Notice of correction 8/11/2014: Panel B of Figure 2 incorrectly duplicated Panel A; the online version of Figure 2B has been corrected.

Postprandial Oxytocin Secretion Is Associated With Severity of Anxiety and Depressive Symptoms in Anorexia Nervosa

Elizabeth A. Lawson, MD, MMSc; Laura M. Holsen, PhD; McKale Santin, BS; Rebecca DeSanti, BA; Erinne Meenaghan, NP; Kamryn T. Eddy, PhD; David B. Herzog, MD; Jill M. Goldstein, PhD; and Anne Klibanski, MD

ABSTRACT

Objective: Anorexia nervosa, a psychiatric disorder characterized by self-induced starvation, is associated with endocrine dysfunction and comorbid anxiety and depression. Animal data suggest that oxytocin may have anxiolytic and antidepressant effects. We have reported increased postprandial oxytocin levels in women with active anorexia nervosa and decreased levels in weight-recovered women with anorexia nervosa compared to healthy controls. A meal may represent a significant source of stress in patients with disordered eating. We therefore investigated the association between postprandial oxytocin secretion and symptoms of anxiety and depression in anorexia nervosa.

Method: We performed a cross-sectional study of 35 women (13 women with active anorexia nervosa, 9 with weight-recovered anorexia nervosa, and 13 healthy controls). Anorexia nervosa was diagnosed according to *DSM-IV-TR* criteria. Serum oxytocin and cortisol and plasma leptin levels were measured fasting and 30, 60, and 120 minutes after a standardized mixed meal. The area under the curve (AUC) and, for oxytocin, postprandial nadir and peak levels were determined. Anxiety and depressive symptoms were assessed using the Spielberger State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory II (BDI-II). The study was conducted from January 2009 to March 2011.

Results: In women with anorexia nervosa, oxytocin AUC and postprandial nadir and peak levels were positively associated with STAI trait and STAI premeal and postmeal state scores. Oxytocin AUC and nadir levels were positively associated with BDI-II scores. After controlling for cortisol AUC, all of the relationships remained significant. After controlling for leptin AUC, most of the relationships remained significant. Oxytocin secretion explained up to 51% of the variance in STAI trait and 24% of the variance in BDI-II scores.

Conclusions: Abnormal postprandial oxytocin secretion in women with anorexia nervosa is associated with increased symptoms of anxiety and depression. This link may represent an adaptive response of oxytocin secretion to food-related symptoms of anxiety and depression.

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Corresponding author: *Elizabeth A. Lawson, MD, MMSc, Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit St, Bulfinch 457-D, Boston, MA 02114 (ealawson@partners.org).*

Anorexia nervosa is a psychiatric illness affecting predominantly young women and characterized by self-induced starvation, endocrine dysregulation, and comorbid psychiatric disease.[1] Anxiety and affective disorders are common in this population, with lifetime prevalences of up to 65% and 80%, respectively,[2] and the effect of these conditions on outcome of anorexia nervosa is empirically unclear. The nutritional effects of dieting and starvation complicate the assessment of anxiety and depressive disorders in anorexia nervosa, and treatment is initially focused on nutritional rehabilitation.

Oxytocin is an anorexigenic (ie, reduces food intake) peptide hormone produced in the hypothalamus and secreted peripherally via the posterior pituitary and centrally in brain regions that include the limbic system. We have reported abnormal oxytocin secretion in anorexia nervosa, associated with symptom severity.[3,4] Nocturnal oxytocin levels were lower in women with active anorexia nervosa (AN) than in healthy controls.[3] In response to a meal, however, oxytocin secretion was higher in AN and lower in weight-recovered anorectics (ANWR) than in controls and was associated with disordered eating psychopathology.[4] Using a food-related functional magnetic resonance imaging (fMRI) paradigm, we demonstrated that AN and ANWR had fasting and postprandial hypoactivation of the amygdala, a brain region involved in emotion, compared to healthy women, and postprandial oxytocin secretion mediated a significant portion of this difference in AN.[4,5] Animal data indicate that oxytocin has anxiolytic and antidepressant properties.[6–10] Oxytocin administration reduces symptoms of anxiety and depression in rodent models, and serotonergic neurons may mediate these effects.[11] Data on the relationship between oxytocin secretion and psychiatric symptoms in humans are lacking.

We therefore investigated the relationship between abnormal oxytocin secretion in anorexia nervosa and psychiatric symptoms. In the analyses, we controlled for secretion of the appetite-regulating hormones leptin and cortisol, which have been linked to anxiety and depression. Levels of leptin, a fat-derived anorexigenic hormone, are low in AN and associated with increased anxiety and depressive symptoms, independent of body fat.[12] Cortisol, an orexigenic (ie, increases food intake) adrenal hormone secreted in response to stress, is increased in AN and has also been implicated in anxiety and depressive symptoms in this population.[13]

METHOD

Subjects

We studied 35 women, 18–28 years old: 13 AN, 9 ANWR, and 13 normal-weight healthy controls (HC) recruited from the community. The study was conducted from January 2009 to March 2011.

