Oxytocin increases autonomic cardiac control: Moderation by loneliness

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Laboratories of G.G.B & A.C.D. contributed equally to work.

1. Introduction

Social behavior has a profound influence on health and well being. This is particularly apparent in the study of cardiovascular disease, for which social isolation and stress are risk factors comparable to smoking and obesity (House et al., 1988). Indeed, social isolation is associated with increased incidence and poorer prognosis among individuals with coronary heart disease (Orth-Gomer et al., 1993). Similarly, socially isolated mice sustain greater neuroinflammation and neuronal damage from experimentally controlled cardiac arrest as compared to socially paired cardiac arrest animals (Weil et al., 2008). Although the physiological mechanisms underlying social influences on cardiovascular health are not known, oxytocin (OT) has been implicated in the mediation of species-specific social behaviors in numerous vertebrate species, including humans, and identified as the upstream causal factor mediating the beneficial effects of social interaction on wound healing in hamsters (Detillion et al., 2004), atherosclerosis in mice (Szeto et al., 2008), depressive-like behavior associated with neuropathic pain (Norman et al., 2010b), and social isolation (Grippo et al., 2009) in mice and prairie voles, respectively. Identifying the mechanism through which social factors influence cardiovascular health has tremendous therapeutic potential; strong inference from existing literature suggests that OT could be one component of the mechanism.

OT is a nonapeptide hormone and neurotransmitter that is released during social interaction and contact (Grewen et al., 2005). Its receptors are widely distributed in regions of the brain associated with social interaction, emotional processing, and stress responsivity (Loup et al., 1991). Intranasal administration of OT to humans appears to modify various social processes. For example, OT decreases amygdala activation to threatening stimuli, increases trust, and promotes the encoding of positive social memories (Kosfeld et al., 2005; Guastella et al., 2009). OT administration also facilitates positive communication (Ditzen et al., 2009; Gouin et al., 2010), reduces psychological arousal to social threat (Norman et al., 2010a) and interacts with social support to decrease physiological stress reactivity (Heinrichs et al., 2003). Furthermore, specific human OT receptor gene polymorphisms have been associated with loneliness (Lucht et al., 2009), adult separation anxiety disorder (Costa et al., 2009), and empathy (Rodrigues et al., 2009).

Thus, despite enormous diversity in affiliative behaviors across...
participants provided written informed consent and received $100 compensation for infection, and current use of prescription medications. Prior to the study, participants or other chronic medical condition and were non-smokers. Further exclusion criteria were sensitivity to the effects of perceived social isolation in humans, which in turn can influence many aspects of health and well being. Here we test the effects of intranasal OT on in humans, which in turn can influence many aspects of health and well being. Here we test the effects of intranasal OT on in humans, which in turn can influence many aspects of health and well being. Here we test the effects of intranasal OT on.

2.1. Subjects

In addition to its well-described role in regulating social function, OT modulates autonomic nervous system activity by exerting direct effects on preganglionic sympathetic (Gilbey et al., 1982; Pardini et al., 1989) and parasympathetic neurons (Higa et al., 2002). OT also may impact autonomic control through its influence on more rostral neural structures (e.g., cingulate cortex, amygdala); many of which express OT receptors and are known to orchestrate complex autonomic response patterns (Tribollet et al., 1992).

High frequency heart rate variability (HF HRV) is an index of parasympathetic control of the heart (Bernston et al., 1997) and was used as such in the present study. Reduced HF HRV is predictive of not just cardiovascular disease, but of all-cause mortality in both high and low risk patient populations (Thayer et al., 2009). Furthermore, factors that decrease HRV are associated with compromised health, whereas factors that increase HRV are associated with improved overall health (Thayer and Lane, 2007). Social environment may be an important modulator of HRV as prolonged social isolation in female prairie voles results in a decrease in resting heart rate and a reduction in heart rate variability (Grippo et al., 2007), which can be reversed by chronic treatment with exogenous oxytocin (Grippo et al., 2009).

