SHORT COMMUNICATION

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Oxytocin Levels in Social Anxiety Disorder

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Oxytocin is a neuropeptide recently associated with social behavior in animals and humans, but the study of its function in populations with social deficits such as autism, schizophrenia, and social anxiety disorder has only recently begun. We measured plasma oxytocin in 24 patients with Generalized Social Anxiety Disorder (GSAD) and 22 healthy controls using an enzyme-linked immunosorbent assay. There were no significant differences in oxytocin level (pg/mL) between patients (M = 163.0, SD = 109.4) and controls (M = 145.0, SD = 52.9, z = 0.21, $P = 0.8$). Within the GSAD sample, however, higher social anxiety symptom severity adjusted for age and gender was associated with higher oxytocin level ($R^2 = 0.21$, $\beta = 0.014$, SE = 0.006, t = 2.18, $P = 0.04$). In addition, dissatisfaction with social relationships was associated with higher oxytocin levels ($R^2 = 0.18$, $\beta = -0.20$, SE = 0.10, t = –2.01, $P = 0.05$). Our data provide preliminary support for a link between social anxiety severity and plasma oxytocin. These findings may suggest a possible role for oxytocin as a facilitator of social behavior, an effect which may not be fully utilized in individuals with severe social anxiety.

Introduction

Emerging data suggest a potential role for oxytocin in social interaction, yet no data examining oxytocin in social anxiety disorder are available. Oxytocin (OT) is a nine-amino-acid peptide (nonapeptide), which is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and projected to the posterior pituitary, limbic areas including the hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens, and other brain regions including the locus coeruleus [1]. OT was first recognized as being involved in labor and lactation across species, but subsequently was found to have a role in the maternal care of offspring, male–female pair bonding, sexual behavior, and nonsexual social relationships [2]. The effect of OT on social behavior has been tested in several species; for example, administration of OT increased the amount of social interactions in rats [3], prairie voles [4], and Mongolian gerbils [5]. Furthermore, in prairie voles (who are monogamous), OT administration facilitated partner preference formation, but an OT antagonist reduced this behavior [6]. In addition, mice with a null mutation in the OT receptor gene demonstrated deficits in social behavior [7]. OT levels have also been examined in two closely related species of macaques with naturally contrasting levels of affiliative behavior; the highly affiliative species (Bonnet Macaque) had higher cerebrospinal fluid (CSF) OT levels than the less social species (Pigtail Macaque) [8].

McCarthy et al. [9] proposed that as the possibility of a social interaction looms, an animal's natural avoidance of proximity may be decreased by the presence of oxytocin. This hypothesis is extended by data that suggest OT has anxiolytic qualities, even outside of a social interaction context. For example, in states of high OT activity such as lactation, blood pressure and the stress hormone cortisol are significantly decreased in humans [10, 11]. There is also some evidence that OT decreases socially related anxiety in humans. In a functional magnetic resonance imaging study of 15 nonpsychiatrically ill men, Kirsch and colleagues examined amygdala activation in response to a series of fear-inducing visual stimuli of either a social nature (angry or fearful faces vs. neutral faces) or a nonsocial nature (threatening scenes vs. neutral scenes) in the presence of OT or placebo administered in double blind fashion [12]. Activation of the amygdala is associated with either type of fear-inducing stimuli, but the presence of administered OT in this study

decreased amygdala activation in both fear conditions. Interestingly, OT had a more pronounced effect on the socially related stimuli, consistent with its putative role in decreasing anxiety related to social interactions. Recent research in rats by Huber and colleagues has identified a pathway by which OT inhibits activation in the amygdala, thereby modulating amygdala output to the autonomic nervous system [13]. This action of OT may in part explain its anxiolytic properties.

Generalized Social Anxiety Disorder (GSAD) is a disorder characterized by fear of performance situations and social interactions, with worries about humiliation or embarrassment in front of others that generalize to most social situations [14]. This typically involves anxiety and constricted behavior in approaching social interactions. For example, in the Liebowitz Social Anxiety Scale [LSAS, 15], the scale most commonly used to measure symptoms of social anxiety, 10 of 24 items involve approach of new or relatively unfamiliar others. Thus, GSAD offers a compelling naturalistic disorder in which to examine the potential role of oxytocin in social and approach behavior in humans with abnormalities in this arena, and prior research suggests that oxytocin is an intriguing neuropeptide candidate that could play a role in the pathophysiology of GSAD. One recent small study by Scantamburlo [16] found a negative correlation between anxiety symptoms and oxytocin in a group of 25 depressed patients. However, other studies have found a positive association between oxytocin and anxiety symptoms; for example, in 29 patients with obsessive compulsive disorder, higher oxytocin was associated with greater anxiety symptoms [17]. To our knowledge, this study is the first to examine oxytocin levels in individuals with GSAD. We hypothesized that individuals with GSAD would have lower levels of plasma oxytocin than controls, reflecting a potential relationship between oxytocin deficits and social deficits.

