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Oxytocin secretion is pulsatile in men and is related to social-emotional functioning

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ABSTRACT

The hypothalamic hormone oxytocin (OXT) plays an important role in a range of physiological processes and social-emotional functioning in both sexes. In women, physiological stimuli, such as suckling and parturition, result in pulsatile release of OXT into the peripheral circulation via the posterior pituitary gland. However, data regarding OXT secretory patterns in men during a state of rest are limited. Further, the relationship between secretory dynamics of OXT and emotional measures has never been evaluated. We hypothesized a pulsatile pattern of OXT secretion in men, and explored the relationship between OXT secretory patterns and social-emotional functioning.

Methods: Deconvolution analysis was performed on serum OXT levels obtained every 5 min over a period of 10 h in 5 healthy normal weight men. Area under the curve (AUC), average OXT values, and pulse characteristics [pulse number, inter-pulse interval, pulse height and mass (area under each pulse)] were calculated. State Adult Attachment Measure (SAAM) assessed types of human attachment. Interpersonal Support Evaluation List (ISEL) assessed perception of social support. Toronto Alexithymia Scale (TAS-20) measured the ability to express and identify one's own emotions.

Results: Mean age was 22.8 ± 1.2 years, and BMI was 21.7 ± 0.4 kg/m^2 (mean ± SEM). Assuming a basal secretion of zero and a half life of five to seven minutes, we demonstrated the following: OXT AUC: 5421 ± 1331 pg/ml, mean OXT level: 9.1 pg/ml, mean pulse number: 22 ± 3/10hr, mean pulse height: 1.81 ± 0.48 pg/ml, mean pulse mass: 30.34 ± 10.29 pg/ml and mean inter-pulse interval: 27 ± 4 min. The SAAM Avoidant scale correlated negatively with mean OXT pulse height ($r = -0.90$, $p = 0.04$) and pulse mass ($r = -0.95$, $p = 0.01$). The ISEL Belonging score correlated positively with OXT AUC ($r = 0.89$, $p = 0.04$) and average OXT ($r = 0.93$, $p = 0.02$). ISEL Appraisal score also had a positive association with mean OXT pulse height ($r = 0.99$, $p = 0.0006$) and pulse mass ($r = 0.98$, $p = 0.003$). Finally, ISEL total score had a significant correlation with average OXT values ($r = 0.90$, $p = 0.04$). While none of the subjects had a score in the alexithymia range, TAS-20 Difficulty describing feelings score had an inverse correlation with OXT pulse height ($r = -0.96$, $p = 0.01$) and pulse mass ($r = -0.99$, $p = 0.001$). TAS-20 total score also had an inverse correlation with OXT pulse height ($r = -0.94$, $p = 0.02$) and pulse mass ($r = -0.96$, $p = 0.009$).

Conclusion: We demonstrate a pulsatile pattern of peripheral OXT secretion in healthy men at rest. Subjects with lower OXT pulse height and pulse mass had a more avoidant style of attachment, felt less supported, and expressed greater difficulty in describing their feelings. Our findings support the concept that OXT is a key mediator of social-emotional functioning. Future studies to determine causality are warranted.

1. Introduction

The neurohypophyseal hormone oxytocin (OXT), long known for its role in lactation and parturition, is increasingly recognized as a key mediator in a range of physiologic processes in both sexes (Caldwell et al., 2017; Heinrichs and Domes, 2008; Neumann, 2008; Uvnas-

Moberg, 1998). Parvocellular neurons of the hypothalamic para-ventricular nucleus (PVN) release OXT within the brain, while action potentials in magnocellular neurons of the PVN and supraoptic nucleus (SON) result in the release of OXT into the peripheral circulation via the posterior pituitary gland (Gimpl and Fahrenholz, 2001). Physiological stimuli such as suckling and parturition are associated with an increase in excitatory bursts in these neurons and result in pulsatile release of OXT into the peripheral circulation (Belin and Moos, 1986). Studies in chronically catheterized female sheep show an episodic OXT release not only during parturition, but also during non-pregnant states (Mitchell et al., 1982).

In humans, peripheral OXT levels increase in response to physio-logical factors such as lactation (McNeilly et al., 1983) and parturition (Fuchs et al., 1991) in women, and sexual stimulation (Carmichael et al., 1987) in men, suggesting pulsatile secretion. However, data regarding the secretory dynamics of OXT in men and women at rest, during which the effect of external stimuli are minimized, and thus variation can be attributed to mostly intrinsic sources, are limited. Further, prior studies utilized the fluctuations in peak peripheral levels over the baseline levels to detect the pulsatile nature of secretion. The "gold standard" for detection of hormone secretory patterns, deconvo-lution, is a mathematical technique that identifies secretory events based on serial peripheral hormone levels (Johnson et al., 2004). Deconvolution-based estimates of secretory bursts largely rely on the rate of elimination of hormones from the circulation and therefore on the sampling frequency. Due to its short half-life (Chard et al., 1970; Fabian et al., 1969), OXT must be measured from blood samples taken at a frequency of at least every five minutes in order to determine secretory patterns. To date, deconvolution studies for OXT have not been performed in humans. Understanding the pattern of OXT secretion may help provide mechanistic insights into the actions of this important hormone.