Social isolation also may influence sympathetic control of the heart. Indeed, socially isolated rodents display increased sympathetic cardiac control (Grippo et al., 2007) and increased sympathetic control is a primary mediator of the deleterious effects of chronic social stress on health outcome in primates (Manuck et al., 1988). Furthermore, high sympathetic cardiac control is a risk factor for cardiovascular disease and is associated with increased mortality among humans (Airaksinen, 1999). In the present study, we utilized the well validated (Sherwood et al., 1990) cardiothoracic impedance derived measure of pre-ejection period (PEP) as a metric of sympathetic cardiac control. Similar to the HRV data discussed above, decreased PEP (increased sympathetic drive) is associated with social-evaluative stress (Bernston et al., 1994) and is sensitive to the effects of perceived social isolation in humans (Cacioppo et al., 2002).

Together, the human and animal literature provide converging evidence to suggest that OT may be part of the mechanism through which social interaction influences autonomic processes in humans, which in turn can influence many aspects of health and well being. We test the effects of intranasal OT on well-validated measures of parasympathetic and sympathetic autonomic cardiac control in healthy, college-age participants. Furthermore, circulating levels of pro-inflammatory cytokines and stress hormones were analyzed in order to determine whether the effects of OT are specific to autonomic function. The specific hypotheses are that (1) exogenous OT will increase HF HRV and decrease PEP, and (2) that elevated levels of perceived social isolation will diminish the autonomic responses to intranasal OT.

2. Methods

2.1. Subjects

Forty participants (20 women and 20 men) were included in this study. An additional five participants were removed from the analysis due to incomplete data sets involving inability to clearly derive HF HRV, PEP and/or collect blood samples. Participants were scheduled for an initial screening visit to determine eligibility for the study. The participants disclosed no history of mental or psychiatric illness, or other chronic medical condition and were non-smokers. Further exclusion criteria included pregnancy, current menstruation, presence of an upper-respiratory infection, and current use of prescription medications. Prior to the study, participants provided written informed consent and received $100 compensation for participation in the study. Participants were required to fast for 5 h prior to the experimental session in order to limit the well described influences of eating and caffeine consumption on cardiovascular and neuroendocrine processes (James, 2004).

All individuals were provided with a meal immediately following the completion of their final visit to the clinical research center. Experimental sessions took place between 12 pm and 2 pm. The study protocol was approved by the Institutional Review Board of The Ohio State University. Within each sex, men and women were randomly assigned to either the OT or placebo group in a double blind manner.

2.2. Experimental design

Upon arriving at the experimental session, electrodes were placed for the measurement of the electrocardiogram (ECG) and impedance cardiogram. Participants then completed measures of depression (Beck Depression Inventory; BD; Beck et al., 1996), anxiety (Beck Anxiety Inventory; BAI; Beck et al., 1988), state anxiety (State Trait Anxiety Scale; Spielberger et al., 1970), loneliness (UCLA Loneliness Scale, Russell et al., 1980), positive and negative affect schedule (PANAS; Watson et al., 1988) and perceived social stress (Perceived Stress Scale: PSS-10; Cohen et al., 1983). After completing the instruments, an indwelling catheter was inserted into the antecubital vein for blood sampling. Administration of oxytocin was initiated and continued for the entire study. To obtain baseline autonomic nervous system (ANS) measures, the participants were asked to sit quietly for 10 min. A baseline blood sample and blood pressure recordings were manually taken immediately following the 10 min baseline period. Participants were then asked to administer the intranasal preparation (Pharmaceutical Technology, Monroe Spring, New York) containing either oxytocin (20 IU; n = 20) or the placebo (the vehicle n = 20). Autonomic data were recorded continuously and serum samples collected at 45 and 90 min post-intranasal administration via an indwelling catheter. During part of the post-administration period, participants were engaged in a computer task where they passively provided verbal responses mimicking a binary choice task (Bertelson et al., 1997). The electrocardiogram (all participants viewed the same set of pictures), and then they were provided with non-arousing reading material for the remainder of the period. Individuals completed the PANAS and state anxiety scale at the completion of the study (90 min following intranasal administration). The OT dosage used in this study is 4 IU lower than the dose used in other studies demonstrating significant effects of OT on psychological variables (Kosfeld et al., 2005; Guastella et al., 2009; Ditzen et al., 2009).

