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Low Oxytocin Levels Are Related to Alexithymia in Anorexia Nervosa

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Abstract

Objective—Anorexia nervosa is associated with social-emotional functioning deficits and low levels of the social neurohormone oxytocin, even after weight gain. The relationship between low oxytocin levels and social-emotional functioning impairment has not been studied.

Method—We performed a cross-sectional study of 79 women (19 who were less than 85% of ideal body weight [IBW] with anorexia nervosa [AN], 26 who were 90–120% IBW with a history of AN [AN-WR], and 34 who were 90–120% IBW with no eating disorder history [H]). We administered the Eating Disorder Examination–Questionnaire (EDE-Q), Liebowitz Social Anxiety Scale–Self Report (LSAS-SR), Dimensional Assessment of Personality Pathology–Basic Questionnaire (DAPP-BQ; suspiciousness and insecure attachment subscales), and the Toronto Alexithymia Scale (TAS-20). We also analyzed fasting serum oxytocin levels.

Results—Most measures of social-emotional functioning showed impairment in women with AN and AN-WR compared to H. Oxytocin levels were low in AN-WR compared to H. Across groups, low oxytocin levels were associated with difficulty identifying feelings ($r=-0.45$, $p=0.008$) and overall alexithymia ($r=-0.34$, $p=0.0489$).

Discussion—We speculate that low oxytocin levels may contribute to alexithymia in women with anorexia nervosa.

Women with anorexia nervosa (AN) are at risk for premature mortality (Crow et al., 2009; Keshaviah et al., 2014) and demonstrate social functioning impairments, including social

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anxiety (Bulik, Beidel, Duchmann, Weltzin, & Kaye, 1991), suspiciousness and insecure attachment (Holliday, Uher, Landau, Collier, & Treasure, 2006), difficulty recognizing others' emotions (Jansch, Harmer, & Cooper, 2009; Russell, Schmidt, Doherty, Young, & Tchanturia, 2009), and alexithymia (difficulty understanding one's own emotions; Bourke, Taylor, Parker, & Bagby, 1992; Lule et al., 2014). Social-emotional functioning deficits predict poorer long-term outcomes in AN (Speranza, Loas, Wallier, & Corcos, 2007) and do not resolve with weight gain (Beadle, Paradiso, Salerno, & McCormick, 2013; Beales & Dolton, 2000; Coulon, Jeammet, & Godart, 2009; Holliday et al., 2006; Parling, Mortazavi, & Ghaderi, 2010; Speranza et al., 2007; Tchanturia et al., 2012).

Oxytocin is an anorexigenic neurohormone that reduces food intake in animals and humans (Blevins & Baskin, 2015) and regulates social-emotional functioning. In animals, oxytocin has anxiolytic (Ring et al., 2006; Windle, Shanks, Lightman, & Ingram, 1997) and pro-social effects (Lukas et al., 2011; Pedersen & Prange, 1979). When administered to humans, oxytocin increases gaze toward the eye region (Guastella, Mitchell, & Dadds, 2008), trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and, particularly in individuals with higher alexithymia scores, the ability to recognize emotional expressions (Aoki et al., 2014; Fischer-Shofty, Levkovitz, & Shamay-Tsoory, 2013; Guastella et al., 2010; Lischke et al., 2012; Luminet, Grynberg, Ruzette, & Mikolajczak, 2011; Marsh, Yu, Pine, & Blair, 2010). Further, oxytocin administration increases the sharing of emotional experiences with others (Lane et al., 2013). We have reported low basal serum oxytocin levels (compared to healthy women, H) in women with AN (Lawson et al., 2011) and those with a history of AN who are now weight-restored and in partial or full recovery (AN-WR; Afinogenova et al., 2016 [same study sample as described here]; Lawson et al., 2012). These data imply that basal oxytocin levels may be low in women with AN regardless of weight status and raise the question of whether low oxytocin levels may contribute to symptoms.