Method

Participants

Twenty-four patients (10 female, 14 male) with GSAD, generalized type, based on the Structured Clinical Interview for DSM-IV [SCID, 18] by a trained psychiatrist or psychologist were recruited among treatment seeking research participants at the Center for Anxiety and Traumatic Stress Disorders at the Massachusetts General Hospital (MGH). Comorbid major depression, dysthymia, or generalized anxiety disorder were allowed if GSAD was deemed the primary disorder. Exclusion criteria included a history of a psychotic disorder, substance abuse or dependence, unstable medical illness, pregnancy, or lactation. Twenty-two healthy controls (11 female, 11 male) recruited with advertising were free of a lifetime history of any psychiatric disorders according to the SCID interview, and met the other noted exclusion criteria. All participants were free of psychiatric medication. All subjects gave informed consent in accordance with the policies of the MGH Institutional Review Board, which approved all procedures.

Oxytocin and Psychometric Measurements

Subjects arrived at the clinic at 8 am and rested for 15 min prior to phlebotomy. Blood was collected in an EDTA tube, placed on ice, and centrifuged at 1500 rpm for 10 min at 4°C. Plasma was then aliquotted into 2 cc plastic tubes, capped and frozen at −70°C. Samples were collected from 2004 to 2006, and oxytocin assays were concurrently performed in December of 2006 at the Endocrine Core Laboratory of the Yerkes National Primate Research Center at Emory University, Atlanta, using an enzyme-linked immunosorbent assay (Assay Designs, Ann Arbor, MI). The inter- and intra-assay coefficients of variations were 10.7% and 12.2%, respectively, and the sensitivity was 11.7 pg/mL.

Social anxiety severity was assessed for participants with GSAD using the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician-rated scale that measures fear and avoidance in social and performance situations [19]. Satisfaction with social relationships was assessed as part of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), a questionnaire that rates various aspects of quality of life [20]. In particular, we examined item 5 of the QLESQ, "Satisfaction with family relationships in the past week."

Statistical Methods

Differences in plasma oxytocin between subjects and controls were examined with a two-sample Wilcoxon rank-sum (Mann-Whitney) test, while the association between psychometric properties and oxytocin levels were examined with multiple regression models. Because power was limited to detect gender or age effects in this initial pilot and subjects were not matched, we included covariates to adjust for potential confounding by age and gender. Because the oxytocin data were skewed according to the Shapiro-Wilk test ($P < 0.0001$), they were log transformed prior to performing the regression analyses.

Results

Twenty-four patients with social anxiety disorder and twenty-two healthy controls participated in the study

Table 1 Subject demographics and disorder characteristics

	GSAD N = 24	Controls N = 20
Age (years), mean (SD)	34 (13)	35.5 (10.1)
Gender, % female (n)	41.7 (10)	45 (9)
Race, % Caucasian (n)	70.8 (17)	85 (17)
Marital status, % partnered (n)	29.2 (7)	30 (6)
Current comorbidity, % (n)		
MDD	8.3 (2)	N/A
Dysthymia	16.7 (4)	N/A
GAD	4.2 (1)	N/A
Duration of illness, mean years (SD)	25.5 (17.5)	N/A
LSAS, mean (SD)	89.3 (17.4)	N/A
QLESQ, mean (SD)	42.5 (8.5)	54.7 (6.5)

N/A = not applicable.
MDD = major depressive disorder; GAD = generalized anxiety disorder.

(see Table 1). Gender (chi-square = 0.05, $P = 0.82$) and age (t = 0.42, df = 40, $P = 0.68$) did not differ between GSAD patients and controls. Oxytocin levels did not significantly differ by gender (Two-sample Wilcoxon rank-sum (Mann-Whitney) z = 0.18, $P = 0.9$) and were not correlated with age (Pearson's R = 0.069, $P = 0.7$). Two control participants had oxytocin values four standard deviations from the mean; these outliers were removed from the data set.

Patients (M = 163.0, SD = 109.4) and controls (M = 145.0, SD = 52.9) did not significantly differ in plasma oxytocin levels (pg/mL; z = 0.21, $P = 0.8$). This range of plasma oxytocin values is similar to those previously reported in the literature [16, 21]. However, within the GSAD sample, after adjusting for covariates for age and gender, higher symptom severity on the LSAS was associated with higher oxytocin level ($R^2 = 0.21$, $\beta = 0.014$, SE = 0.006, t = 2.18, $P = 0.04$). After controlling for the presence of GSAD, higher plasma oxytocin was also associated with less satisfaction in social relationships ($R^2 = 0.18$, $\beta = -0.20$, SE = 0.10, t = –2.01, $P = 0.05$).