2.3. Autonomic measures

Cardiovascular measures of sympathetic and parasympathetic cardiac control, respectively, were derived from pre-ejection period (PEP) and high (respiratory) frequency (0.12–0.40Hz) heart rate variability (HF HRV). Data were scored minute-by-minute and then collapsed into 15 min epochs. PEP, derived from impedance cardiography, is the period between the electrical invasion of the ventricular myocardium (Q wave of the ECG) and the opening of the aortic valve. PEP depends on the time development of intraventricular pressure, it is widely used as an index of myocardial contractility. Because variations in contractility are largely under sympathetic control, PEP is used as a marker of myocardial contractility (Bernston et al., 1997). Lower PEP values represent higher levels of sympathetic cardiac control. PEP values are represented in milliseconds.

HF HRV is a rhythmic fluctuation of heart rate in the respiratory frequency band (respiratory sinus arrhythmia), and has been shown to be a relatively pure index of parasympathetic control (Bernston et al., 1997). The electrocardiogram (ECG) was obtained using the standard lead II configuration. The impedance cardiogram was obtained using the standard tetrapolar electrode system and procedures described elsewhere (Sherwood et al., 1990). The ECG and basal thoracic impedance (20) were measured using a Biowire system (Mindware, Gahanna, OH). Software (Mindware, Gahanna, OH) was used to analyze the ECG waveform to obtain derivation-impedance-derived measures (i.e., PEP). For each subject, ECG and impedance data were ensemble averaged for each minute to produce estimates of the PEF. HF HRV was derived by spectral analysis of the interbeat interval series derived from the ECG, following previously specified procedures (Bernston et al., 1997). The interbeat interval series was time sampled at 4 Hz (with interpolation) to yield an equal interval time series. This time series was detrended (second-order polynomial), end tapered, and submitted to a fast Fourier transformation. HF HRV spectral power was then integrated over the respiratory frequency band (0.12–0.40Hz). HF HRV is represented as the natural log of the heart period variance in the respiratory band (in ms²).

As previously described (Bernston et al., 2008), two metrics of autonomic control were derived from HF HRV and PEP, based on bipolar and bivariate models of autonomic space. A bipolar (parasympathetic to sympathetic) index of autonomic balance, cardiac autonomic balance, was derived as the difference between parasympathetic cardiac control and sympathetic cardiac control (CAB = HF HRVz − (PEPz)). A metric of overall cardiac autonomic regulation (CAR), compatible with a bivariate (sympathetic by parasympathetic) model of autonomic space, was derived as the sum of the normalized values of parasympathetic (HF HRV) and sympathetic (PEP) cardiac control (HF HRVz + (PEPz)). In order to equate the widely different metrics of HF HRV and PEP, we normalized HF HRV values by transforming each data point into a z-score by subtracting individual values from the overall population mean and then divided this value by the pooled standard deviation from the entire population. All participants displayed respiratory rates within the power band for the analysis of respiratory sinus arrhythmia (0.12–0.40Hz).
Blood pressure readings were obtained at the conclusion of the 10 min baseline period and then again at 90 min post-intranasal administration through the use of a mercury sphygmomanometer (PyMah Corporation, Flemington, NJ) by a trained experimenter.

2.4. Serum measures

Blood samples were collected from an indwelling catheter at baseline, and 45 min and 90 min after vehicle (placebo) or OT administration. The samples were quickly placed into a −70 °C freezer where they remained until analyzed. Cortisol levels were assayed using the Cortisol Coat-A-Count RIA (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Plasma catecholamine samples were frozen at −70 °C and assayed by HPLC with ElectroChemical Detection using Standards and Chromistry (alumina extraction) from Thermo-Alko (Beverly, MA). Plasma interleukin-6 (IL-6), CRP (C-reactive protein) and tumor necrosis factor alpha (TNFα) were assayed using Quantikine High Sensitivity Immunoassay kits (R&D Systems, Minneapolis, MN), per kit instructions. Samples were run undiluted in duplicate. All serum samples were analyzed within the same assay, run once the participant had completed the study. Cortisol, epinephrine and norepinephrine were measured to examine the effects of a single administration of OT on hypothalamic-pituitary-adrenal axis hormone levels over time (