Whether low oxytocin levels in women with AN are related to difficulties in social-emotional functioning has not been studied. We therefore investigated the relationship between oxytocin levels and social-emotional functioning in women with AN, AN-WR, and H, hypothesizing that lower oxytocin levels would be associated with increased severity of social-emotional functioning impairment.

Methods

Participants

We studied 79 ambulatory women (19 AN, 26 AN-WR, and 34 H), 18–45 years old. Clinical characteristics and oxytocin levels have been reported (Afinogenova et al., 2016). Social-emotional functioning measures and their relationship to oxytocin levels have not been published. Participants with AN met DSM-5 criteria (American Psychological Association, 2013) and were <85% ideal body weight (IBW). Participants with AN-WR were 90–120% IBW and met DSM-5 criteria for past AN. H were 90–120% IBW, had regular menstrual cycles, and reported no eating disorder history (assessed by the Structural Clinical Interview for DSM-IV [SCID]; First, Spitzer, M., & Williams, 2002) and no significant medical problems. Exclusion criteria for all participants included diabetes, pregnancy, breastfeeding, 3,4-methylenedioxymethamphetamine (MDMA) use, and oral contraceptive use.

Methods

This study was approved by Partners HealthCare, Inc. and Harvard Medical School Institutional Review Boards. Written informed consent was obtained prior to procedures.

Participants presented to the Massachusetts General Hospital Clinical Research Center, where trained personnel confirmed a diagnosis of AN using the SCID. Amenorrhea was not required, making the diagnosis consistent with DSM-5 criteria (not yet published at the time of data collection). We administered a medical history questionnaire and self-report psychological measures, including the Eating Disorder Examination–Questionnaire (EDE-Q; Fairburn & Beglin, 1994), the Liebowitz Social Anxiety Scale–Self Report (LSAS-SR; Rytwinski et al., 2009), the Dimensional Assessment of Personality Pathology–Basic Questionnaire (DAPP-BQ; suspiciousness and insecure attachment subscales; Kushner, Quilty, Tackett, & Bagby, 2011), and the Toronto Alexithymia Scale (TAS-20; Bagby, Parker, & Taylor, 1994).

Bionutritionists measured height, weight, and frame size (determined by comparing elbow breadth with race-specific norms derived from US National Health and Nutritional Examination Survey-I; Frisancho & Flegel, 1983) and calculated %IBW (using the “Metropolitan height and weight tables,” 1983) and body mass index (BMI). A fasting blood draw was performed.

Psychological Measures

On all of these well-validated self-report measures, higher scores indicate increased symptom severity. The EDE-Q, completed by all participants, measures eating disorder psychopathology (Fairburn & Beglin, 1994). A global score plus subscales (dietary restraint, eating concern, shape concern, and weight concern) are calculated, ranging from 0 to 6. The LSAS-SR, completed by 71 participants (19 AN, 24 AN-WR, 28 H), uses 4-point Likert-type scales to assess fear and avoidance of 11 social situations and 13 situations of public performance over the past week (Rytwinski et al., 2009). Scores are calculated by summing the fear or avoidance ratings for each type of situation. For the DAPP-BQ (Kushner et al., 2011), completed by 71 participants (19 AN, 24 AN-WR, 28 H), participants rate 14 suspiciousness and 16 insecure attachment items on a 5-point Likert-type scale from 1 (“Very unlike me”) to 5 (“Very like me”). Scale scores are sum scores. For the TAS-20, 34 participants (9 AN, 14 AN-WR, 11 H) rated 20 items on a 5-point Likert-type scale ranging from 1 (“Strongly disagree”) to 5 (“Strongly agree”). Sum scores are calculated for three subscales (difficulty identifying feelings [7 items], difficulty describing feelings [5 items], and externally oriented thinking [8 items]) and a global score (≤51: non-alexithymia, 52–60: possible alexithymia, ≥61: alexithymia; Bagby, Parker, et al., 1994; Bagby, Taylor, & Parker, 1994). Internal consistency was good for the TAS-20 (α=0.857) and excellent for DAPP-BQ, LSAS-SR, and EDE-Q (α=0.944, 0.968, and 0.942, respectively).

