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The Complex Role of Oxytocin in Major Depressive Disorder

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ABSTRACT

Objective: One proposed mechanism to subclassify depressive illness relates oxytocinergic dysregulation, via its effect on social behavior and Hypothalamic-pituitary-adrenal (HPA) axis inhibition. To further investigate the role of oxytocin in Major Depressive Disorder (MDD), we compared plasma oxytocin levels in patients with MDD to healthy controls.

Methods: Plasma samples from 12 healthy controls and 33 MDD patients were collected at baseline, 8 weeks, and 12 weeks of treatment and oxytocin was measured by enzyme-immunoassay. Depression and anxiety scales were administered at screening, baseline, and at weeks 2, 4, 8, and 12 of treatment. Additionally, we investigated possible associations between blood concentrations of inflammatory biomarkers and oxytocin.

Results: The average baseline oxytocin level was 429 pg/ml in MDD patients and 392 pg/ml in healthy control subjects. A significant negative correlation was found between baseline oxytocin and BMI. Treatment responders had significantly lower baseline oxytocin levels than non-responders. After stratifying patients into *low* and *high* oxytocin groups based on a median split, within the *high* oxytocin group, patients with no prior depressive episodes had significantly higher baseline oxytocin levels. A Chi-square distribution test revealed that African American patients were more likely to belong to the *high* baseline oxytocin group while Caucasian and Hispanic patients were more likely to belong to the *low* baseline oxytocin group. We found significant correlations between oxytocin and Von-Willebrand Factor (VWF) and Epidermal Growth Factor (EGF), only within the *high* oxytocin subgroup. There were no other significant correlations between baseline oxytocin and any other biomarkers.

Conclusion: Within our limited patient cohort, our data adds to the mixed literature regarding the role of oxytocin in MDD. Oxytocinergic dysregulation and confounding factors may play a role for a subset of depressed patients.

Keywords: Depression, oxytocin, social behavior, HPA axis, inflammation

1. INTRODUCTION

Major depressive disorder (MDD) affects a significant portion of the population and is estimated to impact over 300 million people worldwide. Despite intense basic and translational research efforts, unraveling the etiopathology of depression remains a major challenge. This, in large part, is due to the heterogeneity of the disorder, that is further compounded by the complex interactions between genetic, epigenetic, inflammatory, endocrinological, and environmental factors (1,2). Dysregulation of multiple systems has been causally associated with depression, including immunological alterations, metabolic changes, endocrinological disturbances, and variability in the stress response. Stress and stress vulnerability vs. resilience remain significant causative factors. Current treatment regimens often consist of a combination of antidepressant medications and psychotherapy, along with other adjunctive methods to optimize outcome, resulting in variable success rates. Despite the multitude and variety of antidepressants currently available, approximately one-third of patients on the most commonly prescribed antidepressants, SSRIs or SNRIs, achieve the gold-standard of remission, while 30-40% of patients do not respond to their pharmacologic treatment regimen (3). Consequently, diagnostic subclassification and personalized treatment of depressive illness, based on presumptive multifactorial etiopathological mechanisms, underlies current and future research endeavors.

Oxytocin (OXT) is synthesized primarily in the magnocellular neurons of the paraventricular nucleus (PVN) and the

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supraoptic nucleus (SON) within the hypothalamus, and is subsequently secreted into the periphery via the posterior pituitary (2,3). OXT binds to the oxytocin receptor (OXT-R) which mediates its peripheral effects on milk ejection in lactation, cardiovascular control, and uterine contractions during labor. In addition, OXT has been associated with multiple social behaviors including social interactions, decision making during social interactions, mother-infant pair bonding, pair bonding for mating, and emotional reactivity (3,4). Thus, dysregulation of the oxytocinergic system is thought to play a role in multiple psychiatric disorders including autism, eating disorders, schizophrenia, and mood disorders (1). Considering the overlap between depressive symptoms and OXT's involvement in social behavior, it is plausible that aberrations in OXT levels may reflect this hormone's involvement in mediating at least some aspects of depressive illness, as previously reported in the literature. Therefore, alterations in both peripheral and central OXT levels may be observed in this illness (2).