These effects were characterized by significant linear (F(1,38) = 21.53, p < 0.01) and quadratic (F(1,38) = 5.44, p = 0.02) trends for the time contrast, associated with the overall increase and plateau in HF HRV, and a significant linear trend for the time by drug interaction (F(1,38) = 12.28, p < 0.01), reflecting the selective increase in the OT-treated group. Repeated measures ANOVA also revealed a significant decrease in PEP following oxytocin administration (Fig. 1b), reflecting an overall increase in sympathetically mediated myocardial contractility. This was manifest in a main effect of time (F(6,192) = 7.67, p < 0.01; \( \eta_2^p = 0.27 \)) characterized by a significant linear trend (F(6,192) = 17.64, p < 0.01) and a time by drug interaction (F(6,192) = 2.17, p = 0.04; \( \eta_2^p = 0.11 \)). Heart rate was similar for the OT and placebo treated groups (F(6,192) = 0.98, p = 0.59; Fig. 1c).

Because OT significantly increased HF HRV (an index of parasympathetic control) and decreased PEP (the inverse index of sympathetic control), the index of total cardiac autonomic regulation (CAR) also increased significantly (Fig. 2a). Repeated measures ANOVA revealed a significant time by drug interaction (F(6,192) = 2.79, p < 0.01; \( \eta_2^p = 0.13 \); Fig. 2a) characterized by a significant linear trend (F(6,192) = 5.51, p = 0.03). The latter reflected the increase in CAR after OT administration, in contrast to no changes within placebo-treated group. CAB, a model of reciprocal autonomic cardiac control, was not altered following OT or vehicle (placebo) administration (F(6,192) = 0.19, p = 0.98; Fig. 2b).

The effects of OT were most apparent between 45 and 70 min after administration, which is consistent with previous reports on the temporal dynamics of intranasal OT administration (Domes et al., 2007). Although the temporal pattern of OT concentration in the brain after nasal administration is not known, the cardiac autonomic response to OT we observe coincides with the reported peak cerebrospinal fluid levels of the structurally similar neuropeptide vasopressin when administered intranasally (Born et al., 2002). As displayed in Table 2, OT administration did not influence systolic (F(1,38) = 0.67, p = 0.41) or diastolic (F(1,38) = 0.91, p = 0.34) blood press-

Fig. 1. The influence of oxytocin on autonomic cardiac control. Intranasal oxytocin administration (20IU) significantly increased parasympathetic cardiac control as measured by high frequency heart rate variability (HF HRV; a) and increased sympathetic cardiac control, as measured by pre-ejection period (PEP; b) relative to placebo. OT had no influence on heart rate (c). All post-administration data points were subtracted from the baseline values. Therefore, positive values will represent an increase in value following administration relative to their baseline. Data are presented as mean change from baseline ± SEM.