Studies suggest that OXT may play a key role in mediating social-emotional functioning in animal models as well as in humans. In ro-dents, chronic OXT infusion into the lateral ventricles of the brain significantly promotes adult social interactions such as physical contact and auto grooming behaviors (Witt et al., 1992). In humans, the pre-sence of specific single nucleotide polymorphisms in the OXT receptor has been linked to pair bonding behavior in adults, suggesting a role for OXT in social attachment (Walum et al., 2012). Children and adults with autism are characterized by difficulties with social interaction, and a single-dose of intranasal OXT improves social-emotional functioning in this population (Aoki et al., 2014), reinforcing its link with social-emotional functioning. Furthermore, in healthy adults, intranasal ad-ministration of OXT is associated with improved processing of social signals (e.g., decoding facial expressions) (Domes et al., 2007a) and an increase in social trust (Kosfeld et al., 2005). Confirmatory evidence implicating OXT in social-emotional functioning comes from neuroi-maging studies, which demonstrate reduced amygdala activation to fearful faces with OXT administration in healthy males (Domes et al., 2007b).

In addition to its critical role in mediating many aspects of social support and attachment, OXT may be involved in interoception (Quattrocki and Autism, 2014), which refers to the ability to under-stand one's own emotions. It has been proposed that a dysregulation of the OXT system, which plays a major part in encoding interoceptive signals, could be responsible for the verbal and language deficits in autism (Quattrocki and Autism, 2014). However, the relationship be-tween social-emotional functioning and OXT secretory dynamics has not been examined in humans. Deconvolution analysis would allow for in depth examination of the relationship between pulsatile and in-tegrated OXT secretory parameters and social-emotional measures and may improve our understanding of how OXT levels relate to social behavior. Our objective was to determine resting state secretory dy-namics of OXT in men, who are not subject to cyclical changes in hormone levels across the menstrual cycle that are known to impact

OXT secretion in women (Amico et al., 1981). Further, OXT's socio-emotional effects may be sexually dimorphic (Domes et al., 2007b; Domes et al., 2010; Dumais et al., 2013; Murai et al., 1998). In order to reduce the variability of our results from gender specific effects, we limited our recruitment to healthy men only for this preliminary study. We hypothesized a pulsatile pattern of resting state OXT secretion. As a secondary exploratory aim of the study, we examined the relationship between OXT secretory pulse parameters and measures of social-emo-tional functioning.

2. Methods

2.1. Subjects

The study was approved by the Partners Human Research Committee. Informed consent was obtained from all subjects who participated in the study. We recruited five healthy men with normal body weight (BMI between 18.5 and 24.9) from the community be-tween May and September 2013. We excluded subjects with serious medical conditions (e.g., diabetes mellitus, cardiovascular disease, un-treated thyroid disease); anemia; a history of gastrointestinal surgery; psychiatric disease or history of taking psychotropic medications; his-tory of an eating disorder; active substance abuse; tobacco use; or ex-cessive exercise within three months of the study (running more than 25 miles in any one week or having exercised more than 10 h in any one week).

2.2. Study procedures

Eligibility was determined at a screening visit that included a comprehensive medical history, complete physical exam with height, weight, and vital signs, and blood draw for laboratory evaluations. Paffenbarger activity assessment was used to evaluate exercise patterns. The Eating Disorder Module of the Structured Clinical Interview for DSM Disorders-IV (SCID) was administered in person by trained study personnel to evaluate for disordered eating.

All subjects were hospitalized overnight for the main study visit. An intravenous catheter was inserted by 7 p.m., and subjects began fasting at 8 p.m. Frequent serum sampling for OXT was performed every 5 min from 10 p.m. until 8 am to obtain a total of 120 samples from each subject. The frequency of sampling was determined based on the re-quirement for deconvolution analysis of intervals less than or equal to the half-life of OXT (Chard et al., 1970; Fabian et al., 1969). The fol-lowing questionnaires were completed before blood sampling began: State Adult Attachment Measure (SAAM), Interpersonal Support Eva-luation List (ISEL), and the Toronto Alexithymia Scale 20 (TAS-20). Subjects were allowed to sleep through the night in a dark and quiet environment, and any interaction and conversation with subjects during this time was minimized to avoid effects of social stimulation on OXT levels. For the same reasons, subjects were restricted from using television, phones or reading after 9 p.m.

2.3. Questionnaires

2.3.1. State adult attachment measure (SAAM) (Omri Gillath et al., 2009)

This is a measure of attachment of an individual toward others, designed to capture an individual's situation-dependent sense of at-tachment security, anxiety, and avoidance. The measure consists of 21 Likert-like questions. Each scale runs from 1 to 7 with a midpoint of 4. The SAAM measures three different aspects of adult attachment, namely: a. Security; b. Anxiety; and, c. Avoidance. High scores on the Security Scale indicate a current presence of security-related strategies. Higher scores on the Anxiety Scale indicate a higher current anxiety about attachment, while higher scores on the Avoidance Scale indicate a stronger current tendency toward avoidance of attachment.