A well-documented endocrine change in Major Depressive Disorder (MDD) is hypothalamic pituitary adrenal (HPA) axis dysregulation with an associated decrease in negative feedback (5). OXT and arginine vasopressin (AVP) are nine amino acid neuropeptides involved in the regulation of the HPA axis, with only a two amino acid structural difference (3,6). Whereas increased AVP levels are associated with stimulation of the HPA axis, OXT has a reciprocal function in that it is associated with inhibiting the HPA axis in response to stress (1,7). Consequently, a disrupted balance of these neuropeptides in MDD, and shifting of this balance to favor OXT thereby inhibiting AVP, may alleviate depressive symptoms (8).

Given its multifactorial nature, the precise role OXT plays in depression has yet to be elucidated. Current limited data regarding the relationship between peripheral OXT levels and depression are mixed, with studies having demonstrated both increased or decreased oxytocin levels in individuals with depression, as well as increased variability in oxytocin levels, suggesting overall dysregulation in oxytocinergic systems (9). Accordingly, we examined the relationship between plasma OXT levels in MDD patients as compared to healthy control subjects.

Over the past decades, an association has been established between inflammation and depression, and generically stress-related disorders, and inflammation-mediated cytokine release has been documented. Thus, a correlation between inflammatory biomarkers and OXT would be expected (10). Since growth factors and other neurotrophins may play a pathophysiological role in depressive illness, we measured inflammatory biomarkers, growth factors, chemokines and cytokines to further examine their role in depression and their possible association with blood levels of OXT.

2. METHODS

2.1. Study Design

Plasma samples (N=33) were obtained from MDD patients (ages 20-65 years) enrolled in two consecutively conducted studies approved by the Institutional Review Board (IRB) of Loyola University Medical Center. Patients with bipolar depression were not included in this study. Potential candidates were pre-screened with the 17-item Hamilton Depression Rating Scale (HAM-D) to establish the minimum severity requirement for study participation. Prospective subjects with a HAM-D 17 score ≥18, underwent complete screening assessment as stipulated in the study protocol.

The screening process consisted of a structured interview using the Mini International Neuropsychiatric Interview (MINI), the Diagnostic Interview for Genetic Studies (DIGS) and select rater-administered and self-rating scales. Blood chemistries, urinalysis, and toxicology screens were used to rule out any concomitant illnesses or drug use. Exclusion criteria included history of heart or thyroid disease, hypertension, diabetes, current tobacco use, illicit drug use within the preceding 12 months. Eligible patients on anxiolytic or hypnotic medications were permitted to continue at the discretion of the investigators. However, eligible patients on antidepressant or antipsychotic agents at time of enrollment underwent a 4-week washout period prior to beginning the study. Details of the screening and assessment instruments are provided in a related publication from our team (11).

Upon successful enrollment into the studies, blood samples for biomarker analyses were drawn between 9:00 and 10:00 hours to establish a baseline and patients were subsequently started on either Escitalopram (SSRI) monotherapy or Quetiapine (atypical antipsychotic) monotherapy. The latter was used to determine whether Quetiapine monotherapy could exert antidepressant efficacy in doses not exceeding 300 mg/day (12). Antidepressant effect of Quetiapine was secondary to its major metabolite, norquetiapine, being a norepinephrine reuptake inhibitor (12). Escitalopram dosing was initiated at 10 mg/day and maintained in the range of 10–30 mg/day. Quetiapine dosing was initiated at 25 mg/day and titrated up to a 300 mg/day at the investigator's discretion. Enrolled study subjects did not receive any other form of therapy during the entire study period. Follow-up blood draws and assessments using the aforementioned clinician-rated depression and anxiety scales were performed at weeks 2, 4, 8, and 12. Blood was drawn only if patients were deemed free of an active infectious process or bleeding (including menses), as well as recent disruptive life stressors (11).

To be regarded as study completers, patients were required to complete at least 8 weeks of treatment. Those who withdrew on or after 8 weeks of treatment had to complete the final assessment and their results were carried forward for data analysis.

2.2. Healthy Controls

Healthy control subjects (N=12), matched to mean age of patients, were recruited by word of mouth and the posting of campus advertisements. The screening protocol was the same as the one used for MDD subjects (11). Healthy control subjects who met eligibility criteria provided blood samples for biomarker analyses.

2.3. Plasma Oxytocin Assay

Plasma samples were centrifuged at 1600 x g for 15 minutes at 4°C, aliquoted, and stored in a – 80°C freezer. Samples were thawed at room temperature immediately prior to the assay. Plasma OXT was measured using an Enzyme Immunoassay (EIA) purchased from Enzo Life Sciences, Inc. (Farmingdale, New York). The assays were performed according to the manufacturer's instructions. As reported by the manufacturer, the EIA is highly sensitive (minimal detection rate = 15.6 pg/ml) with very little antibody cross-reactivity with other neuropeptides. Samples were diluted 1:8 in assay buffer to give reliable results within the linear portion of the standard curve and assayed in duplicate. The inter – and intra-assay coefficients of variation were <6.8% and <7.9%, respectively, for the assays (13).

