Psychoneuroendocrinology (2010) **35**, 83—93

available at www.sciencedirect.com

ScienceDirect

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

# Effects of intranasal oxytocin on emotional face processing in women

**Gregor Domes** [a,b,1,*], **Alexander Lischke** [b,1], **Christoph Berger** [b], **Annette Grossmann** [c], **Karlheinz Hauenstein** [c], **Markus Heinrichs** [a], **Sabine C. Herpertz** [d]

[a] *Department of Psychology, University of Freiburg, Germany*
[b] *Department of Psychiatry and Psychotherapy, University of Rostock, Germany*
[c] *Department of Radiology, University of Rostock, Germany*
[d] *Department of General Psychiatry, Heidelberg University, Germany*

Received 10 April 2009; received in revised form 10 June 2009; accepted 12 June 2009

**KEYWORDS**
Oxytocin;
Neuropeptides;
Facial emotions;
Women;
Amygdala;
Functional magnetic-resonance imaging

**Summary** The neuropeptide oxytocin (OXT) has previously been found to reduce amygdala reactivity to social and emotional stimuli in healthy men. The present study aimed to investigate the effect of intranasally administered OXT on brain activity in response to social emotional stimuli of varying valence in women. In a functional magnetic-resonance imaging study, sixteen women were presented with fearful, angry, happy and neutral facial expressions after a single dose of 24 IU OXT or a placebo administration in a within-subject design. Group analysis revealed that the blood-oxygen-level-dependent (BOLD) signal was enhanced in the left amygdala, the fusiform gyrus and the superior temporal gyrus in response to fearful faces and in the inferior frontal gyrus in response to angry and happy faces following OXT treatment. This effect was independent of fixation pattern to specific sections of the facial stimuli as revealed by eye tracking and independent of basal plasma levels of OXT, estradiol, and progesterone. The results are at odds with the previously reported effects found in men. Future studies should include both sexes to determine a possible sexual dimorphism in the neural effects of OXT, considering gonadal steroids and OXT receptor affinity.


## 1. Introduction

Over the last decades, numerous animal studies have shown that the neuropeptide oxytocin (OXT) is crucially involved in the regulation of reproduction related behavior in female mammals (Insel et al., 1997). OXT is a nine amino acid peptide that is synthesized in the magnocellular neurosecretory cells of the supraoptic and paraventricular nuclei of the hypothalamus and released through the posterior pituitary in the periphery. In addition, it is released from the paraventricular nuclei into the brain, where it acts on a specific class-1-G-protein-coupled receptor phosphatidylinositol—calcium second messenger system (Kimura et al., 1992), thus enabling

* Corresponding author at: Department of Psychology, University of Freiburg, Stefan-Meier-Strasse 8, D-79104 Freiburg i. Br., Germany.
*E-mail address:* domes@psychologie.uni-freiburg.de (G. Domes).
[1] Shared first authorship.

0306-4530/$ — see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2009.06.016

this neuropeptide to directly influence behavior (Landgraf and Neumann, 2004). OXT is especially involved in mating, pair bonding, and mother—offspring attachment in mammals (Insel and Young, 2001; Young and Wang, 2004). In rodents, behaviorally relevant expression of OXT receptors in the central nervous system has been found in the amygdala (Huber et al., 2005), the hippocampus (Tomizawa et al., 2003), the paraventricular nucleus of the hypothalamus (Blume et al., 2008), and other brain regions including the basal ganglia and the prefrontal cortex (Gimpl and Fahrenholz, 2001). Although these studies might suggest that these areas are also the primary sites of OXT action in humans, marked species differences have been established for different mammals including humans (Tribollet et al., 1992). Critically, the expression of OXT receptors in the living human brain remains to be investigated, for example using positron emission tomography. In humans, OXT is traditionally viewed as a female hormone that is primarily associated with labor, as it induces uterine contraction during parturition and stimulates the letdown reflex during breastfeeding. Based on the animal literature, it has been postulated that beyond these peripheral actions, central OXT modulates cognition in the context of social interactions, thus promoting positive sociality (Donaldson and Young, 2008).

