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Long-term oxytocin administration enhances the experience of attachment

Sylvie Bernaerts[a], Jellina Prinsen[a], Emmely Berra[a], Guy Bosmans[b], Jean Steyaert[c], Kaat Alaerts[a,*]

[a] Research Group for Neuromotor Rehabilitation, Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
[b] Parenting and Special Education, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium
[c] Research Group Psychiatry, Department of Neurosciences, KU Leuven, Leuven, Belgium

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ABSTRACT

The neuropeptide 'oxytocin' (OT) is known to play a pivotal role in a variety of complex social behaviors by promoting a prosocial attitude and interpersonal bonding. Previous studies showed that a single-dose of exogenously administered OT can affect trust and feelings of attachment insecurity. With the present study, we explored the effects of two weeks of daily OT administration on measures of state and trait attachment using a double-blind between-subjects randomized placebo-controlled design. In 40 healthy young adult men state and trait attachment were assessed before and after two weeks of daily intranasal OT (24 IU) or placebo using the State Adult Attachment Scale and the Inventory of Parent and Peer Attachment. Mood, social responsiveness and quality of life were additionally assessed as secondary outcome measures. Reductions in attachment avoidance and increases in reports of attachment toward peers were reported after two weeks of OT treatment. Further, treatment-induced changes were most pronounced for participants with less secure attachment towards their peers. indicating that normal variance at baseline modulated treatment response. OT treatment was additionally associated with changes in mood, indicating decreases in feelings of tension and (tentatively) anger in the OT group, not in the placebo group. Further, at the end of the two-week trial, both treatment groups (OT, placebo) reported to experience an increase in social responsiveness and quality of life, but the effects were only specific to the OT-treatment in terms of reports on 'social motivation'. In summary, the observed improvements on state and trait dimensions of attachment after a multiple-dose treatment with OT provide further evidence in support of a pivotal role of OT in promoting the experience of attachment.

1. Introduction

The neuropeptide 'oxytocin' (OT) is known to play a pivotal role in a variety of complex social behaviors. OT is a nonapeptide produced by the hypothalamic paraventricular and supraoptic nuclei and is secreted into the bloodstream by the posterior pituitary gland. Based on initial animal and human research, the physiological role of OT in lactation and childbirth is well-established (Galbally et al., 2011; Insel, 2010; Kendrick, 2000; Sue Carter, 1998). More recently, different lines of research have shown a strong involvement of OT in complex social behaviors including interpersonal bonding, maternal care, and the ability to establish trust and form social attachments (for reviews see Bakermans-Kranenburg et al. (2013), Bartz et al. (2011), Guastella and MacLeod (2012), but also Nave et al. (2015)).

From genetic research, important insights on the involvement of the oxytocinergic system in pair-bonding and attachment have emerged. For example, recent research showed that genetic variations in the OT-receptor gene (OXTR) of *prairie voles* are related to social attachment and partner preference (King et al., 2015), and that knock-down of the OT receptor inhibited social attachment and parental care (Keebaugh et al., 2015). Also in *human infants*, polymorphisms in the OXTR gene have been associated with variations in attachment security (Chen et al., 2011).

Associations have also been shown between endogenous levels of OT in plasma and maternal or paternal bonding behaviors, attachment-related thoughts and infant social engagement in naturalistic settings (Feldman et al., 2010, 2007; Gordon et al., 2010).

* Corresponding author at: Research Group for Neuromotor Rehabilitation, Department of Rehabilitation Sciences, KU Leuven, Tervuursevest 101 (box 1501), 3001 Leuven, Belgium.
E-mail address: kaat.alaerts@kuleuven.be (K. Alaerts).

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However, studies investigating a link between plasma OT levels and trust behavior in experimental settings (trust game paradigms), have yielded mixed results with some studies reporting tentative links (Zak et al., 2005; Zhong et al., 2012), while others failed to reveal a significant correlation (Christensen et al., 2014).

Other evidence for a role of OT in the establishment of trust and attachment came from studies investigating the effects of exogenously administered OT on behavior and neural functioning. For example, seminal work by Kosfeld et al. (2005) showed that intranasally administered OT can increase trust among human individuals. Particularly, using a social trust game with monetary stakes, Kosfeld et al. (2005) showed that a single-dose of OT significantly increased the readiness to bear social risks arising through interpersonal interactions. Later, Buchheim et al. (2009) showed that OT can increase the experience of attachment security, while De Dreu (2012) proved that intranasal OT can facilitate the development of trust and cooperation in particular in adults with high attachment avoidance (by reducing betrayal aversion). Also self-reports on agency towards self or others were shown to be influenced by single doses of OT administration, indicating that in avoidantly attached individuals, OT positively influenced communal traits and agency towards others (Bartz et al., 2015).