Validation of these assays, as well as challenges associated with the measurement of OXT in bodily fluids are detailed elsewhere (13,14). The decision to measure OXT in unextracted samples is based on the fact that the majority of OXT in plasma is discarded during extraction procedures, leaving values in the low and unstable portion of the standard curve. Two recent studies from other laboratories have directly compared values in extracted versus non-extracted samples; in those studies, significantly stronger relationships between plasma OXT levels and behavioral outcomes were obtained in samples that were not extracted prior to assay (15,16). It is important to note that studies using enzyme-based (or radio-immunoassays) assay kits routinely give OXT values in widely different ranges (17). The sources of this variation remain poorly understood, but this is likely due, in part, to different assay procedures and differences in the antibodies used in these kits. In our studies, within-study associations in humans between plasma OXT, behavior, and other biomarkers are often significant regardless of the procedures employed (extraction or not, or different assay kits). This supports the usefulness of comparisons within a given study, but makes comparisons across studies difficult, even when those studies are done in the same laboratory.

2.4. Biomarker Measurement

Subsequent to an overnight fast, subjects rested in a reclined position for 30 minutes prior to venipuncture. Blood draws were scheduled between 9:00 and 10:00 hours. To separate plasma and serum, whole blood samples were spun, and immediately frozen and stored at – 80 degrees centigrade until analyzed. "Using "Evidence Investigator™" by Randox Technologies, multiple cytokines, chemokines, and growth factors were measured in a single sample (11). We have validated this Biochip array technology for blood samples in our previous studies. For each individual parameter, Biochip results are reliable and comparable to results obtained via individual ELISAs.

3. RESULTS

No significant difference was found between baseline OXT in MDD patients and healthy controls. At baseline the average OXT level was 429 pg/ml in MDD patients and 392 pg/ml in healthy controls (p=0.74). Male MDD patients (N=15) had average baseline levels of 457 pg/ml in comparison to female MDD patients (N=18), who had an average level of 406 pg/ml (p=0.69). No significant difference was found in baseline OXT levels between premenopausal and postmenopausal patients (p=0.2662). Within premenopausal patients, there was no significant difference between baseline OXT in healthy and depressed patients (p = 0.7459). MDD patients younger than 40 (N=14) had average baseline OXT levels of 372 pg/ml in comparison to MDD patients 40 and older (N=19), who had an average level of 470 pg/ml (p=0.43) although a trend may be evident. Compared to baseline OXT levels, MDD patients at week 8 (N=20) had OXT levels of 404 pg/ml (p=0.78) and week 12 (N=22) levels of 413 pg/ml (p=0.85).

Since baseline OXT levels showed a wide distribution of values, we sought to determine whether subgroups may exist. Accordingly, OXT levels were split into a *high* baseline group (N=17) and a *low* baseline group (N=16) based on the median value of the distribution. We also assessed possible confounding factors and determined that baseline OXT and BMI were significantly negatively correlated (r=-0.359, p=0.04) (Figure 1). A Chi-square distribution test revealed that African American patients were more likely to belong to the *high* baseline OXT group (9 high: 0 low) whereas Caucasian (6 high: 10 low) and Hispanic patients (1 high: 6 low) were more likely to belong to the *low* baseline OXT group (p=0.001).

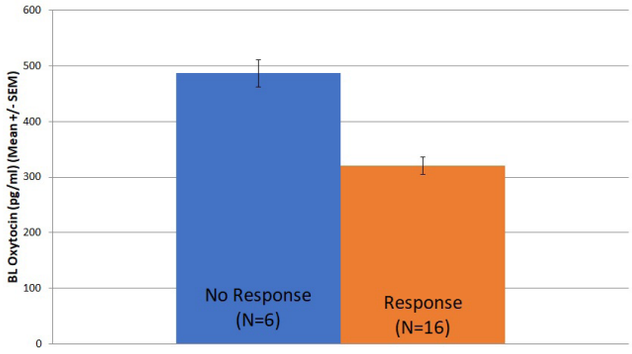

Figure 1. *Baseline oxytocin vs. BMI (R=-.359, p=0.04). Captions: Correlational analysis between baseline oxytocin levels and BMI revealed a significant negative correlation (r=-0.359, p=0.04)*

In the high OXT group, patients who had no prior depressive episodes (1141 pg/ml, N=3) had significantly higher baseline OXT levels than patients who had at least one prior depressive episode (472 pg/ml, N=14) (p=0.009) (Figure 2).

