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Boosting recovery rather than buffering reactivity: Higher stress-induced oxytocin secretion is associated with increased cortisol reactivity and faster vagal recovery after acute psychosocial stress

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ABSTRACT

Animal models and human studies using paradigms designed to stimulate endogenous oxytocin release suggest a stress-buffering role of oxytocin. We here examined the involvement of stress-induced peripheral oxytocin secretion in reactivity and recovery phases of the human psychosocial stress response. Healthy male and female participants ($N = 114$) were subjected to a standardized laboratory stressor, the Trier Social Stress Test. In addition to plasma oxytocin, cortisol was assessed as a marker of hypothalamic-pituitary-adrenal (HPA-) axis activity, alpha-amylase and heart rate as markers of sympathetic activity, high frequency heart rate variability as a marker of vagal tone and self-rated anxiety as an indicator of subjective stress experience. On average, oxytocin levels increased by 51% following psychosocial stress. The stress-induced oxytocin secretion, however, did not reduce stress reactivity. To the contrary, higher oxytocin secretion was associated with greater cortisol reactivity and peak cortisol levels in both sexes. In the second phase of the stress response the opposite pattern was observed, with higher oxytocin secretion associated with faster vagal recovery. We suggest that after an early stage of oxytocin and HPA-axis co-activation, the stress-reducing action of oxytocin unfolds. Due to the time lag it manifests as a recovery-boosting rather than a reactivity-buffering effect. By reinforcing parasympathetic autonomic activity, specifically during stress recovery, oxytocin may provide an important protective function against the health-compromising effects of sustained stress.

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1. Introduction

The neuropeptide oxytocin is best known as a modulator of social behavior (Lee et al., 2009; McCall and Singer, 2012; Meyer-Lindenberg et al., 2011; Neumann and Landgraf, 2012). As such, it plays a critical role in social cognition, affect (McCall and Singer, 2012; Winslow and Insel, 2004), attachment and pair bonding (Insel and Young, 2001). Above and beyond its role as a social hormone, oxytocin is hypothesized to act as a stress buffer in the mammalian stress response, including humans (Engelmann et al., 2004; Heinrichs et al., 2009; Neumann, 2002).

Oxytocin is primarily synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei (PVN, SON) of the hypothalamus (Gimpl and Fahrenholz, 2001). The bulk of the neuropeptide is transported to the posterior pituitary where it is released into the systemic blood stream. Lesser amounts are released into the central nervous system and act as neuromodulator via widely distributed pathways (Gimpl and Fahrenholz, 2001). The animal literature describes two approaches to the study of oxytocin-stress interactions. Stimulation studies inform about whether relatively increased central oxytocin release after lactation or central oxytocin administration reduces the magnitude of acute stress responses. Alternatively, investigating the effect of stress induction on oxytocin release can demonstrate whether the organism makes use of this buffering mechanism in naturalistic conditions, i.e., when exposed to acute stress. Both approaches to studying oxytocin-stress interactions are well established in animal research (Engelmann et al., 2004; Neumann, 2002; Neumann and Landgraf, 2012).

In humans, the measurement of neuropeptides in the cerebrospinal fluid is highly invasive and not feasible in experimental research. As a result, central oxytocin effects are typically studied

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in breastfeeding women with elevated endogenous oxytocin levels or after intranasal oxytocin administration, believed to provide a direct pathway to the brain (Macdonald and Macdonald, 2010; Neumann et al., 2013). The most frequent outcome of these stimulation studies has been blunted hypothalamic-pituitary-adrenal (HPA-) axis reactivity as measured by reduced cortisol secretion following acute psychosocial (Ditzen et al., 2009; Heinrichs et al., 2003, 2001; Quirin et al., 2011) or exercise stress (Altemus et al., 1995; Cardoso et al., 2013). Additional buffering effects on subjective-psychological (de Oliveira et al., 2012; Heinrichs et al., 2003) and sympathetic reactivity (Light et al., 2000) following psychosocial stress have been established. One study examining oxytocin-autonomic stress interactions (Kubzansky et al., 2012) found that vagal rebound (a sharp increase in heart rate variability during early recovery; Arai et al., 1989; Mezzacappa et al., 2001), was faster in oxytocin- compared to placebo-treated participants. While gonadal steroids influence oxytocin synthesis (Patisaul et al., 2003) and the expression of oxytocin receptors (Richard and Zingg, 1990), the stress-buffering effects of central oxytocin have been found in both men (Cardoso et al., 2013; Ditzen et al., 2009; Heinrichs et al., 2003; Quirin et al., 2011) and women (Altemus et al., 1995; Ditzen et al., 2009; Heinrichs et al., 2001; Light et al., 2000). Surprisingly, only a few studies indicate the presence of sex differences in the stress-induced autonomic, emotional and behavioral effects of intranasal oxytocin (Ditzen et al., 2013; Kubzansky et al., 2012). In perhaps the most striking example, men and women show opposite amygdala responses to emotional stimuli following intranasal oxytocin administration (Domes et al., 2007, 2010).

