke volume responses to both tasks, to reduction in heart rate to the cold pressor, as well as to lower plasma NE and higher prolactin levels. In contrast, higher NE was linked to increases in heart rate and decreases in stroke volume. These data support a cardioprotective role for OT, which may influence the magnitude and hemodynamic determinants of cardiovascular stress responses.

1. Introduction

1.1. Oxytocin is a cardiovascular hormone

In the past decade substantial attention has been focused on the role of the neuropeptide, oxytocin (OT), in social behaviors. However, OT has also been identified as a cardiovascular hormone (Petersson, 2002). OT synthesis and receptors are reported in both cardiac and vascular tissue in non-human mammalian species (Gutkowska et al., 2000; Jankowski et al., 1998, 2000), and OT acts both centrally and peripherally at multiple sites including brainstem, heart, and vessels to exert acute and long-term inhibitory effects on cardiovascular activity (Meisenbert and Simmons, 1983; Nakamura et al., 2000; Petersson et al., 1996, 1997, 1999a,b; Sofroniew, 1983; Stock and Uvnas-Moberg, 1988; Thibonnier et al., 1999a,b). In animal models, daily peripheral administration of exogenous OT for 5 days leads to blood pressure (BP) decreases lasting 2 months or more (Holst et al., 2002; Petersson and Uvnas-Moberg, 2008). Similarly, OT administered *in vitro* reduces the rate and force of cardiac cells' intrinsic contractions causing them to 'beat' more slowly and contract less forcefully (Mukaddam-Daher et al., 2001). In humans, studies reporting on BP effects of chronic OT administration are lacking. However short term intravenous (IV) administration of OT to women to enhance uterine contractions or decrease blood loss during labor or caesarean delivery confirm its effect in decreasing blood pressure (Sartain et al., 2008; Simpson and Knox, 2009; Thomas et al., 2007). This hypotensive response to OT is due to decreases in total vascular resistance despite compensatory increases in heart rate, stroke volume and cardiac output. In fact, even though specific organs and tissues may show local vasoconstriction with OT administration, decreases in total vascular resistance and BP that are potentially life threatening can occur (Archer et al., 2008).

1.2. Oxytocin and social interactions both influence cardiovascular function

Social behaviors are related to both OT and cardiovascular activity, and OT may serve as an important physiological mediator of the cardioprotective benefit of social bonding (Knox and Uvnas-Moberg, 1998). Animal studies reveal that affiliative social interactions elicit increases in OT activity, which then activate and integrate an 'anti-stress' response that promotes bonding, relaxation and growth, while reducing cardiovascular and neuroendocrine stress responsivity (Callahan et al., 1989; Petersson and Uvnas-Moberg, 2007, 2008; Uvnas-Moberg, 1998; Uvnas-Moberg et al., 2001; Uvnas-Moberg and Petersson, 2004; Wsol et al., 2008). In rats, daily ventral stroking for 5 days is linked to long-lasting BP

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decreases very much like those induced by exogenous OT administration, and it is presumed that this effect is due to increases in endogenous OT activity (Holst et al., 2002). In female prairie voles, social isolation (considered a stressor), results in higher basal heart rate (HR) levels and decreased HR variability, and these effects are reversed with subcutaneous OT administration (Grippo et al., 2009). In humans, a number of studies have linked higher plasma OT to lower BP. We observed this in early postpartum mothers both on days when they had recent infant contact and when they did not, and in married women studied after 10 min of structured warm contact with their husbands (Grewen et al., 2005; Light et al., 2000, 2005a,b). In addition to lower BP in laboratory studies, higher OT responses to structured affectionate interaction with infants were associated with lower maternal 24-h ambulatory BP levels at home (Light et al., 2000, 2004). We also reported consistent inverse associations between plasma OT and the sympathetic biomarker, norepinephrine (NE), in women during rest and in response to pleasant partner contact (Grewen et al., 2005), but we have not measured these hormones simultaneously during stress. Similarly, a month-long intervention in couples, involving caring support through Rosen listening touch, a therapeutic method using light touch to communicate acceptance, empathy and caring and to sense subtle physical and emotional responses felt by another (Rosen, 2003), resulted in increases in salivary OT and decreases in the indirect sympathetic marker, salivary alpha-amylase, in both husbands and wives. In addition, in husbands but not wives, 24-h BP was also reduced. However, since the wives had lower BP prior to the intervention, this may have been due to a 'floor effect' (Holt-Lunstad et al., 2008).