Biochemical Analysis

Serum was stored at −80°C. Oxytocin was measured in unextracted serum by ELISA (Assay Designs, Inc., Ann Arbor, MI, USA; Afinogenova et al., 2016). We have demonstrated a robust correlation between extracted and unextracted serum oxytocin levels (Lawson et al.,

2013). The detection limit was 12.5 pg/mL. In-house QCs had a mean of 152 and 338 pg/mL and a between-assay CV of 15 and 18%, respectively.

Data Analysis

We used JMP 12 (SAS Institute, Inc., Cary, NC, USA) for statistical analyses. We compared clinical characteristics, psychiatric measures, and oxytocin levels using Fisher's Least Significant Difference test. We utilized Hedges' g to determine effect sizes for pairwise comparisons and Pearson's correlations to examine the relationship between oxytocin levels and psychological measures. To control for potential confounders (BMI and amenorrhea), we used multivariate least square analyses. To analyze contributors to TAS-20 scores, we used hierarchical regression. Data are reported as mean±SEM. Statistical significance is defined as a two-tailed p-value <0.05.

Results

Clinical Characteristics

Table 1 shows clinical characteristics as reported in Afinogenova et al. (2016). Self-reported mean time since recovery of AN-WR was 40.8±6.6 months (range: 5–104 months). Amenorrhea was reported by 14 participants with AN (of 19 who provided this information), 3 of 26 with AN-WR, and 0 of 34 H.

Fasting oxytocin levels were lower in participants with AN-WR (984±93 pg/mL, range: 115–1,962 pg/mL) than H (1,501±114 pg/mL, range: 882–4,110 pg/mL). This difference remained significant after controlling for BMI and amenorrhea ($p=0.003$). Oxytocin levels in women with AN were numerically between AN-WR and H (mean: 1,230±86 pg/mL, range: 690–1,938 pg/mL) but did not significantly differ from either group.

Social-Emotional Functioning (Table 1)

LSAS-SR—On the social fear, public fear, and social avoidance subscales, scores were lowest in H, intermediate in women with AN-WR, and highest in women with AN ($p\leq0.03$). On the public avoidance subscale, scores were higher in women with AN than women with AN-WR and H ($p\leq0.002$), who did not differ on this measure ($p=0.10$).

DAPP-BQ—Suspiciousness was lowest in H, intermediate in participants with AN-WR, and highest in participants with AN ($p\leq0.047$). Insecure attachment scores were higher in participants with AN than participants with AN-WR and H ($p\leq0.03$), and did not differ between participants with AN-WR and H ($p=0.35$).

TAS-20—Difficulty describing feelings, difficulty identifying feelings, and total alexithymia scores were higher in participants with AN and AN-WR than H ($p\leq0.002$) and did not differ between participants with AN and AN-WR ($p\geq0.20$). Groups did not differ on the externally oriented thinking subscale ($p=0.17$).

Relationship Between Oxytocin and Social-Emotional Functioning

Across groups, oxytocin was negatively associated with difficulty identifying feelings ($r=-0.45$, $p=0.008$) and TAS-20 total score ($r=-0.34$, $p=0.049$; Figure 1). These relationships remained significant after controlling for BMI and estrogen status (presence or absence of amenorrhea; $p=0.005$ and 0.02, respectively). There were no significant associations between oxytocin and other social-emotional measures ($p\geq 0.12$).

In a hierarchical multiple regression model with Oxytocin (step 1), BMI (step 2), and Estrogen Status (step 3), Oxytocin and BMI accounted for 13.3% ($p=0.02$) and 13.1% ($p=0.01$) of variance in TAS-20 total score, respectively. Using the same model, Oxytocin and BMI accounted for 20.3% ($p=0.005$) and 11.3% ($p=0.07$) of variance in difficulty identifying feelings, respectively.

Discussion

To the best of our knowledge, our study is the first to show that low levels of the neurohormone oxytocin are associated with greater severity of alexithymia. This novel finding is important, because it raises the question of whether oxytocin might be a potential mediator of alexithymia, which predicts poorer outcomes in women with AN.

