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Plasma Oxytocin Immunoreactive Products and Response to Trust in Patients with Social Anxiety Disorder

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Abstract

Background—Generalized Social Anxiety Disorder (GSAD) is characterized by excessive fear and avoidance of several types of social and performance situations. The pathophysiology is not well understood, but research in animals and humans has provided evidence that oxytocin helps regulate normal social affiliative behavior. Previous work in healthy male subjects demonstrated a rise in plasma oxytocin after receiving a high trust signal. To examine the oxytocin system in GSAD, we measured plasma oxytocin in GSAD patients and controls, before and after the social "Trust Game," a neuroeconomic test examining trust behavior and reaction to trust using real monetary incentives.

Methods—Thirty-nine subjects with GSAD and 28 healthy controls provided three blood samples for oxytocin measurement before the Trust Game, and one sample after the game. Plasma estradiol was also measured at baseline. The Trust Game protocol version prioritized the sending of a signal of high cooperation and trust to all participants. All analyses controlled for gender and estradiol levels.

Results—Mean oxytocin levels post-Trust Game ($p=0.025$), and overall (area under the curve, $p=0.011$) were lower in GSAD patients compared to controls, after controlling for sex and estradiol. There was no significant change in oxytocin levels after the Game in either group.

Conclusions—We report low plasma oxytocin levels in patients with generalized social anxiety disorder during a pro-social laboratory task paradigm. Additional research will be important to further examine the relationship between oxytocin and social behavior in GSAD.

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MESH terms

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Introduction

Generalized Social Anxiety Disorder (GSAD) is a psychiatric condition characterized by excessive fear and avoidance of several types of social and performance situations. While the disorder can sometimes be successfully treated with serotonergic medications, the underlying pathophysiology of GSAD is largely unknown. Research in animals and humans has provided evidence for a role of oxytocin in social affiliative behavior, a hormone of interest for research on this disorder of social deficits. Oxytocin is a nine amino-acid neuropeptide which is synthesized in the hypothalamus. Parvocellular neurons in the paraventricular nuclei project to brain areas such as the amygdala and hypothalamus, and magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus project oxytocin axonally to the posterior pituitary, which then releases it into the peripheral blood circulation [1], [2]. In addition, there is evidence that magnocellular neurons also project to brain regions such as the nucleus accumbens, which suggests that peripheral release and central release from these neurons might be linked (Ross 2009). Oxytocin receptor mRNA expression has been associated with rat social approach to odors of other healthy rats [3]. In human studies, women with high levels of oxytocin due to recent childbirth reported an increased desire to interact socially with others, and the level of pro-social feelings correlated with their oxytocin levels [4]. In addition, positive social interactions, such as physical contact or hugs by a family member, have been demonstrated to increase oxytocin levels in humans [5], [6], [7].

Several lines of evidence suggest that oxytocin can decrease anxiety, which may result in lower boundaries of inhibition for social interaction. In rodents, administration of oxytocin in the brain intracerebroventricularly increases open field activity and decreases anxious behavior in the elevated plus-maze test [8], [9], [10]. Primate studies furthered this connection by showing that oxytocin administered under high stress conditions was associated with decreased in adrenocorticotropic hormone secretion [11]. In healthy human subjects, oxytocin administration was associated with lower ratings of anxiety in response to a speech task [12]. In fragile X syndrome, a condition characterized by extreme social anxiety and intellectual disability [13], oxytocin administration lowered levels of cortisol after a social stress task. Several other studies have suggested that oxytocin promotes social affiliation behavior, possibly through betrayal aversion (trust behavior after knowledge of betrayal) among other effects (i.e. [14]; for review see [15]).

There has been a great deal of interest in determining whether oxytocin pathways are abnormal in disorders associated with social deficits, such as autism, or deficits in social functioning, such as social anxiety. Research findings to date on endogenous levels of oxytocin in autism spectrum disorders have been conflicting, showing lower [16] and higher [17] levels compared to controls. Genetic studies using linkage and association methods support a possible relationship between specific gene variants in the oxytocin gene and oxytocin receptor gene in autism, but findings have not been consistent (see [18]). While methodologically quite different, studies of oxytocin administration in patients with autism suggest that supplementing oxytocin in these patients can reduce psychiatric symptoms [19–

21]. Obsessive-compulsive disorder has been associated with higher oxytocin levels in one study [22], but this finding was not replicated in a subsequent study [23]