A Chi-square distribution test revealed no significant relationship between response to treatment and prior depressive episodes (p=0.47). However, total cohort analysis of baseline OXT revealed that MDD patients who were treatment responders had significantly lower OXT levels (320 pg/ml, N=16) than MDD patients who did not respond to treatment (486 pg/ml, N=6) (p=0.047) (Figure 3).

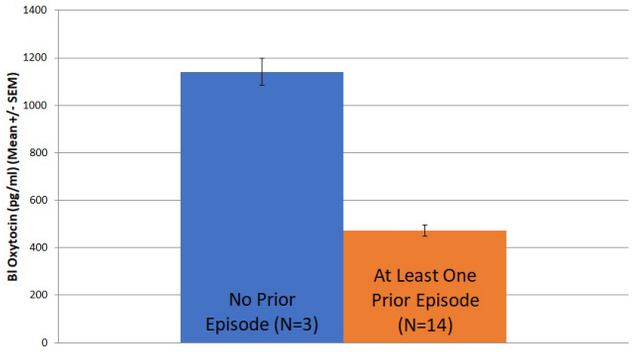

Figure 2. *Relationship between baseline oxytocin levels and depressive episodes (p=0.009). Captions Subjects were divided into high and low oxytocin groups via median split. For the high oxytocin group, patients who had no prior depressive episodes (1141 pg/ml, N=3) had significantly higher baseline oxytocin levels compared to patients who had at least one prior depressive episode (472 pg/ml, N=14) (p=0.009)*

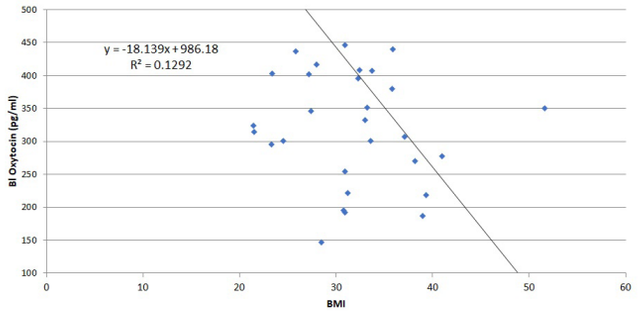

Figure 3. *Baseline oxytocin & response to treatment (p = 0.047). Captions: Analysis of baseline oxytocin levels of the total cohort found that MDD patients who were treatment responders had significantly lower oxytocin levels (320 pg/ml, N=16) than MDD patients who did not respond to treatment (486 pg/ml, N=6) (p=0.047)*

Correlational analyses in the total cohort between OXT and biomarkers revealed a trend toward statistical significance between OXT and Von Willebrand factor (VWF) (r=0.305, p=0.09) (Table 1). Correlational analysis between the *high* OXT group and biomarkers revealed significant correlations between OXT and VWF (r=0.577, p=0.015) and EGF (r=0.503, p=0.04) (Table 1).

Overall, no significant correlations were found between baseline OXT levels and scales for depression or anxiety. However, correlational analysis between the *high* OXT group and rating scales revealed a trend toward significance between OXT and HAM-D 17 (r=0.461, p=0.06).

Table 1. *Plasma Oxytocin and Biomarkers. Biomarkers were compared to baseline oxytocin levels. No significant relationship was found between any inflammatory biomarker and baseline oxytocin levels upon overall comparison of values. Overall analysis revealed a trend toward significance between oxytocin and VWF (r=0.305, p=0.09). After a median-split division of oxytocin into low and high oxytocin subgroups, significant correlations (*) were found between baseline oxytocin and VWF (r=0.577, p=0.015) and EGF (r=0.503, p=0.04) in the high oxytocin group.*