In order to determine the effects of OT on autonomic functioning, baseline HF HRV (parasympathetic) and PEP (sympathetic) values were recorded for 10 min prior to intranasal administration of the placebo or OT. Analysis of baseline autonomic cardiac control measures revealed that the OT and placebo groups displayed equivalent basal levels of autonomic cardiac control (p > 0.05) as measured by PEP (placebo = mean = 110.94, SD = 7.56, oxytocin = 109.92, SD = 10.05) and HF HRV (placebo = mean = 6.87, SD = 1.01 vs. oxytocin = mean = 6.83, SD = 0.96). Participants treated with OT displayed a significant increase in HF HRV relative to baseline and the placebo group, which did not vary significantly across time (Fig. 1a). Repeated measures ANOVA revealed a significant time effect (F(6,192) = 5.89, p < 0.01; \( \eta_2^p = 0.44 \)) as well as a time by drug interaction (F(6,192) = 3.88, p < 0.01; \( \eta_2^p = 0.16 \)). These effects were characterized by significant linear (F(1,38) = 21.53, p < 0.01) and quadratic (F(1,38) = 5.44, p = 0.02) trends for the time contrast, associated with the overall increase and plateau in HF HRV, and a significant linear trend for the time by drug interaction (F(1,38) = 12.28, p < 0.01), reflecting the selective increase in the OT-treated group. Repeated measures ANOVA also revealed a significant decrease in PEP following oxytocin administration (Fig. 1b), reflecting an overall increase in sympathetically mediated myocardial contractility. This was manifest in a main effect of time (F(6,192) = 7.67, p < 0.01; \( \eta_2^p = 0.27 \)) characterized by a significant linear trend (F(6,192) = 17.64, p < 0.01) and a time by drug interaction (F(6,192) = 2.17, p = 0.04; \( \eta_2^p = 0.11 \)). Heart rate was similar for the OT and placebo treated groups (F(6,192) = 0.98, p = 0.59; Fig. 1c).

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Table 1

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Placebo Mean ± SD</th>
<th>Oxytocin Mean ± SD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%) female</td>
<td>55.00 ± 0.00</td>
<td>45.00 ± 0.00</td>
<td>0.28</td>
</tr>
<tr>
<td>Ethnicity (%) Caucasian</td>
<td>85.00 ± 0.00</td>
<td>80.00 ± 0.00</td>
<td>0.49</td>
</tr>
<tr>
<td>Married (%)</td>
<td>35.00 ± 0.00</td>
<td>30.00 ± 0.00</td>
<td>0.36</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.92 ± 1.02</td>
<td>13.16 ± 1.31</td>
<td>0.65</td>
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<tr>
<td>Annual income (in thousands of $)</td>
<td>21.53 ± 2.12</td>
<td>22.54 ± 1.92</td>
<td>0.73</td>
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<tr>
<td>BAI</td>
<td>3.34 ± 1.22</td>
<td>4.90 ± 1.15</td>
<td>0.35</td>
</tr>
<tr>
<td>PSS-10</td>
<td>10.81 ± 1.57</td>
<td>9.64 ± 1.31</td>
<td>0.57</td>
</tr>
<tr>
<td>UCLA</td>
<td>36.06 ± 2.10</td>
<td>36.82 ± 2.09</td>
<td>0.79</td>
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</table>
sure. Also, there was no effect of OT on state anxiety ($F_{1,19} = 1.35$, $p = 0.24$) or ratings PANAS ratings at 90 min following intranasal administration (PANAS; $F_{1,19} = 0.33$, $p = 0.58$).

3.2. Intranasal OT and serum cytokine, hormone and catecholamine concentrations

Blood samples were taken prior to drug administration and then 45 min and 90 min following intranasal administration of OT or the placebo to determine whether the effects of OT on autonomic nervous system functioning were associated with alterations in serum factors (see Table 2). The OT and placebo groups displayed comparable basal levels of cytokines, hormones and catecholamine levels ($p > 0.05$). A 2 (oxytocin vs. placebo) × 3 (baseline, 45 min post, 90 min post) ANOVA revealed that neither OT nor vehicle (placebo) administration altered serum concentrations of cortisol ($F_{2,76} = 0.58, p = 0.45$), ACTH ($F_{2,76} = 1.50, p = 0.23$), TNFα ($F_{2,76} = 1.55, p = 0.22$), CRP ($F_{2,76} = 2.03, p = 0.14$), IL-6 ($F_{2,76} = 0.03, p = 0.96$), epinephrine ($F_{2,76} = 1.33, p = 0.26$), norepinephrine ($F_{2,76} = 1.42, p = 0.25$) or dopamine ($F_{2,76} = 0.15, p = 0.86$). The OT and placebo groups did not differ in baseline autonomic or serum measures ($p > 0.05$). However, consistent with previous findings, baseline levels of circulating IL-6 were inversely related to HF HRV ($p < 0.05$). As predicted, the results showed that loneliness predicted significant changes in HF HRV for the oxytocin group ($b = -0.015, SE = 0.007, t_{19} = 2.26, p < 0.05$), but not for the placebo group ($b = 0.001, SE = 0.06, t_{19} = 0.49, p < 0.05$, Fig. 3a). Loneliness did not significantly predict PEP responses to OT ($b = 0.14, SE = 0.08, t_{19} = 1.75, p > 0.05$; Fig. 3b) or placebo ($b = -0.12, SE = 0.12, t_{19} = 1.02, p < 0.05$; Fig. 3b). However, this null findings may be the result of low power as the relationship approaches significance ($p = 0.10$) and the direction of the relationship is consistent with the findings described with HF HRV above (diminished sympathetic reactivity to OT among lonely individuals). Alternatively, the limited association between loneliness and PEP reactivity to OT may reflect a greater sensitivity of the parasympathetic system to the moderating effects of loneliness (Porges, 2001). Future studies with larger sample sizes will be necessary in order to better determine the potential relationship between sympathetic cardiac control, loneliness and oxytocin. As a result of the findings discussed above, CAR reactivity negatively associated with levels of loneliness ($p < 0.05$) within the OT group but not placebo group ($p > 0.05$). CAB was not related to loneliness within either OT or placebo groups ($p > 0.05$).