The potential connection between GSAD and oxytocin is supported by studies showing that in patients with social anxiety disorder, oxytocin administration decreased amygdala hyperresponsivity in fMRI to pictures of faces showing fear and sadness ([24], [25]). However, there is relatively little data assessing endogenous levels of oxytocin in individuals with social anxiety disorder. Research in our laboratory found a weak association between plasma levels of oxytocin and anxiety severity in individuals with social anxiety disorder, but we did not detect a difference in oxytocin levels between patients with GSAD and controls [26]. Limitations of this study were use of a single time point measure, which may not represent integrated blood levels of this pulsatile hormone, and use of blood samples that were taken immediately after venipuncture, a stress that could potentially increases levels.

Previous research has also measured the relationship between trust and oxytocin in individuals interacting with strangers while playing the "Trust Game," a neuroeconomic test examining trust and selfish behavior using real monetary incentives [27–30] or while sharing a personal secret [31]. The Trust Game has been used in several studies examining cooperation and reciprocation in humans ([28, 32–34]. In this paradigm,"trust" is measured as the amount of money Player 1 sends to Player 2 because this transfer involves a risk; the lost money is only regained if Player 2 voluntarily reciprocates, by sending money back to Player 1.

In a randomized, placebo-controlled study by Kosfeld et al, study participants were administered intranasal oxytocin or placebo before they played the trust game with a stranger [35]. Those who received oxytocin transferred higher amounts of money to the other player than those who received placebo. In a study measuring endogenous oxytocin secretion, Zak et al. measured serum oxytocin levels in 156 students after the trust game was played [27]. Subjects who played the game with other people (involving an intention of trust and cooperation) had higher levels of oxytocin than those in the control condition whose outcome was generated by a computer (but who received equivalent amounts of money). Thus, subjects involved in a true social interaction had higher oxytocin levels in response to a trust signal than those simply receiving a monetary award.

In the present study, we compared oxytocin levels between GSAD patients and healthy controls, and also aimed to extend the aforementioned findings by Zak and colleagues [27], by using the Trust Game to measure the effect of a high trust signal during the Trust Game in patients with GSAD, compared to control subjects. Therefore, we arranged for all subjects to receive a large amount of money (a sign of high trust) from the other game player, who was a member of the study staff not known or met by the patient. Given recent research showing that peripheral oxytocin administration decreases social anxiety in humans, we hypothesized that subjects with GSAD would have lower plasma oxytocin levels at baseline compared to controls, and a muted oxytocin response to the Trust Game compared to controls.

Materials and Methods

Participants

Study participants were treatment seeking individuals and/or were participating in research studies at the Center for Anxiety and Traumatic Stress Disorders at the Massachusetts General Hospital (MGH) between 2007 and 2010. Healthy controls were recruited with print advertisements. All study procedures were approved by the Partners HealthCare institutional

review board. All participants gave written informed consent. Eligibility was limited to men and women aged 18 years and over with no significant medical disease, steroid or hormone use including oral contraceptives, nor any type of diabetes or other endocrine disease including thyroid disease, who were willing and able to comply with study procedures. Women who were pregnant or lactating were excluded.

Healthy controls were required to have no current affective, anxiety, substance dependence or psychotic Axis I DSM-IV diagnosis, as determined by the Structured Clinical Interview for DSM-IV (SCID) [36] completed within the past 6 months. Participants with GSAD were required to have a primary diagnosis of GSAD as defined by theSCID.. Psychiatric diagnostic assessments were performed by trained MD or PhD level study clinicians. GSAD subjects with concurrent anxiety disorders or depression were eligible if GSAD was clinically determined to be the predominant disorder. Exclusion criteria for the GSAD group, in addition to those listed above, included a history of schizophrenia, psychotic disorders, bipolar disorder, mental disorder due to a medical condition or substance, alcohol or substance abuse or dependence within the past six months, or risk of suicide. Enrolled subjects with GSAD were not taking psychiatric medication, and completed this study before any treatment began.

GSAD subjects completed the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician-rated scale that measures symptom severity with items asking about fear and avoidance in social and performance situations [37]. Both GSAD subjects and controls completed thethe Childhood Traumatic Events Scale, a questionnaire that asks about 6 types of trauma that occur before age 17 (death of family/friend, parent divorce/separation, rape/molestation, violence, illness/injury, and other), asking about the age of occurrence, severity of trauma, and whether or not confiding in others occurred [38].