Overall		CRP	VWF	IL-2	IL-4	IL-6	IL-8	IL-10	IFNG	TNF-α	EGF
Baseline Oxytocin	Pearson Correlation	-0.045	0.305	-0.266	-0.090	0.064	-0.113	-0.123	-0.080	-0.124	0.013
	Sig. (2-tailed)	0.806	0.089	0.141	0.650	0.729	0.538	0.540	0.669	0.497	0.943
	N	32	32	32	28	32	32	27	31	32	32
Low Oxytocin Group		CRP	VWF	IL-2	IL-4	IL-6	IL-8	IL-10	IFNG	TNF-α	EGF
Baseline Oxytocin	Pearson Correlation	0.217	-0.051	0.261	0.021	-0.141	0.180	0.320	0.304	0.190	-0.243
	Sig. (2-tailed)	0.419	0.858	0.347	0.942	0.617	0.521	0.265	0.291	0.498	0.382
	N	16	15	15	14	15	15	14	14	15	15
High Oxytocin Group		CRP	VWF	IL-2	IL-4	IL-6	IL-8	IL-10	IFNG	TNF-α	EGF
Baseline Oxytocin	Pearson Correlation	0.057	0.577*	-0.477	-0.093	0.169	-0.081	-0.112	-0.179	-0.227	0.503*
	Sig. (2-tailed)	0.833	0.015*	0.053	0.751	0.515	0.758	0.716	0.491	0.380	0.040*
	N	16	17	17	14	17	17	13	17	17	17

4. DISCUSSION

4.1. OXT and Depression

The current literature is mixed regarding the association between OXT levels and depressive illness (2,18–21). While decreased peripheral OXT levels have been correlated with increased depressive symptoms, interestingly, patients with worsening depression (as well as other clinical disorders) have sometimes shown increased and/or dysregulated OXT levels (22). Given the broad functions of OXT, including HPA axis and autonomic regulation, social behavior, and a role in inflammation, multiple confounding factors likely play a mechanistic role. Another proposed explanation for the inconsistent data is that multiple prior studies were conducted without a proper control group, relied on a single biological sample, or consisted of a mixed population of patients afflicted by other disorders, such as fibromyalgia or bipolar disorder (18,19).

We found no statistically significant differences between baseline plasma OXT levels in MDD patients and healthy controls. Van Londen et al. (1997) reported similar findings, although they noted that patients trended towards higher OXT levels (21). Scantamburlo et al. (2005) compared concentrations of neurophysin-I in plasma and cerebrospinal fluid and found no significant difference between patients and healthy subjects in either sample. Neurophysin-I is the prohormonal carrier protein associated with OXT and more structurally stable, and thus proposed as indicative of chronic neurohormonal secretion (20). Furthermore, it has been suggested that multiple samples of OXT levels should be drawn due to diurnal variation of OXT (23,24). Single samples may be especially problematic in depressed patients, whose OXT level is reportedly variable than in healthy controls and depressed women are more likely than controls to display a dysregulated pattern of peripheral OXT release (22).

Some studies have reported decreased OXT levels in depressed patients. According to Ozsoy et al. (2009), not only did patients exhibit lower serum OXT concentrations, but this was true at both pre-treatment and post-treatment. This trend pertained mostly to women, however, the study included few men (18). Yuen et al. (2014) found significantly lower plasma OXT levels in female depressives compared to healthy female controls, yet some post-hoc statistical tests for males revealed no significance due to higher variability in male OXT levels.

To further complicate the issue, several studies have reported increased plasma OXT concentrations in depressive illness and that these increases peak most significantly during the night (1,19). Parker et al. (2010) measured plasma OXT levels over a 16-hour period and found a significantly increased nocturnal plasma OXT level in depressed patients. They noted this elevation occurred in the absence of corresponding depression-related alterations in AVP and cortisol levels, indicating an effect independent of the HPA axis. It was postulated that in these patients, oxytocinergic dysregulation manifests itself symptomatically as distress and impaired social behavior (19). Increased OXT in depression has been further supported by a study of OXT mRNA levels in depressed patients. Notably, the trend of increased OXT mRNA levels was only seen in autopsy measures of OXT in the PVN of patients with melancholic depression, not when comparing the entire cohort of depressed patients to controls (26). This suggests that a dysregulated oxytocinergic system may represent a subset of depressed patients, thereby possibly contributing to the mixed findings in the literature. This further supports the notion of a dysregulated oxytocin-vasopressin system in MDD patients, and may also reflect changes to the system over the lifespan, secondary to stressful and emotional experiences that may epigenetically modify OXT, vasopressin, and their receptors (9,22).