OT was not associated with baseline levels of depression, anxiety, social stress, or PANAS ratings ($p > 0.05$; Table 2). Furthermore, the effects of loneliness on HF HRV responses remained significant even after individually controlling for BAI, STAX, PANAS, BDI, BAI, STAX, UCLA, PANAS, PSS-10.

Table 2

The influence of intranasal OT on hormonal, inflammatory and psychosocial variables. OT had no effect on circulating cytokines, catecholamines or the HPA axis hormones cortisol and ACTH ($p > 0.05$). OT had no effect on measures of systolic or diastolic blood pressure ($p > 0.05$). Abbreviations: Adrenocorticotropin hormone (ACTH), C-reactive protein (CRP), Interleukin-6 (IL-6), tumor necrosis factor α (TNFα), systolic blood pressure (SBP), diastolic blood pressure (DBP), positive and negative affect schedule (PANAS). State-train anxiety inventory (STAI). Data are presented as mean ± SEM.

<table>
<thead>
<tr>
<th></th>
<th>Oxytocin (BSL)</th>
<th>Oxytocin (45 mm)</th>
<th>Oxytoan (90 mm)</th>
<th>Placebo (BSL)</th>
<th>Placebo (45 mm)</th>
<th>Placebo (90 mm)</th>
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<tr>
<td>Cortisol (ng/ml)</td>
<td>12.78 ± 1.5</td>
<td>10.71 ± 1.4</td>
<td>10.93 ± 1.2</td>
<td>11.62 ± 1.3</td>
<td>12.59 ± 1.5</td>
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<td>ACTH (pg/ml)</td>
<td>16.27 ± 1.9</td>
<td>15.34 ± 2.2</td>
<td>14.09 ± 1.5</td>
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<td>Epinephrine (pg/ml)</td>
<td>41.59 ± 7.6</td>
<td>44.48 ± 10.4</td>
<td>40.25 ± 7.5</td>
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<td>38.5 ± 6.1</td>
<td>33.35 ± 4.1</td>
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<td>Norepinephrine (pg/ml)</td>
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<td>345.54 ± 30.4</td>
<td>368.36 ± 38.3</td>
<td>414.22 ± 53.5</td>
<td>306 ± 22.8</td>
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<td>Dopamine (pg/ml)</td>
<td>21.41 ± 2.9</td>
<td>19.41 ± 2.4</td>
<td>20.36 ± 2.36</td>
<td>18.95 ± 1.8</td>
<td>18.35 ± 1.9</td>
<td>16.45 ± 1.5</td>
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<td>CRP (pg/ml)</td>
<td>1.75 ± 0.3</td>
<td>2.01 ± 0.6</td>
<td>1.83 ± 0.5</td>
<td>1.87 ± 0.6</td>
<td>2.11 ± 0.4</td>
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<td>IL-6 (pg/ml)</td>
<td>2.15 ± 0.3</td>
<td>1.89 ± 0.4</td>
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<td>1.97 ± 0.4</td>
<td>2.09 ± 0.5</td>
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<td>TNFα (pg/ml)</td>
<td>1.8 ± 0.3</td>
<td>1.91 ± 0.4</td>
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<td>SBP</td>
<td>117.23 ± 8.2</td>
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<td>DBP</td>
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<td>PANAS</td>
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<td>56.92 ± 2.2</td>
<td>55.81 ± 2.0</td>
<td>–</td>
<td>15.01 ± 2.3</td>
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Fig. 2. Bivariate and bipolar models of autonomic cardiac control following intranasal OT. Measures of overall cardiac autonomic regulation (CAR), a bivariate measure of sympathetic and parasympathetic co-activity, were significantly higher in the OT group as compared to placebo controls (a). Derived metrics of the reciprocal activation of sympathetic and parasympathetic branches revealed no significant effects of OT (b). Data are presented as mean change from baseline ± SEM.
Fig. 3. The moderational effect of loneliness on cardiac autonomic reactivity to OT. (a) Elevated levels of perceived social isolation are significantly predictive of the effect of OT on high frequency heart rate variability change scores with higher levels of social isolation associated with reduced sensitivity to intranasal OT. (b) Pre-ejection period was not significantly associated with levels of perceived social isolation. HF HRV and PEP are presented as mean change from baseline ± SEM. High vs. low loneliness is presented at 1 standard deviation (SD) above and below the population mean.