Oxytocin, a key hormone involved in social interaction, has been implicated in disorders involving social deficits, e.g., autism. Females with AN have elevated autistic traits (Baron-Cohen et al., 2013; Tchanturia et al., 2013), suggesting overlap between these disorders, which have both been associated with single-nucleotide polymorphism (SNP) variations in the oxytocin receptor gene (Acevedo, Valencia, Lutter, & McAdams, 2015; Jacob et al., 2007; Wu et al., 2005). Here, we report significantly lower fasting serum oxytocin levels in women with AN-WR than healthy controls, while oxytocin levels in AN were numerically lower than those of healthy controls at the trend level. Across all groups, we found that lower oxytocin levels were associated with increased alexithymia, in particular in identifying one's own feelings, independent of BMI and estrogen status. Whether oxytocin plays a role in the social-emotional functioning deficits observed in individuals with a life-time diagnosis of AN merits investigation.

Alexithymia is a well-described social-emotional functioning deficit in adult women and adolescents with AN (Corcos et al., 2000; Speranza et al., 2005; Speranza et al., 2007) and a poor prognostic factor. In a three-year prospective study of 63 women with AN and 39 with bulimia nervosa, the difficulty identifying feelings subscale of the TAS-20 was negatively associated with clinical improvement at follow-up (Speranza et al., 2007). Furthermore, it has been hypothesized that deficits in emotional processing serve as a barrier to effective cognitive therapy (Jansch et al., 2009). The recognition of oxytocin as a potential mediator of these processes is important, as identifying the underlying neurobiology is a critical step in developing targeted treatments and improving outcomes. A prior study showed an interaction between oxytocin receptor genotype and childhood attachment in predicting adult alexithymia as well as brain structure and functioning in regions involved in salience processing and mentalizing (Schneider-Hassloff et al., 2016). Others have shown that administration of oxytocin improves key processes that are impaired in alexithymia: emotion

recognition (Aoki et al., 2014; Fischer-Shofty et al., 2013; Guastella et al., 2010; Lischke et al., 2012; Luminet et al., 2011; Marsh et al., 2010) and emotion expression (Lane et al., 2013), further emphasizing the link between oxytocin and social-emotional functioning. Based on this, oxytocin has recently been proposed as a potential novel therapy in patients with alexithymia. Our data linking low serum oxytocin levels to higher alexithymia scores in women with AN are consistent with these findings and support the hypothesis that low oxytocin might contribute to these symptoms. A study investigating the impact of single-dose intranasal oxytocin (40 IU) did not find evidence for an improvement of social-emotional functioning in AN (Leppanen, Cardi, et al., 2017), and a recent meta-analysis showed improvements of social-emotional functioning following intranasal oxytocin administration in healthy individuals but not in clinical populations (Leppanen, Ng, Tchanturia, & Treasure, 2017). However, it is important to note that these studies used supraphysiologic levels of oxytocin, while our study investigated the link between physiologic levels of oxytocin and social-emotional functioning. It is conceivable that the revealed link between oxytocin levels and total alexithymia and difficulty identifying feelings only exists within the physiologic range of oxytocin, which emphasizes the need for studies of endogenous oxytocin levels in this population.

Limitations of this study include its small sample size, which may have introduced bias and/or reduced our ability to detect associations between oxytocin levels and social-emotional functioning. Even so, we demonstrated correlations between oxytocin levels and measures of alexithymia. This is a cross-sectional study, and therefore causality cannot be determined. Longitudinal studies in larger sample sizes of women with AN will be important to investigate the role of oxytocin in impaired social-emotional functioning. In addition, future studies are required to identify factors explaining individual variance in oxytocin levels within individuals with current or past AN.

In summary, we demonstrate that low oxytocin levels are associated with increased alexithymia, independent of BMI and estrogen status. Further investigation is needed to determine whether low oxytocin levels contribute to symptoms of alexithymia in AN.