We also examined the relationship between baseline OXT and past depressive episodes. Within the *high* OXT subgroup, patients with no previous depressive episodes had significantly higher baseline OXT levels than patients who had suffered at least one prior episode ($p=0.009$). Given this strong statistical significance, it is plausible that OXT is a physiological diagnostic marker indicative of first episode of depressive illness, an observation warranting further exploration. In the current study particularly high levels of OXT were measured in the small group of patients who did not have a prior history of depression (Figure 2). it is possible that in these individuals increases in OXT were associated with early compensation for disease-associated processes, including inflammation (9). Notably, this relationship was not found in the *low* OXT group or for overall baseline OXT comparisons. Within the general population, variable OXT concentrations have been reported (5). Given the antagonistic effect of OXT on the HPA axis and its positive role in social functioning, it is plausible that higher OXT levels may confer protection against depressive episodes. This is further supported by a study that examined the relationship of OXT with social support and degree of loneliness (27). This study found a negative correlation between levels of loneliness and social support within the high OXT subgroup, further suggesting that in the presence of adequate OXT levels, the presence of good social support may diminish loneliness in depressed patients, and thus attenuate depressive symptoms. Interestingly, high OXT has been reported as predictive of greater post-partum depression (PPD) severity in women previously diagnosed with MDD. Furthermore, a higher plasma OXT concentration during the third trimester was associated with more severe symptomatology for PPD in females with a history of depression (28). Dose-dependent effects of OXT have been suggested by several experiments, with high doses of OXT even hypothesized to activate the vasopressin receptor, which may counteract OXT's protective role against stress. If confirmed, this would result in making the effects of OXT more difficult to predict, as chronically increased OXT levels may be secondary to vasopressin receptor stimulation and corresponding downregulation of the OXT receptor, and thus paradoxically result in more defensive responses (7).

4.2. OXT and Rating Scales

Given the proposed association of OXT with depressive illness, a correlation should be expected between OXT levels and depressive symptomatology, as reflected in depression and anxiety rating scales. While we found no significant correlations between baseline OXT levels and depression or anxiety scores, correlational analysis between the *high* OXT group and rating scales revealed a nearly significant positive correlation between plasma OXT and HAM-D 17 scores. This is supported by a study of sub-clinical depression in which an intervention group received "warm touch" from their spouses. This study found a positive correlation between greater depressive symptomatology and plasma and salivary OXT during the pre-intervention period. Interestingly, for this intervention group, salivary OXT levels did not remain elevated during the intervention. In the post-intervention phase, there were no longer any significant differences in plasma OXT levels in relation to depressive symptomatology. It was postulated that increased OXT levels were secondary to excessive stress levels, thus the "warm touch" intervention successfully lowered salivary OXT levels (29).

A direct association between OXT levels and Beck Depression Inventory (BDI) scores has been reported (23,30,31). In a study of HIV-positive African American and Caribbean women, those with very-high or very-low plasma OXT levels exhibited increased depressive symptomatology, as measured by the BDI (23). Furthermore, in the outpatient setting, a positive correlation was found between plasma OXT levels and temperament and character inventory (1,32). The study by Bell et al. (2006) further specified that the reward dependence sub-score accounted for 17% of the variability in plasma OXT levels.

However, there are also reports of negative correlations between plasma OXT and depressive symptomatology (6,33). These findings were based predominantly on the HAM-D, and the Spielberger State-Anxiety Inventory (1,33). In another study, females with fibromyalgia had a negative correlation between BDI scores and OXT levels in depressed versus to non-depressed patients. Subgroup analysis revealed a negative correlation between OXT levels and pain, stress, and depression scores. Interestingly, a positive correlation has been observed between OXT levels and happiness scores, suggesting that OXT may play a role in improving depressive symptoms such as anhedonia and impaired social reward responsiveness (34,35). The discrepant relationship between depressive symptoms and OXT levels further suggests that a dysregulated oxytocinergic pathway not only plays a role in depression but may also explain why there are mixed reports in the literature (31). This non-linear relationship could also help to explain why overall baseline OXT levels may not correlate with baseline scales for depression or anxiety (18).