4. Discussion

Intranasal OT administration to healthy university aged participants produced significant increases in both sympathetic and parasympathetic autonomic cardiac control, as indexed by HF HRV and PEP, respectively. The effects of OT on HF HRV are similar to what has been reported for social interaction. Indeed, positive social functioning provides a buffer against the HF–HRV reducing effects of stress in women (Egizio et al., 2008). Likewise, socially paired prairie voles have higher HF–HRV than socially isolated voles at baseline and during stress (Grippo et al., 2009) and administration of exogenous OT to socially isolated animals was successful in increasing HF–HRV to a level that was indistinguishable from pair housed voles (Grippo et al., 2009).

The links among social behavior, OT, and autonomic cardiac control raise the possibility that OT may be part of the mechanistic process through which social behavior affects cardiovascular health. Diminished cardiac autonomic control is a risk factor for all-cause mortality and morbidity (Dekker et al., 1997; Thayer et al., 2009) and is associated with a myriad of disease states (Masi et al., 2007; Thayer et al., 2009). Indeed, concurrent activation of the parasympathetic branch, as indicated by the OT-induced increase in HF HRV, may mitigate the potentially deleterious effects of heightened sympathetic output (Thayer and Sternberg, 2006) by increasing autonomic flexibility or regulatory capacity, which could confer an adaptive advantage if it permits increased flexibility in responding to ever-changing physiological demands (Berntson et al., 2008; Thayer and Sternberg, 2006).

An important finding of the present study is that loneliness ratings negatively predict OT-associated changes in autonomic cardiac control independent of depression, anxiety and serum measures. Specifically, regression analysis revealed that individuals with elevated levels of loneliness were less responsive to the effects of OT on HF HRV and CAR. Consequently, loneliness may shift a potentially salubrious response (autonomic coactivation) to a deleterious state (selective sympathetic activation).

It is important to note the distinction between objective social isolation and loneliness. While the quantity of social connections is predictive of psychological and physiological processes in human and animals, it appears that subjective perception of such isolation also compromises health in humans (Patterson and Veenstra, 2010). Thus, although objective social isolation can be applied to both humans and animals, the inherently subjective nature of loneliness limits its applicability in animal models.