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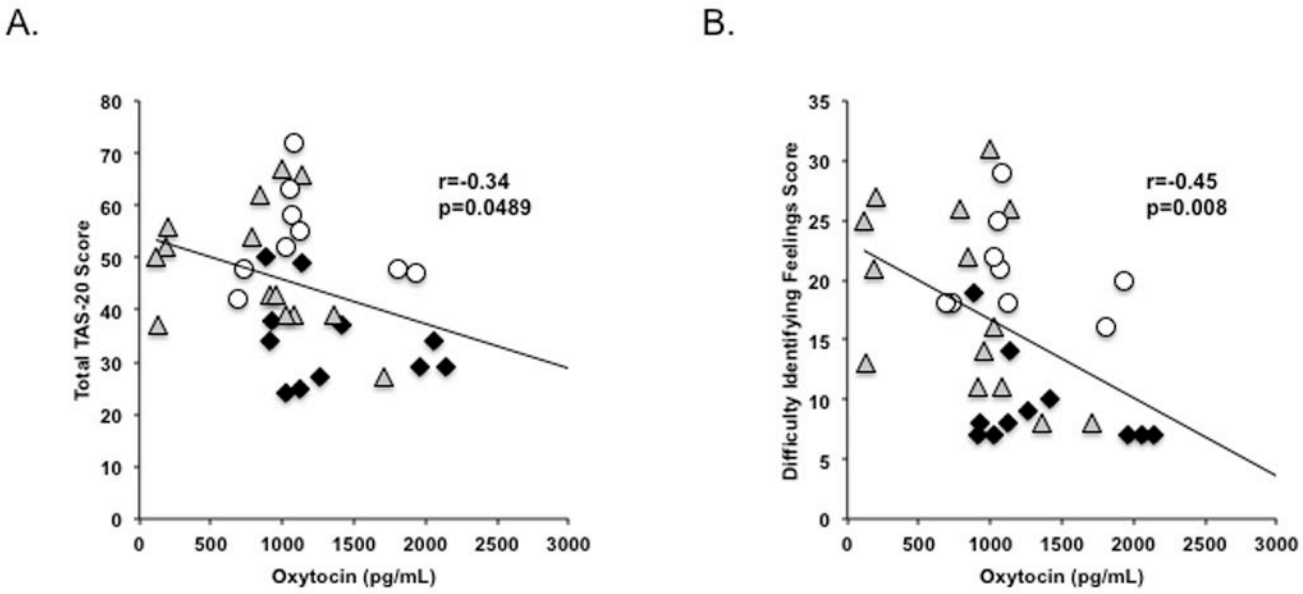

Figure 1. Relationship Between Oxytocin and (A) Total TAS-20 Score and (B) Difficulty Identifying Feelings

Oxytocin levels were negatively associated with (A) total alexithymia and (B) the difficulty identifying feelings subscale of the TAS-20. Black diamond, H; white circle, AN; gray triangle, AN-WR. These relationships were significant after controlling for BMI and amenorrhea ($p \leq 0.02$). Abbreviation: TAS-20, Toronto Alexithymia Scale–20.