Procedure

Participants were scheduled for the Trust Game and blood collection procedure between 1:00 and 4:00pm. Informed consent was obtained prior to any data collection or procedures. An intravenous (IV) catheter was inserted by a Clinical Research Center nurse, and the subject was instructed to rest. Blood was collected five, ten, and fifteen minutes after the IV placement for the baseline measurements of oxytocin and estradiol, and again at endpoint, immediately after the Trust Game (approximately 20 minutes after venipuncture), for oxytocin measurement. The study nurse kept conversation to a minimum during this procedure, and held constant across all participants the amount of physical contact, in order to minimize inadvertent psychosocial effects of verbal or physical contact on oxytocin levels.

Trust Game

Immediately after the 15 minute blood draw, the Trust Game was played (for details, see [27]). The study staff member explained to the subject that s/he would be paired with another player in a different room, and that each player would start the game with $10 (which the participant earned for agreeing to participate). The subject was also informed that s/he would be in the role of Player 2.

Trust Game:

1. Player 1 has the opportunity to give a portion, none, or all of his/her $10 to Player 2.
2. After money is given to Player 2, but before the money is received, the amount given is tripled.

3. Player 2 receives the tripled money, and chooses how much to send back to Player 1 (if any). Player 2 keeps the money that he/she does not send back to Player 1.
4. End.

The subject was given instructions for the Trust Game. He or she was told that the other player (Player 1), whom s/he would not meet in person, would play first, and that the amount of money Player 1 sends to Player 2 will be tripled. Each player only has one turn. For example, if Player 1 sends $2 to Player 2, this will be tripled to $6. Player 2 will now have 10 + 6 = $16, while Player 1 will have the $8 that s/he kept. Subjects were given an envelope with the amount of money that was reported to be transferred from Player 1. The role of Player 1 was played by a member of the study staff, who always gave $8 to the subject (a "high trust signal"). After subjects received the money, they were left in the room alone to decide how much, if any, to return to Player 1, and to place this money into the provided envelope. Subsequently, the subject rang a bell, the nurse returned to draw another blood sample from the IV. After IV removal, the subject was free to go home with the money he/she chose to keep.

Hormones

Blood was collected in EDTA tubes and immediately placed on ice, then centrifuged at 1500 rpm for 10 min at 4°C. Plasma was then transferred into 2 cc plastic tubes, capped and frozen at −70°C until processing. Oxytocin was measured at the Clinical Research Laboratory Core at MGH, in unextracted plasma by ELISA (Assay Designs, Inc., Chicago, IL). The minimum reportable concentration of this test is 15.6 pg/mL. Testing was monitored using in-house frozen quality control plasma pools. The intra-assay CVs are 7.3%, 10.1%, and 8.7 % for quality control sera containing 30, 371 and 508 pg/mL, respectively. The inter-assay CVs across reagent lots are 14.4% and 11.8% for frozen quality control sera containing 33 and 344 pg/mL, respectively. Estradiol was measured at +10 minutes at the Harvard Catalyst Central Laboratory, using a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of estradiol levels in human plasma using the Access Immunoassay Systems; assay precision of 12–21%.

Statistical Methods

Baseline characteristics were compared using Fisher's exact tests for categorical covariates, and Student's t-tests for continuous covariates; significant imbalances were adjusted for in multivariate analyses. Oxytocin levels were log-transformed in order to achieve normality.

The initial step of our analysis was to compare mean oxytocin levels by diagnosis using two-tailed t-tests, and followed by multivariate regression modeling to adjust for sex and estradiol, since estradiol is a key regulator of oxytocin secretion [39]. Baseline oxytocin level was calculated by averaging the 5-, 10- and 15-minute measurements, in order to provide a more precise and stable measure of this pulsatile hormone. Endpoint oxytocin level was reported as the final blood measurement, after the Trust Game. We also looked at whether change in oxytocin levels (from baseline to endpoint) differed significantly by diagnosis after controlling for sex and estradiol. Within GSAD patients, we examined the association between oxytocin levels and history of trauma, history of depression (past or current), and LSAS total score.

