Hormones and Behavior 105 (2018) 157–165

Contents lists available at ScienceDirect

Hormones and Behavior

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

Adolescent oxytocin response to stress and its behavioral and endocrine correlates

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ARTICLE INFO

Keywords:
Salivary oxytocin
Salivary cortisol
Adolescents
TSST
Control-TSST

ABSTRACT

Oxytocin (OXT) shows anxiolytic and stress-reducing effects, but salivary OXT response to laboratory-induced stress has only been assessed in one study in healthy adults. The present study aimed at extending these findings by assessing salivary OXT stress reactivity in healthy adolescents (aged 11–18) compared to a control condition. A higher salivary OXT response to stress compared to the control condition was expected. In addition, the association between OXT, cortisol (CORT) and psychological reactivity patterns was explored. Psychosocial stress was induced using the Trier Social Stress Test (TSST; 13 males, 15 females), while the Control-TSST (14 males, 15 females) served as a non-stress control condition. Salivary OXT increased in response to the TSST with a peak at +1 and decline at +10 min after stress. Baseline OXT correlated negatively with experienced anxiety and insecurity, while both correlated positively with OXT reactivity. OXT and CORT increase as well as OXT increase and CORT recovery were positively correlated. Results indicate that salivary OXT in response to the TSST is a valid method to assess biological effects of laboratory-induced stress also in adolescents. Due to a rapid increase and decline, salivary OXT needs to be assessed directly after stress exposure. Given the interplay of OXT with affective symptoms and CORT response, the combined measure of salivary OXT and CORT reactivity adds to studying stress reactivity in typically developing and clinical samples.

1. Introduction

The neuropeptide oxytocin (OXT) has become very popular in neuroendocrinological research over the last decades not only due to its influence on sexual, maternal and social behavior, but also because of its assumed stress-protective and anxiolytic effects (for reviews see Churchland and Winkielman, 2012; Jurek and Neumann, 2018; Lee et al., 2009; Neumann and Landgraf, 2012). Moreover, alterations of the OXT system have been found in mental disorders characterized by social dysfunctions, such as social anxiety, depression, autism spectrum disorder and conduct disorder (Cochran et al., 2013; Dadds et al., 2014; Netherton and Schatte, 2011; Neumann and Slattery, 2016). As many mental disorders associated with OXT impairments develop in childhood or adolescence, it is important to investigate the OXT system in this age group.

OXT is released from the neurohypophysis into blood, where it reaches various peripheral organs (e.g. uterus, placenta) expressing the OXT receptor. It is also released from centrally projecting OXT neurons within the hypothalamic and other limbic regions of the brain (for reviews see Churchland and Winkielman, 2012; Landgraf and Neumann, 2004; Meyer-Lindenberg et al., 2011). OXT concentrations can be quantified in plasma, urine or saliva, but also in cerebrospinal fluid (CSF), reflecting the activity of the peripheral and central OXT system, respectively (for details see de Jong et al., 2015). Of these, salivary OXT assessment has been established as a non-invasive method not requiring medical care, which allows for repeated testing in both laboratory and naturalistic settings, especially with vulnerable populations (e.g. children, adolescents, clinical samples). Despite initial skepticism (Horvat-Gordon et al., 2005) and limitations (McCullough et al., 2013) of salivary OXT assessments, reliable salivary OXT levels have been repeatedly reported (Carter et al., 2007; de Jong et al., 2015; Lebowitz et al., 2016; Lipschitz et al., 2015; White-Traut et al., 2009). Salivary OXT concentrations were found to be correlated with plasma OXT levels (Feldman et al., 2010; Grewen et al., 2010), while plasma OXT did

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https://doi.org/10.1016/j.yhbeh.2018.08.010
Received 10 November 2017; Received in revised form 20 August 2018; Accepted 24 August 2018

not correlate with CSF OXT levels (Kagerbauer et al., 2013). However, a recent study reported a significant correlation between plasma and CSF OXT levels (Martin et al., 2018). Remarkably, they found a stronger correlation between salivary OXT and CSF, suggesting salivary OXT as a helpful approach to assess CSF OXT concentrations in humans. While OXT measured in saliva still mainly reflects peripheral OXT release, most physiological and psychosocial stimuli triggering OXT release into blood also stimulate central OXT secretion in selected brain regions (Jurek and Neumann, 2018; Neumann and Landgraf, 2012). Substantial increase in salivary OXT is also induced by intranasal administered OXT crossing the blood-brain barrier and reaching the central nervous system (Born et al., 2002; Daughters et al., 2015; Weisman et al., 2012). Thus, previous research assumed a coordination of peripheral and central OXT release (Carter et al., 2007; Martin et al., 2018; Ross and Young, 2009; Weisman et al., 2012) suggesting salivary OXT as a valid OXT measure.