Loneliness is a complex psychosocial phenomenon that incorporates feelings of dysphoria and dissatisfaction with social support and can increase the motivation to repair and maintain social connections (Cacioppo and Patrick, 2008). Furthermore, lonely individuals display altered brain activity patterns when processing social information as compared to non-lonely individuals (Cacioppo et al., 2009). In light of the relationship between naturally occurring polymorphisms in the OT receptor gene and loneliness (Lucht et al., 2009), it would be interesting to know whether these polymorphisms are functionally significant, and may underlie, in part, the observed relationship between loneliness and reduced sensitivity to exogenous OT. Alternatively, or additionally, environmental factors may influence OT responsiveness. Early life-threatening experiences modify the OT response to social stress (Meinschmidt and Heim, 2007), raising the possibility that prior experiences may shape the autonomic response to OT as well. Thus, alterations in social variables, such as loneliness, may reflect or contribute to altered central activity within the OT system, which in turn may have important health implications because of the broad influences of social behavior on health.

OT administration had no acute effects on circulating cytokine, hormone or catecholamine levels in the current study. Although there is some evidence supporting inhibitory effects of OT on inflammation (Clodi et al., 2008) and cortisol (Heinrichs et al., 2003), these studies were conducted within the context of immune stimulation (endotoxin administration) or stress reactivity whereas the present study took place during relatively basal conditions. Previous studies have reported no influence of OT on basal cortisol concentrations in humans (Clodi et al., 2008) suggesting that OT influences the physiological reactivity to neuroendocrine or immune challenges without significantly altering baseline levels of hormone or cytokine levels in the short term.

Additionally, no sex differences were detected in the present study, which is consistent with previous data collected in men and women (Ditzen et al., 2009; Theodoridou et al., 2009). Thus, intranasal OT selectively increases autonomic cardiac control (increased sympathetic and increased parasympathetic output) without immediately influencing serum adrenal hormones or inflammatory factors. Also, because OT enhanced activity of both autonomic branches, these functional autonomic changes were not manifest in alterations of heart rate. They were also not apparent from the vantage of a reciprocal model of cardiac autonomic control (CAB). The absence of effects on heart rate and CAB highlights the importance of an appropriate measurement model that can capture the independent activities of the autonomic branches.

While the present study cannot rule out the potential influence of peripheral OT receptors, the finding that OT responses are associated with perceived levels of social isolation, coupled with previous work on the psychological effects of intranasal OT, suggest a more central mechanism. Indeed, peptide hormones, when administered
intranasally, accumulate in the cerebrospinal fluid (Born et al., 2002). Additionally, rodent studies indicate that likely central sites of action would be the preganglionic sympathetic neurons (Gilbey et al., 1982; Pardini et al., 1989) and the parasympathetic neurons of the dorsal motor nucleus of the vagus (Higa et al., 2002). However, OT also may impact autonomic control through the activation of limbic structures, such as the amygdala and hypothalamus, which contain OT receptors and are known to modify autonomic output (Huber et al., 2005). Interestingly, OT receptor expression is known to vary widely across various social mammals, including humans which may result in distinct species-specific physiological responses to OT both within and between species (Carter et al., 2008). Future studies will be necessary in order to examine the potential role that differential OT receptor expression within distinct neurological substrates may play in the autonomic responses to intranasal OT in humans. Additional studies are necessary in order to determine whether the effects of OT on ANS activity are generalizable across distinct end organ responses (e.g., skin conductance) or isolated to cardiac output.

In summary, administration of intranasal OT to healthy, young adults increases HF-HRV and decreases PEP, thereby increasing overall autonomic cardiac control without altering circulating levels of pro-inflammatory cytokines or stress hormones. However, the magnitude of the effect of OT on HF-HRV and CAR is reduced among lonely individuals. Thus, loneliness may transform the potentially salubrious effects of OT associated with coactivation of autonomic branches to negative effects associated with selective sympathetic activation; a pattern previously thought to contribute to health (Thayer and Lane, 2007; Mancia et al., 2007). However, future studies will be necessary in order to determine the potential relevance of the differential effects of oxytocin on ANS reactivity and health. Together, these data provide further evidence highlighting the link between social processes and physiological responsiveness to OT, and support for the hypothesis that OT may be part of the physiological mechanism through which social factors influence cardiovascular health.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.biopsycho.2010.11.006.

References