To determine if GSAD patients had differing oxytocin levels overall compared with controls, we plotted oxytocin levels over time for subjects with more than 2 oxytocin measurements, and calculated the area under the curve (AUC) using the trapezoidal approximation between the discrete time points (the endpoint measurement was considered to occur at 20 minutes). The mean AUC was compared by diagnosis, and we hypothesized

that GSAD patients would have lower AUC oxytocin levels than healthy controls. A two-sided alpha=0.05 significance level was used in all analyses, which were conducted using STATA version 11.1 for Windows (StataCorp LP, College Station, TX).

Results

Oxytocin and Diagnosis

A total of 65 subjects with oxytocin data were analyzed, including 38 patients with GSAD and 27 healthy controls. Only three of the 65 patients missed up to two of the four measurements (5-min, 10-min, 15-min, and endpoint, which occurred at approximately 20-min), and were excluded from the AUC analyses. Estradiol levels were also missing for three of the 65 patients, who are excluded from the multivariate regression modeling. Estradiol was not correlated with oxytocin at baseline (r= −0.04, p=0.75). Descriptive characteristics of the analysis population are shown in Table 1. There were no significant differences between the groups in age, race, or history of trauma, but gender differences were marginally significant, with more males than females in GSAD patients compared to controls.

Mean oxytocin levels did not differ between GSAD patients and healthy controls in univariate analyses at baseline (see Table 1). Mean oxytocin measured immediately after the Trust Game (Endpoint) was 273 pg/ml in the GSAD group and 353 pg/ml in the healthy controls; this differerence was only at the level of a trend, and not statistically significant at (p=0.07).”Change in oxytocin from baseline to endpoint did not significantly differ between the groups. In analyses conducted within the GSAD group, we did not see a significant association between LSAS score and oxytocin levels.

In multivariate regression models, after controlling for sex and estradiol, we found that mean baseline oxytocin was numerically lower in the patients with GSAD, but bit this difference was only at the level of a trend (B=−.270, SE=0.14, p=0.059), and not statistically significant. The mean endpoint oxytocin was significantly lower in patients than controls (B= −.41, SE=0.18, p=0.025). The change score (magnitude of change in oxytocin from baseline to endpoint) was not different between the groups, however (p=1.0). The oxytocin AUC measurements were significantly smaller in patients with GSAD compared to control subjects after controlling for sex (B= −6.4, SE=3.2, p=0.050), and also after controlling for sex and estradiol (B= −9.0, SE=3.4, p=0.011). Six subjects with GSAD had comorbid anxiety disorders (4 had generalized anxiety disorder, 1 had panic disorder, and 1 had both). The overall oxytocin AUC’s were not different in this comorbid group (82.3 versus 82.1), and the multivariate analyses yielded the same results when these subjects were excluded.

Oxytocin, Trauma History, and Depression

Patients with GSAD who also had a history of current and/or past depression had lower baseline levels of oxytocin compared with GSAD patients with no history of depression, but not significantly (p=0.10). There were no differences between endpoint, change, and AUC oxtyocin, in univariate analyses or after controlling for sex and estradiol. We also did not observe any significant differences between subjects with and without a history of childhood trauma when comparing mean oxytocin at baseline, endpoint, change between baseline and endpoint, or AUC either in the univariate analyses or after controlling for sex and estradiol.

Discussion

Our study of oxytocin levels before and after the Trust Game found lower levels in pre- and post-game blood samples after controlling for sex and estradiol levels, which was significant at endpoint (post-Trust Game) in patients with GSAD relative to controls. Although we did

not see the hypothesized difference in the oxytocin change score after the Trust Game, we found lower levels of oxytocin across the four combined timepoints in GSAD patients (based on the AUC), after adjusting for sex. These data contrast with our earlier study, which did not show a difference using a single measure of oxytocin taken immediately after venipuncture and did not measure estradiol [26]. Of note is the fact that the AUC measurement incorporates a behavioral probe with a pro-social trust signal. This, taken together with the lower mean oxytocin levels in GSAD patients compared to controls after the Trust Game could potentially reflect a decreased ability to respond pro-socially to an indication of trust from another person. These data raise the question of whether altered oxytocin dynamics in GSAD contribute to the social deficits.

The finding of lower oxytocin in patients with a condition involving social deficits is consistent with literature showing lower levels in autism [16]. In this study, plasma oxytocin levels were lower in the 29 autistic children compared to 30 age-matched healthy control children. A later study found the opposite (lower levels in controls), but subjects were less symptomatically severe and there were only 10 patients and 14 controls in the study [17]. Oxytocin levels have also be investigated in schizophrenia, another psychiatric disorder characterized by social deficits.