1.3. Oxytocin may attenuate physiological response to stress

Although less studied than the OT-social affiliation links, findings from both animal and human studies suggest that plasma OT may reduce physiologic stress responses. OT knockout mice exhibit greater BP and corticosterone responses to acute and chronic stress (Bernatova et al., 2004; Michelini et al., 2003). In rats, blocking central OT with intracerebral infusion of OT antagonist enhances HR and BP responses to acute stress but does not effect resting levels (Wsol et al., 2008). Findings from human studies are mixed, however. This may be due to differences in the kinds of stressors used and/or in the subject populations being studied. Light et al. (2005a,b) reported that in postmenopausal women participating in a hormone replacement therapy (HRT) trial, greater treatment-induced increases in oxytocinergic activity (indexed by plasma levels of an OT precursor) were associated with greater post-treatment reductions in BP and vascular resistance reactivity to a battery of experimental stressors including speech, stroop and cold pressor tasks. More recently, Taylor et al. (2006) reported that although postmenopausal women self-selected for HRT had higher plasma OT compared with non-treated women, higher OT was not related to blood pressure or heart rate reactivity to the Trier Social Stress Test (TSST). Similarly, Altemus et al. (2001) reported that in postpartum lactating and non-lactating women and reproductive-aged control women, OT levels were not associated with blood pressure or heart rate reactivity to the TSST, but lactation was related to greater parasympathetic cardiac control.

2. The present study

In the current study we investigated how circulating OT may be related to cardiovascular and sympathetic nervous system responses to stress in women tested between 2 and 6 months postpartum. We measured BP and HR, as well as the hemodynamic determinants of BP, cardiac output and vascular resistance. Although prior studies have sometimes, but not always, shown relationships between OT and BP responses to stressors in postpartum women (Altemus et al., 2001), we are not aware of any prior study that has examined whether higher endogenous levels of plasma OT may be reliably associated with altered cardiac or vascular resistance responses to stress. Because both the heart and the vasculature have OT receptors (Gutkowska et al., 2000), decreases in BP associated with higher circulating OT may be related to either decreased vascular resistance, decreased cardiac rate and/or contractile force (as reflected in cardiac output and Heather index), or a combination thereof. We recruited 28 mothers of infants, and repeatedly obtained blood samples for OT while monitoring their cardiovascular responses to a stressful speech task followed by the forehead cold pressor test. Based on our prior research, we hypothesized that mothers who showed higher overall levels of plasma OT (reflecting higher overall oxytocinergic activity) would demonstrate lesser vasoconstriction response to one or both of these stressors, and lower levels of plasma norepinephrine, the primary sympathetic nervous system biomarker mediating increases in heart rate and alpha-adrenergic vasoconstriction. We also assessed another lactation hormone, serum prolactin, to serve as a validation of the OT measurement. We expected strong positive OT-prolactin correlations, since simultaneous OT and prolactin increases are necessary to accomplish lactation. Consistent with our previous mother–infant protocols, we measured maternal stress reactivity following a 10-min affectionate mother–infant interaction. Because of the pulsatile release of OT, and because of our interest in how hormone levels influence cardiovascular responses over time, Area Under the Curve (AUC) values were calculated for each of the three hormones measured: oxytocin (OT), norepinephrine (NE), and prolactin (PRL). Using this method, two values are created for each hormone: an unadjusted AUC measure (AUC_G = "AUC with respect to Ground"), and a measure adjusted for differences in baseline level (AUC_I = "AUC with respect to Increase"). AUC_I is described as a measure of reactivity, while AUC_G is described as an index of overall hormone activity across the protocol (Pruessner et al., 2003). Prior work has not addressed whether overall levels or reactivity to stressors are better indices of OT effects on cardiovascular function. Therefore, we examined both measures to better understand the cardiovascular-OT relationship.

3. Method

3.1. Participants

Twenty-eight healthy mothers were recruited from the community during the perinatal period for testing within the window of 2–6 months postpartum. Of these, 18 breastfed exclusively from birth, 5 formula-fed exclusively, and 5 endorsed combined breast and formula-feeding. Three subjects were cigarette smokers (2 exclusive formula, 1 exclusive breast). Exclusion criteria included self-report at telephone screening interview of prescription or nonprescription drug use, recent history of major depressive disorder and other psychological disorders, history of chronic disease in mother or infant, multiple birth, and low birth weight (less than 2500 g).

3.2. Protocol

All procedures were approved by the university institutional review board and all participants underwent informed consent before testing. Mothers were instrumented with cardiovascular electrodes for measurement of cardiovascular activity and an intravenous catheter was then inserted into an antecubital vein, with normal saline drip set at 0.25–1.00 drops s^{-1} to maintain lumen patency. The protocol consisted of the following events in fixed order: instrumentation, habituation (10 min), baseline rest (6 min), mother–infant interaction (10 min), speech task (7 min), forehead cold pressor (2.5 min), post-stress recovery (6 min). The first blood draw was done at least 1 h after the last infant feeding. Infants were present in the room for the entire protocol, cared for by a female research assistant. Mothers were allowed to direct care throughout, and to talk to and touch their infants *ad libitum* during segments when measurements were not being taken. On a separate day, mothers completed questionnaires at home including the Edinburgh Postnatal Depression