The literature is much less conclusive on whether acute stress influences peripheral (e.g. plasma or saliva) oxytocin levels in humans. Several studies found no evidence for stress-induced oxytocin secretion in women with different hormonal status (Altemus et al., 2001; Cyranowski et al., 2008; Heinrichs et al., 2001; Taylor et al., 2006). Others have shown significantly increased oxytocin responses to uncontrollable noise stress (in high emotionality women; Sanders et al., 1990), oral administration of hydrocortisone (in healthy women; Tops et al., 2007) and psychosocial stress (in both sexes; Jong et al., 2015; Pierrehumbert et al., 2010). However, stress-induced oxytocin secretion in these studies was not accompanied by decreased cortisol reactivity, a hallmark of the human stress response. This lack of association between peripheral oxytocin and cortisol stress responses may originate from the substantially different temporal dynamics of peripheral secretion and central release of oxytocin (Neumann and Landgraf, 2012). In sum, while the current evidence speaks for the general involvement of peripheral oxytocin in the human stress response, its stress-buffering role remains unconfirmed.

To close this gap, we examined the involvement of stress-induced peripheral oxytocin secretion into the blood during reactivity and recovery phases of the human psychosocial stress response. The recovery phase, providing information about the degree to which reactivity persists after stressor termination, is often neglected in stress research (Linden et al., 1997). Yet, as indicated by the work of Kubzansky et al. (2012), assessing recovery may be critical to revealing the stress-reducing properties of oxytocin. Participants were subjected to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a psychosocial laboratory stressor. Using a multi-method approach, self-rated state anxiety as an indicator of subjective stress experience, cortisol as a marker of HPA-axis activity, alpha-amylase and heart rate as markers of sympathetic activity, and the high frequency band of heart rate variability (HF-HRV) as a marker of parasympathetic activity were assessed. While a decrease in HF-HRV during a stressful task indicates sympathetic dominance to autonomic activity, the vagus nerve re-establishes control and increases HF-HRV after stressor termination.

We expected an increase in plasma oxytocin levels after stress induction. Based on the summarized animal literature and human stimulation studies, we further expected to find reduced cortisol, sympathetic and subjective-psychological stress reactivity with higher stress-induced oxytocin secretion. Considering Kubzansky et al.'s (2012) finding of faster vagal rebound after intranasal oxytocin relative to placebo administration, we also assessed whether higher stress-induced oxytocin levels were linked to faster post-stress recovery of HF-HRV. Lastly, assuming an influence of gonadal steroids on the oxytocin system (Gimpl and Fahrenholz, 2001; Patisaul et al., 2003; Richard and Zingg, 1990), we expected the secretion and stress-reducing action of oxytocin to be dependent on the participants' sex and estrogen status (i.e. stronger in women than men, and strongest in high-estrogen women).

2. Materials and methods

2.1. Participants

Participants were a subsample ($N = 114$; 65 women; age mean ± SD: 40.18 ± 8.73 years; age range 22–55 years) of a group of 130 participants subjected to the TSST at the baseline measurement time point of the *ReSource Project* (Singer et al., 2016). The *ReSource Project* is a longitudinal mental training study conducted at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig and Berlin. Sixteen participants of the original group did not provide blood samples for oxytocin assessment and were therefore excluded from the current analysis. All volunteers underwent a comprehensive face-to-face mental health diagnostic interview with a trained clinical psychologist. The interview included a computer-assisted German version of the Structured Clinical Interview for DSM-IV Axis-I disorders, the SCID-I DIA-X (Wittchen and Pfister, 1997), and a personal interview for Axis-II disorders, the SCID-II (First et al., 1997; Wittchen et al., 1997). Volunteers were excluded if they fulfilled criteria for an Axis-I disorder within the past two years, or for schizophrenia, psychotic disorder, bipolar disorder, substance dependency or an Axis-II disorder at any time in their life. Volunteers taking medication influencing the HPA-axis were also excluded. Details of the multistep recruitment procedure, inclusion/exclusion criteria and the final sample description of the *ReSource Project* can be found in Singer et al. (2016). At the testing time point reported here, all participants were training-naïve. Female hormonal status was assessed via self-report on the testing day. Twenty women had no menstrual cycle due to menopause or polycystic ovary syndrome, 15 had a natural cycle and were in their luteal cycle phase, 16 had a natural cycle and were in their follicular cycle phase and 14 took hormonal contraceptives (10 ethinylestradiol-containing, 4 estrogen-free products). The *ReSource Project* was registered with the Protocol Registration System of ClinicalTrial.gov under the title "Plasticity of the Compassionate Brain" (Identifier NCT01833104). It was approved by the Research Ethics Boards of Leipzig University (ethic number: 376/12-ff) and Humboldt University Berlin (ethic numbers: 2013-20, 2013-29, 2014-10). Participants gave their written informed consent, could withdraw from the study at any time and were financially compensated.

2.2. Experimental design and procedure

Since cortisol secretion is characterized by a strong circadian rhythm (Dallman et al., 2000), testing was performed between 12 pm and 6 pm in one 130-min session. To adjust blood sugar levels, participants had a standardized snack upon arrival. Throughout testing, they refrained from taking anything by mouth except water. Fifteen minutes after arrival, a baseline questionnaire

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