Oxytocin Influences Processing of Socially Relevant Cues in the Ventral Tegmental Area of the Human Brain

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Background: Evidence accumulates that the neuropeptide oxytocin plays an important role in mediating social interaction among humans and that a dysfunction in oxytocin-modulated brain mechanisms might lie at the core of disturbed social behavior in neuropsychiatric disease. Explanatory models suggest that oxytocin guides social approach and avoidance by modulating the perceived salience of socially meaningful cues. Animal data point toward the ventral tegmental area (VTA) as the brain site where this modulation takes place.

Methods: We used functional magnetic resonance imaging and a social incentive delay task to test the hypothesis that oxytocin modulates the neural processing of socially relevant cues in the VTA, hereby facilitating behavioral response. Twenty-eight nulliparous women (not taking any hormones) received intranasal oxytocin or placebo in a double-blind randomized clinical trial with a parallel-group design.

Results: Oxytocin significantly enhanced VTA activation in response to cues signaling social reward (friendly face) or social punishment (angry face). Oxytocin effects on behavioral performance were modulated by individual differences in sociability with enhanced performance in women scoring low but decreased performance in women scoring high on self-reported measures of agreeableness.

Conclusions: Our data provide evidence that the VTA is the human brain site where oxytocin attaches salience to socially relevant cues. This mechanism might play an important role in triggering motivation to react at the prospect of social reward or punishment.

Key Words: Anticipation, dopamine, faces, mesolimbic system, oxytocin, punishment, salience, social reward

The neuropeptide oxytocin has been dubbed "the social hormone" because animal data provide strong evidence that social contact enhances oxytocin levels in the brain, which in turn sets the biological basis for the formation of social bonds (1). In recent years, evidence has accumulated that oxytocin might facilitate social bonding also among human interaction partners. Intranasal application of oxytocin has been found to increase trust toward strangers (2) and to enhance the ability to recognize the relevance of social cues (3–5). On the basis of these findings, oxytocin is currently discussed as a promising candidate to treat social processing deficits in neuropsychiatric disorders (6–8). However, the neural mechanisms through which oxytocin influences social behavior are not yet well-understood. Moreover, the effects seem to be divergent in men and women. Although neuroimaging studies in male participants suggest that oxytocin might modulate social behavior by attenuating neural responses to faces in the amygdala (9–11), face-induced amygdala activation was found to be increased by oxytocin in women (12). The picture is further complicated, because oxytocin is likely to influence behavior via several different routes. Recently, Gamer *et al.* (5) found that, although reducing threat-related neural activity in some subregions of the amygdala, oxytocin enhanced neural activation in a different sub-region and shifted attention to socially relevant cues. This finding suggests that oxytocin might influence behavior via at least two parallel psychobiological mechanisms, reduction of anxiety and increase of salience. The aim of the present study was to specifically address the role of oxytocin in salience processing. To gain better understanding about the effects of oxytocin in women, we restricted our study to female participants. The assumption that oxytocin enhances the salience of social cues (13,14) gains considerable support from both animal and human data. Specifically, findings that oxytocin enhances the frequency of attention shifts toward the eye region of a face (5,15,16) suggest that oxytocin alters the readiness of the brain to orient to socially meaningful stimuli. The underlying neural mechanism is not yet well-understood. Animal data have given rise to the proposition that oxytocin changes the salience of social cues by interacting with the neurotransmitter dopamine. Salience of social as well as nonsocial stimuli is known to be coded by dopamine neurons projecting from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens (NAc) (17). Animal research has provided accumulative evidence that this projection can be modulated by oxytocin (18–20). This finding opens up the intriguing possibility that oxytocin, released in social situations, enhances the salience of social cues by boosting the dopaminergic coding signal (14). Support for this assumption comes from rodent species that typically show a strong partner preference for the conspecific they previously mated with. Blocking oxytocin release during mating in these animals significantly diminishes motivation to seek close contact with the previous mating partner (21,22). The same effect can be observed when blocking dopamine during mating (22). Further evidence for an oxytocin-dopamine interaction was provided by Shahrokh *et al.* (20), who found oxytocin injection into the VTA to

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enhance NAc dopamine levels in female rats during pup grooming. The hypothesis that oxytocin changes salience of social cues by modulating dopaminergic brain circuitry has not yet been tested in human subjects. On the basis of the data outlined in the preceding text, we inferred that oxytocin might modulate salience-related VTA activity during processing of socially relevant cues also in the human brain. Human imaging studies found VTA activation to reflect stimulus salience of reward predictive cues (23–25), and pharmacological manipulation with dopaminergic agents has successfully been used to alter VTA activation and reward-related behavior (26,27). In line with our assumption that oxytocin might act on dopamine neurons in the human VTA, postmortem studies found this region to be rich in oxytocin receptors (28). Here, we used functional magnetic resonance imaging (fMRI) and a social incentive delay task (29,30) to test the assumption that oxytocin modulates neural activation during processing of cues that are predictive of socially relevant outcome. Given that salience facilitates reaction, we expected performance to increase under oxytocin. However, reviewing previous evidence for oxytocin effects on human behavior, Bartz *et al.* (31) pointed out that the effects of oxytocin seem to be highly person-dependent. Specifically, there is evidence that the performance-improving effects of oxytocin in social tasks are especially pronounced in individuals who report difficulties in handling social situations (32,33). To account for a possible modulation of oxytocin effects by individual differences in social personality, we asked participants to self-assess their proficiency and motivation to be and to interact with others and integrated it into our analyses and interpretations.