4.3. Oxytocin and Treatment

We observed no statistically significant changes in plasma OXT levels over the course of treatment. Normalization of the HPA axis has been a major target of recent treatments for stress-related diseases, such as depression and anxiety, as their etiology is often multifactorial, including a dysregulated stress response and other factors such as genetic predisposition (5,36). Consequently, several clinical studies have examined the relationship between OXT and antidepressant treatment, often demonstrating that treatment does not significantly affect OXT levels (5,20). In a study of acute apomorphine or clonidine injections on OXT neurophysin levels in depressed patients there was no effect of ether medication (20). This was further supported by Ozsoy et al. (2009), who found that neither antidepressant drug treatment nor ECT had a significant effect on serum OXT levels (18). Of note, the patient population for this study consisted of patients with bipolar disorder and MDD patients. Similarly, Keating et al. (2013) found no significant change in OXT and cortisol concentrations in pre-SSRI and post-SSRI conditions (5). The relationship between OXT and SSRI is of interest, as serotonin is known to increase plasma OXT and plasma vasopressin levels (37). Consequently, it is plausible that OXT administration would also augment the effectiveness of antidepressant treatment. This has been demonstrated by one open trial study that found an improvement in depressive symptomatology with the combined administration of intranasal OXT and oral escitalopram. It is important to note that this trial consisted of a small patient cohort and did not include a control group. Consequently, it could not be differentiated whether the positive effect on depressive illness was secondary to the medication combination or due to a placebo effect (36). Unfortunately, while animal models of depression have suggested an antidepressant effect from OXT, this effect does not seem to be an effective alternative treatment, at least at this point. While intranasal OXT does not demonstrate a significant side effect profile, it has been ineffective in and of itself in ameliorating symptoms of depression or anxiety (38). However, research regarding OXT as adjunctive treatment and long-term use of OXT merits further investigation. In conjunction with pre-clinical data demonstrating increased OXT mRNA in the magnocellular PVN subsequent to acute citalopram administration, further research is warranted to examine this relationship. It is also important to consider that pre-clinical data did not demonstrate an increase in OXT mRNA levels subsequent to chronic citalopram (39).

After stratifying into *low* and *high* OXT subgroups, we found that responders to treatment had recorded significantly lower OXT levels at baseline compared to non-responders. Additional statistical analysis demonstrated that MDD patients who responded to treatment were no more likely to fall into the *low* OXT group than those who did not respond to treatment. A study by Lien et al. (2017) found that in the post-treatment condition, OXT levels in bipolar patients remained elevated whereas MDD patients demonstrated a slight decrease. Comparatively, MDD patients had significantly lower OXT levels, compared to bipolar patients, after treatment (6). Interestingly, one study of African American male veterans found a significant increase in psychiatric

medication use among those with higher OXT levels, even after adjusting for BMI (40).

4.4. Oxytocin and Metabolic Effects

We found a significant negative correlation between plasma oxytocin and BMI. Obesity has been associated with inflammation specifically characterized by a chronic state of systemic inflammation that contributes to insulin resistance, dyslipidemia, diabetes and cardiovascular disease (41). The physiologic effects of OXT on metabolism and its therapeutic potential for metabolic disorders have been discussed in a review article by McCormack et al. (42). In model systems, OXT promotes weight loss by decreasing energy intake. Pre-clinical studies have suggested that OXT plays a critical role in glucose and lipid metabolism, controlling weight, increasing motivation for being physically active, and decreasing consumption of food (43). This was supported by a study of African American male veterans that found lower HbA1c levels, BMI, and weight in those whose oxytocin levels were most elevated. Overall, these observations suggest a positive metabolic role of OXT (40). In the literature OXT has been referred to as a "satiety hormone" and has been demonstrated to be anorexigenic by affecting the reward pathway (18,44,45). Furthermore, preclinical studies have shown reduced plasma OXT levels in mice with diet-induced obesity and a subsequent increase in OXT levels in synatpotagmin-4 deficient mice that are protected against diet-induced obesity (46,47). It has also been shown that patients afflicted by Type 2 Diabetes and obesity are more likely to have lower oxytocin levels (40,47). Interestingly, the literature is mixed, as one study reported a weak positive correlation between plasma OXT levels and BMI in male patients only (18). Given the overlap between OXT's metabolic effects and the symptoms of decreased appetite and weight changes that may be seen in depression, it is plausible that these symptoms may be, at least partially, induced by a dysregulated oxytocinergic pathway (26).

4.5. OXT and Demographics

We found that African Americans were more likely to belong to the *high* OXT subgroup, whereas Caucasians and Hispanics were more likely to belong to the *low* OXT subgroup. In the context of pain tolerance, differences have been demonstrated between OXT, an inhibitor of the pain response, and ethnicity. African American women exhibited lower tolerance to ischemic pain as well as lower plasma OXT levels. In this study Grewen et al. (2008) also reported that African American females had significantly lower plasma OXT levels at baseline compared to non-Hispanic White females. A subset of study participants also underwent the Trier Social Stress Test (TSST), which elicits cardiovascular and neuroendocrine stress responses. Subsequent to the TSST stressor, a strong correlation was found between elevated baseline OXT and elevated OXT levels after stress. Interestingly, this study also noted a significant negative correlation between OXT levels and systolic blood pressure only in African American participants (48).