Research has been mixed, with some showing lower levels of oxytocin in cerebral-spinal fluid in schizophrenia [40] and others finding no difference [41]. More recently, oxytocin levels were negatively correlated with the severity of psychotic symptoms [42] and were lower in schizophrenics compared to healthy controls during a secret-sharing trust task [43]. It appears that while something in the oxytocin system might be dysregulated in individuals with schizophrenia, replication studies are needed, with differing and improved methodologies to determine the reasons for discrepant findings in the existing literature.

There were several limitations in our study. First, the small sample size, particularly of female subjects, limits the generalizability of our findings and may have limited power for some analyses. Second, we did not collect information about menstrual history, and estrogen levels are known to effect levels of oxytocin in the blood [44]. Therefore, we measured estrogen during baseline and entered it in the regression analysis. Estradiol levels differed in male and female cases and controls, possibly due to differences in timing of the menstrual cycle and fat mass. After controlling for estradiol levels and sex, our findings of decreased oxytocin secretion in GSAD were significant. Another potential limitation is that we did not use the extraction step in the enzyme-linked immunosorbent assay (EIA) for oxytocin. Some groups have used the EIA extraction step in human studies, involving either solid-phase extraction or solvent extraction ([5, 45, 46]) and others have not ([27, 47, 48]). Comparison between extracted and unextracted specimens have yielded high correlations in some studies ($r = 0.89$; [49]) but not others ($r = 0.09$; [50]). Because our central hypothesis involved measuring oxytocin change scores after the trust game, we chose not to use the extraction step in order to minimize variability introduced by the extra assay steps.

Conclusion

In summary, we report evidence of decreased oxytocin secretion during the Trust Game in a well-characterized set of patients with Generalized Social Anxiety Disorder compared to healthy controls. Previous research provides data suggesting that oxytocin decreases anxiety and promotes social behavior, suggesting that oxytocin levels, or oxytocin functioning, may be altered in populations with persistent social deficits. Our data, while preliminary, support this overall hypothesis and indicate that oxytocin secretion may be abnormal in GSAD patients. Additional research will be important to replicate these findings and further explore the clinical significance of altered oxytocin dynamics in social anxiety disorder.

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Table 1

Characteristics of the Analysis Population and Univariate Analyses of Oxytocin Levels (pg/mL)

Characteristic	Controls *(n=27)*	GSAD *(n=38)*	p-value†
Sex: N (%)			0.079
Male	17 (63)	32 (84)	
Female	10 (37)	6 (16)	
Race: N (%)			0.31
White	20 (74)	31 (82)	
Black	5 (19)	2 (5)	
Asian	2 (7)	4 (11)	
Other	0 (0)	1 (2)	
Age (years): Mean (SD)	40 (13)	36 (12)	0.21
History of Childhood Trauma N (%)	12 (44)	23 (61)	0.22
LSAS score (in GSAD subjects only): Mean (SD)		80 (22)	
History of Depression (current and/or past): N (%)	0 (0)	14 (37)	*
Oxytocin at Baseline (average of 5-, 10-, & 15-min), mean(SD)	354 (181)	299 (138)	0.22
Oxytocin at Endpoint (20-min), mean(SD)	353 (171)	273 (172)	0.07
Change in Oxytocin: Endpoint – Baseline, mean(SD)	−0.89 (132)	−0.26 (198)	0.50
Estradiol levels in Women, pg/mL, mean(SD)	46.3 (38.7)	100 (68.6)	0.07
Estradiol levels in Men, pg/mL, mean(SD)	31.5 (20.1)	45 (17.3)	0.02

*measured in GSAD subjects only (exclusion criteria for controls)

†p-values for oxytocin levels are based on regression with log-transformed values

Table 2

Multivariate and AUC Analysis of Oxytocin levels by Diagnosis (Controls, n=27, GSAD, n=38)

	β	SE(β)	p-value
Log(Oxytocin) at Baseline (average of 5-, 10-, & 15-min)	−.270	0.14	0.059
Log(Oxytocin) at Endpoint (20-min)	−.41	0.18	0.025
Change in Log(Oxytocin): Endpoint – Baseline	−.0002	0.59	1.0
Area Under the Curve (AUC) of Log(Oxytocin) over Time	−6.4	3.4	0.011