Discussion

Our finding of higher circulating oxytocin levels associated with greater social dissatisfaction and increased severity among individuals with social anxiety disorder provide preliminary support for a link between social anxiety and plasma oxytocin level, albeit in the opposite direction to that originally hypothesized. However, it is worth noting that other research also suggests that increased oxytocin activity may be associated with anxiety. For example, Purba et al. [22] found increased oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depressed patients, consistent with increased oxytocin production and release, which they suggest may also contribute to anxiety symptoms associated with depression. Furthermore, this finding is consistent with the finding of increased oxytocin in another group of individuals with social deficits, adults with autistic spectrum disorder [23]. Recently, Lerer and colleagues [24] replicated and extended research demonstrating the association of alternate haplotypes in gene coding for the oxytocin receptor in patients with autistic spectrum disorder. In addition, Modahl and colleagues [25] reported that among autistic children, higher oxytocin was associated with increased social and developmental deficits, though overall levels were lower compared to age-matched controls. Examination of a group of anxiety patients also found a higher level of OT: Leckman et al. [17] demonstrated higher OT in the CSF of patients with OCD, although researchers failed to replicate this finding in a later study [26]. Further, plasma oxytocin was positively correlated with anxiety composite scores in a study of healthy women [27]. Based on the above findings, we hypothesize that patients with social deficits due to anxiety or autism may have higher than normal levels of OT perhaps as a compensatory mechanism in the face of malfunctioning oxytocin receptors.

We also found an association between oxytocin and relationship dissatisfaction. Oxytocin may increase as part of an organism's attempt to facilitate social interactions in individuals with deficient relationships. This hypothesis is supported by animal studies showing that oxytocin promotes social behavior by reducing anxiety associated with social interactions [4, 9, 28, 29]. Similarly, human research demonstrates that administered oxytocin decreases the amygdalar response to fearful and angry faces [12] and autonomic responses to aversive pictures [30]. Our seemingly counter-intuitive finding of increased oxytocin in more socially anxious individuals may thus be explained as secondary to increased release of oxytocin in an attempt to reduce anxiety and facilitate social behavior, in the face of malfunctioning oxytocin receptors. For example, if oxytocin is not stimulating its receptors, it may be released in higher quantities and be observed as higher plasma levels. There is some preliminary evidence that oxytocin receptors may be abnormal in some psychiatrically ill individuals [24].

The association between oxytocin and relationship dissatisfaction has also been found in studies of healthy subjects [31–33]. For example, Turner et al. [32] measured baseline plasma oxytocin in 25 healthy women and found that higher levels of oxytocin were associated with anxiety in relationships and in the lack of a primary romantic relationship. Marazziti and colleagues also demonstrated that anxiety about close relationships was associated with increased plasma oxytocin in healthy subjects [33]. Akin to these findings, recent data demonstrate that students

with higher basal levels of oxytocin have a lower oxytocin response to the trust game described earlier, as well as less engagement in this cooperative task, which may have implications for socially anxious individuals with high oxytocin (P. J. Zak, unpublished data).

This study has a number of limitations, including a small sample size and inclusion of only treatment-seeking individuals, which may limit generalizability. In addition, although blood collection time was standardized, it immediately followed venipuncture, which may have affected acute oxytocin levels; however, this method has been used in other human studies [21, 25]. Furthermore, we did not control for phase in menstruation cycle in female subjects, although other research has shown no changes in plasma oxytocin over the menstrual cycle [34]. Finally, we examined peripheral rather than brain measures of oxytocin, although animal research suggests central and peripheral release are coordinated [35, 36]. Lastly, plasma osmolality was not measured, which may influence plasma oxytocin levels.

While the relevance of oxytocin for social deficits in psychiatric disorders has been posited [7, 12, 37–41], relatively little research regarding endogenous oxytocin is available in psychiatric populations, and this is the first report addressing this issue in individuals with social anxiety disorder. Findings from this study suggest that increased oxytocin levels may be associated with anxiety about or dissatisfaction with social relationships, perhaps in order to facilitate social behavior. While acknowledging that our study has several limitations, we speculate that the positive correlation between oxytocin levels and social anxiety may mean that for individuals with severe social anxiety, oxytocin secreted as a compensatory response may not provide sufficient anxiolysis to improve their social functioning.

Conflict of Interest

Individual Author Financial Disclosures

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Author Contribution

Elizabeth Hoge and Paul Zak designed the study, and Dr. Hoge wrote the protocol and first draft of the manuscript. Rebecca Kaufman managed literature searches and the data set. Mark Pollack and Naomi Simon made changes to the manuscript and assisted Dr. Hoge with the statistical analyses and interpretation of results. All authors contributed to and have approved the final manuscript, which has not been published before and is not under consideration for publication elsewhere.

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