Biological Psychology 86 (2011) 174–180

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Oxytocin increases autonomic cardiac control: Moderation by loneliness

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ARTICLE INFO

Article history:
Received 19 May 2010
Accepted 23 November 2010
Available online 30 November 2010

Keywords:
Oxytocin
Loneliness
Autonomic
Cytokines
Cortisol

ABSTRACT

The current study examined the role of perceived social isolation in moderating the effects of oxytocin on cardiac autonomic control in humans. Intranasal administration of 20 IU oxytocin resulted in a significant increase in autonomic (parasympathetic and sympathetic) cardiac control. Specifically, oxytocin increased high frequency heart rate variability, a relatively pure measure of parasympathetic cardiac control, and decreased pre-ejection period, a well-validated marker of enhanced sympathetic cardiac control. Derived metrics of autonomic co-activity and reciprocity revealed that oxytocin significantly increased overall autonomic cardiac control. Furthermore, the effects of oxytocin on cardiac autonomic control were significantly associated with loneliness ratings. Higher levels of loneliness were associated with diminished parasympathetic cardiac reactivity to intranasal oxytocin. The effects of OT on autonomic cardiac control were independent of any effects on circulating pro-inflammatory cytokine or stress hormone levels. Thus, lonely individuals may be less responsive to the salubrious effects of oxytocin on cardiovascular responsivity.

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

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doi:10.1016/j.biopsycho.2010.11.006

vertebrate taxa, a well-conserved role for OT and its homologues in modulating physiology and behavior among highly social species is apparent.

In addition to its well-described role in regulating social processes, 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 (Berntson 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 an increase 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 (Berntson 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. Here 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 (1) that 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 to 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; BDI; 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, and ECG and impedance data collection 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 (Pharmacy Specialist, Altamonte Springs, FL) 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 valance ratings of picture stimuli as part of an unrelated study (all participants viewed the same set of pictures), and then they were provided with non-arousing reading material for the remained 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 (0.12–0.40 Hz) 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 commonly used as a noninvasive measure of sympathetic cardiac control (Berntson 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 (Berntson 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 (Z0) were measured using a Bionex system (Mindware, Gahanna, OH). Software (Mindware, Gahanna, OH) was used to analyze the dZ/dt waveforms to obtain impedance-derived measures (i.e., PEP). For each subject, ECG and impedance data were ensemble averaged for each minute to produce estimates of the PEP. HF HRV was derived by spectral analysis of the interbeat interval series derived from the ECG, following previously specified procedures (Berntson 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 (0.12–0.40 Hz). HF HRV is represented as the natural log of the heart period variance in the respiratory band (in ms^2).

As previously described (Berntson 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 normalized values of parasympathetic cardiac control and sympathetic cardiac control (CAB = HF HRV$z - (-$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 HRV$z + (-$PEPz)). In order to equate the widely different metrics of PEP and HRV, we normalized PEP and 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 respiration rates within the power band for the analysis of respiratory sinus arrhythmia (0.12–0.40 Hz).