While we found no statistically significant differences between male and female patients, there is literature suggesting a gender disparity in OXT levels. In a study by Holt-Lunstad et al. (2011), females with high depressive symptomatology demonstrated significantly elevated plasma OXT levels compared to males and non-depressed females (29). Some, but not all, studies have shown that females have higher OXT levels and increased expression of the OXTR (49,50). Furthermore, this sexual dimorphism has been observed in areas of the brain where OXT exhibits behavioral effects, such as the ventromedial hypothalamic nucleus (50,51). Notably, the literature is mixed regarding the relationship between gender and OXT, as several studies have demonstrated no significant difference or even decreased OXT levels in females (6,18,25). It has been hypothesized that one contributor to variation in female OXT levels may be gender-specific features, such as lactation history and birth history. Peripheral OXT levels also fluctuate during various phases of the menstrual cycle, and may also vary in those who use oral contraceptives, making it more difficult to interpret baseline OXT levels (52). It has also been postulated that females may be more sensitive to the interplay between OXT and stress, as ovarian hormones, such as estrogen, may serve as an additional factor involved in regulating the HPA axis (18).

4.6. Oxytocin and Measured Biomarkers

Inflammation-mediated cytokine release in depressive illness is well established. A correlation between inflammatory biomarkers and OXT is plausible given literature regarding an inflammatory pathophysiology of depression in conjunction with HPA axis overactivation and oxytocinergic dysregulation in depressed patients. Interestingly, while we did not find any significant relationships between plasma OXT levels and measured interleukins, we found a nearly significant positive relationship between baseline OXT and Von Willebrand factor (VWF). After stratifying patients into *high* and *low* OXT subgroups, there was a significant positive relationship between plasma OXT level and VWF and Epidermal Growth Factor (EGF) within the *high* OXT group. Within the limited literature relating OXT to inflammation, especially in the context of depressive illness, there are also mixed data (47,53). EGF has been discussed in relation to OXT, in the context of the inflammatory cascade during pregnancy. EGF is a growth factor that accumulates in amniotic fluid and can be measured in maternal and fetal blood. EGF binds to the EGF receptor, activating tyrosine kinase and several subsequent signaling cascades to induce prostaglandin production. OXT is an agonist of prostaglandin production, with both EGF and OXT stimulating cyclooxygenase-2 (COX-2) expression in myometrial cells. COX-2 inhibition produces an augmented antidepressant response and even reversal of treatment resistance in both MDD and bipolar disorder (54,55). Furthermore, it was found that this signaling requires

protein kinase c activity (53). Interestingly, OXT has also been postulated to have anti-inflammatory effects. Animal studies found a negative correlation between serum OXT levels and High Sensitivity C-Reactive Protein (*hs*-CRP), in the context of dyslipidemia. Treatment with OXT resulted in decreased expression of Interleukin-6 and Monocyte Chemoattractant Protein-1 (MCP-1) and elevated Adiponectin, however, these trends did not reach statistical significance (47). In summary, further investigation is warranted to elucidate the role of these biomarkers and their possible relationship with OXT in the context of depressive illness.

5. CONCLUSION

While there were no significant correlations between baseline OXT levels and any rating scores, a significant positive relationship was found between MDD patients in the *high* OXT group and HAM-D 17. Treatment responders had significantly lower OXT levels at baseline than non-responders, indicating that comparatively low OXT may be a predictor of response to treatment. Within the high OXT group, patients who had no previous depressive episodes had significantly higher baseline OXT levels than those with one or more prior episodes, suggesting OXT may be a potential diagnostic marker for depressive illness. Significant positive relationships were found between patients in the *high* OXT group and VWF and EGF. There was a significant negative relationship between OXT and BMI.

One potential limitation of our study is the use of plasma OXT, as peripheral blood levels may not be an accurate representation of central OXT levels. Furthermore, we did not account for temporal variations in OXT.

Ethical Statement

1. This material has not been published in whole or in part elsewhere
2. The manuscript is not currently being considered for publication in another journal
3. Informed consent was obtained for experimentation with human subjects

Declaration of conflicting interests

The authors declare no conflict of interest with respect to the research, authorship, or publication of this article. The authors are responsible for the content and writing of the paper.

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