To date, most of the studies in humans on the effects of OXT social cognition and behavior have been conducted with men (Heinrichs and Domes, 2008). The majority of these studies used intranasal applications of synthetic OXT. In sum, these studies have provided accumulating evidence for the involvement of OXT in human social cognition and behavior (Heinrichs et al., 2009). In particular, recent experiments have shown that OXT promotes trusting behavior (Baumgartner et al., 2008; Kosfeld et al., 2005), enhances facial emotion recognition (Domes et al., 2007b) and memory for positive social information (Guastella et al., 2008b; Rimmele et al., 2009), reduces social stress (Heinrichs et al., 2003), improves social cognition in socially impaired individuals with autism (Hollander et al., 2007), and alters dysfunctional cognitions in social phobia (Guastella et al., 2009). Functional imaging studies have just begun to elucidate the underlying neural correlates of these pro-social effects. A number of studies have provided evidence that the amygdala might be a key structure for the mediation of the social cognitive effects of OXT (Domes et al., 2007a; Kirsch et al., 2005; Petrovic et al., 2008; Singer et al., 2008). A first study by Kirsch et al. (2005) has shown that a single dose of OXT reduced amygdala reactivity to pictures of aversive scenes and faces with negative valence. Recent studies extended this finding by showing that the amygdala responding is also reduced to positive facial expressions (Domes et al., 2007a), aversively conditioned emotional response to social stimuli (Petrovic et al., 2008), and to pain (Singer et al., 2008).

As noted above, all of these studies investigated OXT effects in healthy men, in order to rule out possible interactions with circulating gonadal steroids in women. Thus, it is not yet clear whether the results obtained in male samples may be generalized to women. This is of particular interest as there are obvious functional differences of OXT in men and women, and significant sex differences in neuropeptidergic functioning have been repeatedly found in animal studies (Carter, 2007). In animals a number of studies have investigated the sexual dimorphism of the OXT system. For example, OXT plasma levels tend to be higher in females (Kramer et al., 2004) and synthesis as well as OT receptor affinity appears to be modulated by gonadal steroids such as estradiol and progesterone (Gimpl et al., 2002). On the behavioral level, several studies have shown sexual dimorphisms of neuropeptides in different species. For example, in prairie voles, female parenting behavior is more dependent on OXT, whereas male parenting behavior is associated with AVP (Bales et al., 2004). Another study demonstrated that aggression is associated with OXT in females, but not in males (Bales and Carter, 2003). Sex differences in OXT receptor binding depend on the brain area and the species. For example, female prairie voles show higher binding of OXT receptors in the medial prefrontal cortex (PFC) (Smeltzer et al., 2006), whereas in female rats, higher OXT binding was found in the hypothalamus but not in the central amygdala (Uhl-Bronner et al., 2005). Given these sex differences in the central OXT system and the sexual dimorphisms with regard to the behavioral consequences in rodents, behavioral effects of OXT previously found in men may not be generalized to women.

In the present study, we thus investigated a group of young healthy women using intranasal administrations of OXT before assessing neural activity in response to emotional faces of varying valence during functional magnetic-resonance imaging (fMRI). Specifically, we focused on potential effects of OXT on amygdala activity in response to negative affective stimuli. In addition, we expected modulatory effects of OXT on neural activity in brain areas involved in the processing of emotional information from facial expressions, i.e. the inferior occipital lobe, the fusiform gyrus (FG), the superior temporal lobe and the inferior frontal gyrus (IFG) (Adolphs, 2002; Gallese et al., 2004).

## 2. Methods

### 2.1. Participants

Sixteen healthy adult women (mean age $\pm$ s.d., $24.2 \pm 2.5$ years) were enrolled for participation in this study through announcements on the institutional bulletin board. All participants were right-handed, free of psychoactive and endocrinologically relevant medication (including oral contraceptives), had normal or corrected to normal vision, and did not report a history of neurological or endocrine disease. All participants gave written-informed consent to the study procedures which were in accordance with the Declaration of Helsinki and had previously been approved by the ethics committee of the medical faculty of the University of Rostock.

### 2.2. Procedure

On the scanning days, participants were instructed to abstain from smoking, caffeine, and analgesic medication. Subsequently, participants completed a set of questionnaires and were familiarized with the imaging procedures, the administration of the neuropeptide, and the stimuli during scanning.

In order to rule out possible interactions of exogenous OXT with fluctuations of gonadal steroids over the menstrual