Table 1

Clinical Characteristics and Assessments of Psychopathology

				P Values, Hedges' g			
	H (n=34)	**AN-WR (n=26)**	**AN (n=19)**	**AN-WR vs. H**	**AN vs. H**	**AN-WR vs. AN**	**Overall ANOVA**
Age (Years)	23.9 ± 0.8	22.9 ± 0.5	25.1 ± 1.7	-	-	-	0.38
Weight (kg)	61.5 ± 0.9	60.7 ± 1.4	47.2 ± 1.1	0.59, 0.13	**<0.0001, 2.72**	**<0.0001, 2.09**	**<0.0001**
% Ideal body weight	101.2 ± 1.1	100.2 ± 1.6	80.7 ± 1.1	0.58, 0.14	**<0.0001, 3.36**	**<0.0001, 2.76**	**<0.0001**
Body mass index (kg/m^2)	22.6 ± 0.3	22.5 ± 0.4	17.7 ± 0.2	0.72, 0.07	**<0.0001, 3.36**	**<0.0001, 2.93**	**<0.0001**
Lowest adult body mass index (kg/m^2)	20.8 ± 0.3	17.1 ± 0.5	14.9 ± 0.5	**<0.0001, 1.78**	**<0.0001, 3.09**	**0.001, 1.01**	**<0.0001**
Oxytocin	1501 ± 114	984 ± 93	1230 ± 86	**0.0005, 0.86**	0.09, 0.46	0.14, 0.56	**0.002**
Eating Disorder Examination - Questionnaire							
Dietary Restraint	0.5 ± 0.1	2.1 ± 0.3	2.7 ± 0.3	**<0.0001, 1.32**	**<0.0001, 2.04**	0.16, 0.34	**<0.0001**
Eating Concern	0.14 ± 0.03	1.8 ± 0.3	2.8 ± 0.3	**<0.0001, 1.59**	**<0.0001, 3.42**	**0.002, 0.72**	**<0.0001**
Shape Concern	0.9 ± 0.2	3.3 ± 0.3	3.8 ± 0.3	**<0.0001, 1.64**	**<0.0001, 2.13**	0.31, 0.28	**<0.0001**
Weight Concern	0.6 ± 0.2	2.9 ± 0.4	2.7 ± 0.4	**<0.0001, 1.57**	**<0.0001, 1.64**	0.73, 0.08	**<0.0001**
Global Score	0.5 ± 0.1	2.5 ± 0.3	3.0 ± 0.3	**<0.0001, 1.70**	**<0.0001, 2.50**	0.20, 0.32	**<0.0001**
Dimensional Assessment of Personality Pathology[a]							
Suspiciousness	17.8 ± 1.0	24.0 ± 2.3	29.8 ± 2.6	**0.02, 0.70**	**<0.0001, 1.44**	**0.047, 0.51**	**0.0002**
Insecure Attachment	22.6 ± 1.4	24.8 ± 1.4	30.8 ± 2.7	0.35, 0.31	**0.002, 0.86**	**0.03, 0.63**	**0.007**
Leibowitz Social Anxiety Scale[a]							
Social Fear	5.4 ± 1.0	9.7 ± 1.1	15.8 ± 1.6	**0.01, 0.80**	**<0.0001, 1.70**	**0.001, 0.96**	**<0.0001**
Public Fear	6.8 ± 1.0	11.2 ± 1.0	17.4 ± 2.0	**0.01, 0.84**	**<0.0001, 1.52**	**0.002, 0.89**	**<0.0001**
Social Avoidance	5.0 ± 0.7	8.5 ± 1.2	14.5 ± 1.8	**0.03, 0.71**	**<0.0001, 1.63**	**0.001, 0.86**	**<0.0001**
Public Avoidance	5.0 ± 0.9	8.0 ± 1.1	14.3 ± 2.0	0.10, 0.58	**<0.0001, 1.37**	**0.002, 0.88**	**<0.0001**
Toronto Alexithymia Scale[b]							
Difficulty Describing Feelings	9.3 ± 0.8	14.6 ± 1.0	14.4 ± 1.0	**0.0004, 1.50**	**0.002, 1.72**	0.89, 0.05	**0.0006**
Difficulty Identifying Feelings	9.4 ± 1.2	18.5 ± 2.1	20.8 ± 1.4	**0.0005, 1.38**	**0.0001, 2.77**	0.37, 0.33	**0.0002**
Externally Orienting Thinking	15.5 ± 1.2	15.0 ± 1.1	18.7 ± 2.1	-	-	-	0.17
Total Score	34.2 ± 2.7	48.1 ± 3.2	53.9 ± 3.1	**0.002, 1.26**	**0.0002, 2.09**	0.20, 0.50	**0.0005**

Values expressed as mean ± SEM. Boldface indicates significance.

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[a] Based on 28 H, 24 AN-WR, and 19 AN.

[b] Based on 11 H, 14 AN-WR, and 9 AN.

Abbreviation: ANOVA, analysis of variance.