Most studies, especially in clinical samples, have focused on the effect of exogeneous OXT, such as through intranasal administration. Only a minority of human studies assessed the activity of the body's OXT system (mainly by single, basal OXT measurements in plasma or saliva), and few studies examined endogenous OXT in response to defined stimuli (Neumann and Slattery, 2016). Recent meta-analyses indicate associations between OXT and hypothalamic-pituitary-adrenal-axis (HPA-axis) functioning. OXT administration attenuated cortisol (CORT) response to laboratory tasks with more robust effects in clinical populations suggesting an important role of OXT for HPA-axis dysfunction related with psychopathology (Cardoso et al., 2014). Further, in participants anticipating a challenging experimental task a positive correlation of baseline OXT and CORT emerged (Brown et al., 2016). The relation between endogenous OXT and CORT has rarely been studied under stress conditions. In rodents, endogenous OXT has repeatedly been shown to be released in response to stress (Lang et al., 1983; Neumann et al., 2000; Onaka, 2004; Torner et al., 2017). In humans, examining OXT response to experimentally induced stress could provide a more valid approach to explore its role in stress regulation than via basal measurements. To study socially induced stress, the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) has been widely used as a valid and reliable method of assessing stress reactivity in a controlled laboratory setting, as indicated by psychological ratings and increases in CORT levels (Allen et al., 2014; Frisch et al., 2015). Surprisingly, few studies in adult humans examined endogenous OXT under laboratory stress conditions. One study reported no changes in plasma OXT in response to the TSST (Taylor et al., 2006), while three recent studies (two in plasma, one in saliva) showed a significant OXT increase with a peak at one minute (min) and a decline to baseline levels 20 min post stress in men and women (de Jong et al., 2015; Engert et al., 2016; Pierrehumbert et al., 2010). With an earlier peak increase compared to CORT, neurohypophysial OXT release was suggested to precede CORT release from the adrenal gland. Release patterns of OXT and CORT under stress seem to be co-activated. De Jong et al. (2015) described a positive correlation between both basal and peak salivary OXT with peak salivary CORT in women, while Engert et al. (2016) reported a positive association of plasma OXT secretion with CORT reactivity and peak CORT levels in both sexes. Furthermore, Engert et al. (2016) reported a negative correlation of OXT secretion and vagal recovery after stress exposure. Taking these results together, it was suggested that the stress-reducing effect of OXT appears as a “recovery-boosting” rather than a “reactivity-buffering” effect. However, despite the limited TSST studies focusing on recovery effects, they provide important information about healthy stress adaption (Engert et al., 2016; Linden et al., 1997). Of note, stress reactivity and recovery have rarely been studied together.

To date, there is a lack of studies assessing endogenous OXT in response to stress in child or adolescent samples. Given that OXT response may show an influence on CORT response to stress via its anxiolytic effects, and given the major role of social stress in adolescence increasing the risk for developing a psychiatric disorders (e.g. social anxiety, depression; Johnson et al., 2012; Monroe and Harkness, 2005; Rapee and Spence, 2004), there is a need for empirically validated and biologically plausible methods of social stress research in adolescents. Applying salivary measures to assess OXT levels repeatedly under stress is an easy and convenient method especially for use in vulnerable populations such as adolescents. However, it is not known whether saliva samples are sensitive enough to measure changes in OXT levels from adolescents' stress responses. If a salivary OXT reactivity to stress can be shown in healthy adolescents, this would support future work investigating possible dysfunction of the OXT system of adolescent clinical populations when under stress.

Taken together, two aspects of the salivary OXT response to social stress remain unsolved. Can the findings by de Jong et al. (2015) be replicated in adolescents? And, do salivary OXT and CORT reactivity and recovery along with psychological outcome measures in response to stress in adolescents correlate, and if so, how is this relationship best described? Therefore, this study aims to monitor changes in salivary OXT concentration in response to acute psychosocial stress in male and female healthy adolescents in a standardized laboratory setting using an experimental design with two groups (TSST, Control-TSST) to control for the influence of confounding factors. Additionally, CORT levels will be assessed in the TSST group to investigate their association with OXT and psychological measures under stress. First, a significant group × time interaction effect of OXT is expected indicating a higher salivary OXT response to stress in the TSST compared to the Control-TSST group. Second, exploratory analyses assessed the relationship between psychological as well as OXT and CORT reactivity and recovery in the TSST group.

2. Material and methods

2.1. Inclusion criteria

Fifty-seven healthy adolescents, aged 11 to 18 years, were recruited from the local community of Frankfurt am Main. All participants and their parents provided informed consent prior to taking part in the experiment. Ethical approval was obtained by the University Hospital Frankfurt am Main's Ethics Committee before the start of the study. Participants received 35 € re-imbursement. Exclusion criteria were IQ < 70, pre-pubertal status, known genetic syndrome / disorder, epilepsy, any other chronic neurological disorder, history of traumatic brain injury, history of DSM-IV TR autism spectrum disorder, schizophrenia, bipolar disorder, mania, disruptive behavior or attention deficit/hyperactivity disorder, and any current psychiatric disorder according to DSM-IV TR criteria. Current and history of psychiatric disorders of the participant were assessed using the summary of two semi-structured diagnostic interviews conducted separately with the participant and a parent (K-SADS-PL; Kaufman et al., 1997). IQ was estimated from the matrix reasoning and vocabulary subtests of the Wechsler Intelligence Test (German version; 11–16 years: Petermann and Petermann, 2011; > 16 years: Von Aster et al., 2006). Pubertal status was assessed via self-report using the Pubertal Development Scale (Petersen et al., 1988) to assure at least early-pubertal status. Educational status of parents was assessed as the mean of the highest maternal and paternal self-reported school or occupational degree following ISCED criteria (0 = pre-primary level of education, 1 = primary level of education, 2 = lower secondary level of education, 3 = upper secondary level of education, 4 = post-secondary level of education, 5 = first stage of tertiary education, 6 = second stage of tertiary education; Organisation for Economic Co-operation and Development, 1999).

2.2. Procedure

Participants were assigned to either the TSST group (n = 15