Interestingly, subsequent neuroimaging work provided indications that the effects of exogenously administered OT on trust and trust adaptation were associated with reductions in neural activity of brain regions that are implicated in fear processing (amygdala and midbrain regions) (Baumgartner et al., 2008).

Together, these aforementioned studies provide promising indications that a single-dose of exogenously administered OT can affect trust and attachment behavior in humans. To extend this line of work, the present study aimed to provide an initial investigation on the effects of multiple-dose treatments with OT on measures of state and trait attachment. To do so, we conducted a double-blind between-subjects randomized placebo-controlled trial assessing the effects of two weeks of daily OT administration using the State Adult Attachment Measure (SAAM) (Gillath et al., 2009) and the Inventory of Parent and Peer Attachment (IPPA) (Armsden and Greenberg, 1987) as primary outcome measures. The IPPA is constructed to measure perception of secure attachment towards peers, parents and significant others at a trait level. The SAAM on the other hand, is constructed to measure transient changes in attachment anxiety, attachment avoidance and attachment security at a state level.

To explore whether changes after multiple-dose OT intake were potentially related to changes in mood, we additionally assessed changes in mood states using the Profile of Mood States questionnaire (POMS) (McNair and Lorr, 1964). Additional secondary outcome measures were included to obtain an assessment of social responsiveness and general reports of quality of life. To this end, the adult self-report version of the Social Responsiveness Scale (SRS) (Constantino and Gruber, 2005) and the abbreviated version of the World Health Organization Quality of Life questionnaire (WHO-QOL) (WHO, 1998) were used, respectively.

2. Materials and methods

2.1. Study design

The study design involved a randomized, double-blind, placebo-controlled, between-subjects trial to assess multiple-dose effects of intranasal oxytocin (OT) administration. Written informed consent was obtained from all participants prior to the study. Consent forms and study design were approved by the local Ethics Committee for Biomedical Research at the University of Leuven, KU Leuven (S56327) in accordance to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The trial was registered with the European Clinical Trial Registry (Eudract 2014-000586-45) and the Belgian Federal Agency for Medicines and Health products.

2.2. Participants

A total of 40 healthy young adult males were included in the study. Participants were randomly allocated to receive OT or placebo (PL) nasal sprays (20 OT, mean age = 20.70, S.D. = 2.72; 20 PL, mean age = 21.55, S.D. = 2.39). All participants were right-handed (self-reported) and mean age did not differ between OT and PL groups.

All participants were recruited through advertisement within the university, such that 90% of the included sample were university students. Only male participants were recruited to avoid sex differences in OT response or potential interactions with the female hormonal cycle. Exclusion criteria were (i) age below 18 or above 30 years old (ii) a diagnosed psychiatric or neurological disorder, (iii) intake of psychotropic medication, (iv) history of neurological disease, and (v) history or evidence of other diseases (cancer, hematologic illness, endocrine disease, cardiovascular disease, respiratory condition, renal disease, liver condition or gastrointestinal illness).

2.3. Drug protocol

Sprays were prepared by the KU Leuven University Hospital pharmacist. OT (Syntocinon®, Sigma-tau) and placebo (PL) (saline natrium-chloride solution) were administered in amber 15 ml glass bottles with metered pump (ACA Pharma). Each puff per nostril contained 4 international units (IU) of OT. Each participant received a total of 14 doses of 24 IU, delivered daily over 14 consecutive days. All participants received clear instructions about the use of the nasal spray. At first use, air present in the nasal spray was removed by pumping the spray until a fine mist was observed. Participants were instructed to keep one nostril closed, to take a deep breath through the nose and to tilt their head slightly backwards during nasal administration in order to minimize gravitational loss of the spray. To assure proper use of the spray and to validate tolerability, each subject administered the first dose in front of the experimenter and commented on their experience (e.g. particular smell or taste). All participants were monitored onsite until approximately one hour after nasal spray administration. Participants were asked to take the nasal spray in the morning; and to keep a daily record of the time point of nasal spray administration and whether or not they were alone or in company of others the first two hours after administration (records were not returned by 2 OT participants and 2 PL participants). Percentage of days at which the spray was administered in the presence of others was not significantly different between treatment groups (OT: 75.6% (SD 23.8); PL: 69.8% (SD 28.6); $t(34) = 0.32$; $p = 0.75$).

All participants were screened for potential adverse events or side effects. The side effects questionnaire and a frequency table of reported side effects are provided as Supplementary Tables 1 and 2. As listed in more detail in Supplementary Table 2, only minimal side effects were reported and effects were independent of treatment (e.g., participants from both treatment groups reported to feel more focused (2 OT; 2 PL) or confident (1 OT; 1 PL)). Finally, at the end of the trial, participants were asked if they thought they had received OT or PL. Only two participants correctly guessed to have received the OT treatment. All other participants thought they had received PL.