Methods and Materials

Participants

Twenty-eight right-handed female volunteers (mean age = 26.64 ± 5.55 years, range = 20–42 years) with no neurological or psychiatric history participated in the study. All women were nonsmokers, heterosexual, nulliparous, spontaneously cycling, and were not taking any medication including hormones. The study was approved by the Ethics Committee of the Medical Faculty of the RWTH Aachen University and registered in the European Clinical Trials Database (EudraCT number 2009-015538-30). The clinical trial also included women with high social anxiety, but results for that group will be reported elsewhere. Participants gave written informed consent and were paid a fee for participation. Participants were randomly assigned to the oxytocin group ($n = 14$) and the placebo group ($n = 14$) in a double-blind fashion on the basis of the randomization code generated by the assigned drug provider (InPhaSol, Heidelberg, Germany). Groups did not differ with regard to age, baseline saliva cortisol levels, or hormone plasma levels including oxytocin (Table 1). The number of women in the respective phase of the menstrual cycle (follicular or luteal) at the time of testing was equal in both treatment groups ($n = 7$/phase in each group).

Social Proficiency Questionnaires

Before receiving nasal spray, participants filled out the Empathy Quotient Questionnaire (EQ) (34), the Temperament and Character Inventory (TCI) (35), and the Rejection Sensitivity Questionnaire (36). The EQ provides a conjunct measure of self-experienced social proficiency on the basis of two components of empathy (cognitive empathy and emotional reactivity) as well as social skill. The TCI covers a comprehensive spectrum of personality dimensions, including sensitivity to social approval (TCI reward dependence) and agreeableness (TCI cooperativeness). Individuals with high "cooperativeness" scores are highly sociable. They like to be with others and have been found to be more emotionally responsive in social situations than individuals with low agreeableness scores. The Rejection Sensitivity Questionnaire assesses the readiness of an individual to perceive and react to social rejection.

Experimental Design

The study adopted a randomized, double-blind, placebo-controlled parallel-group design. All participants underwent fMRI scanning. Before drug administration, blood and saliva samples were collected for basal levels of oxytocin, testosterone, progesterone, prolactin, estradiol, and cortisol. Participants self-applied 5 puffs

Table 1. Group Comparisons of Age, Baseline Saliva Cortisol Levels, Hormone Plasma Levels, and Measures of Individual Differences

Variable	Placebo Group	Oxytocin Group	*t*	*p*
Age	26.1 ± 1	27.1 ± 1	.470	.643
Baseline Estradiol (Plasma)	384.3 ± 84 pmol/L	444.3 ± 119 pmol/L	.412	.684
Baseline Testosterone (Plasma)	.99 ± .1 nmol/L	.87 ± .1 nmol/L	−.613	.545
Baseline Progesterone (Plasma)	18.6 ± 6 nmol/L	14.8 ± 4 nmol/L	−.520	.608
Baseline Prolactin (Plasma)	361.7 ± 39.1 pmol/L	565.2 ± 94 pmol/L	1.973	.059
Baseline Oxytocin (Plasma)	5.11 ± 2.97 pmol/L	6.27 ± 2.41 pmol/L	1.128	.270
Baseline Cortisol (Saliva)	18.8 ± 6 nmol/L	15.1 ± 2 nmol/L	−.584	.564
EQ	41.5 ± 2	42.8 ± 2	.423	.676
Cognitive empathy	12.9 ± 2.6	14.1 ± 4.8	.769	.451
Emotional reactivity	13.1 ± 3.8	13.3 ± 4.1	.154	.879
Social skills	9.0 ± 2.7	8.8 ± 1.8	−.260	.797
RSQ	5.5 ± .5	6.6 ± .5	.904	.375
TCI				
Novelty seeking	40.6 ± 3	39.4 ± 2	−.333	.742
Harm avoidance	32.4 ± 4	24.6 ± 2	−1.856	.079
Reward dependence	50.1 ± 3	49.7 ± 3	−.097	.923
Persistence	49.9 ± 3	52.0 ± 2	.527	.603
Self-directedness	55.5 ± 5	60.5 ± 1	1.572	.132
Cooperativeness	63.1 ± 2	66.2 ± 2	1.104	.280
Transcendence	25 ± 3	24.4 ± 3	−.145	.886

EQ, Empathy Quotient; RSQ, Rejection Sensitivity Questionnaire; TCI, Temperament and Character Inventory.