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Clinical Points

- Animal data suggest that the hormone oxytocin may have anxiolytic and antidepressant effects.
- Women with anorexia nervosa have abnormal postprandial secretion of oxytocin, even after weight recovery.
- Abnormal postprandial oxytocin secretion in women with anorexia nervosa is associated with increased symptoms of anxiety and depression.
- These associations may represent an adaptive response of oxytocin secretion to food-related symptoms of anxiety and depression.

Subjects were excluded for active drug or alcohol abuse, use of hormones or medications affecting hormone levels (including estrogen) within 8 weeks, use of depot medroxyprogesterone within 6 months, diabetes mellitus, gastrointestinal surgery, pregnancy/breastfeeding within 8 weeks, or hematocrit < 30%.

AN met diagnostic criteria as assessed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID), including intense fear of gaining weight, body image disturbance, weight < 85% of ideal body weight,[14] and amenorrhea ≥ 3 months.[15] AN met criteria for restricting-subtype and had no more than 1 binge and 1 purge episode per month in the prior 3 months. Subjects with a history of psychosis according to the SCID were excluded.

ANWR were at 90%–110% of ideal body weight with regular menstrual cycles and stable weight for ≥ 6 months. ANWR met a diagnosis of past anorexia nervosa, by *DSM-IV* criteria other than amenorrhea, as assessed by SCID. ANWR had not exercised > 10 h/wk or run > 25 miles/wk in the prior 3 months.

HC were at 90%–110% of ideal body weight with regular menstrual cycles. HC had no history of amenorrhea and no history of a psychiatric disorder (including an eating disorder) as assessed by SCID. HC were excluded if they had exercised > 10 h/wk or run > 25 miles/wk in the prior 3 months.

Procedures

This study was approved by the Partners Human Research Committee. Written informed consent was obtained prior to procedures. Subjects were seen at the Massachusetts General Hospital Clinical Research Center (Boston and Charlestown, Massachusetts) and Athinoula A. Martinos Imaging Center (Charlestown, Massachusetts). Subject characteristics, psychiatric scores, and levels of oxytocin, cortisol, and leptin have been reported.[4,5] However, the relationship between oxytocin secretion and severity of anxiety and depressive symptoms has not been described.

At the screening visit, height, weight, and elbow breadth were measured; blood was drawn; and a history (including exercise patterns and alcohol intake) and physical examination were performed. Percentage of ideal body weight and body mass index (BMI) were calculated. Frame size was determined by comparing elbow breadth to race-specific norms derived from the US Health and Nutritional Examination Survey-I.[16] The mood episode, psychotic and associated symptoms, mood disorder, anxiety, somatoform, substance abuse, and disordered eating modules of the SCID were administered.[15]

At the main visit, percentage of ideal body weight and BMI were reevaluated. A brief medical history was performed. ANWR and HC were studied during the follicular phase of the menstrual cycle, the time when estradiol levels are lowest and therefore most similar to those of the amenorrheic women with anorexia nervosa. Subjects were asked to fast for 12 hours. Given the roles of oxytocin, cortisol, and leptin in appetite regulation, we measured levels fasting and in response to food. Subjects were given a 400-kcal mixed breakfast meal standardized for nutrient content (approximately 20% of calories from protein, 20% from fat, and 60% from carbohydrates) at 9 AM and asked to eat the entire meal over 15 minutes. Upon completion, bionutrition staff weighed the meal to determine exact caloric intake. Blood was drawn serially for hormones at 4 time points: fasting immediately premeal and 30, 60, and 120 minutes postmeal. The Spielberger State-Trait Anxiety Inventory (STAI)[17] and Beck Depression Inventory II (BDI-II)[18] were self-administered. STAI state was assessed premeal and postmeal.

Biochemical Analysis

Samples were stored at −80°C. Serum oxytocin levels were measured following extraction using an enzyme-linked immunosorbent assay (ELISA) kit (Assay Designs; Ann Arbor, Michigan) as previously described.[4] The intraassay coefficient of variation (CV) is less than 6.0%. The interassay CV for the extracted, then assayed specimens was 16.5%; the lower limit of detection was 7.0 pg/mL. Serum cortisol levels were measured using a chemiluminescent immunoassay (Beckman-Coulter; Fullerton, California). The interassay CV was 6.4%–7.9%; sensitivity was 0.4 μg/dL. Plasma leptin levels were measured using a radioimmunoassay (LINCO Research; St. Charles, Missouri). The intraassay CV was 3.4%–8.3%; sensitivity was 0.5 ng/mL. Area under the curve (AUC) was calculated using the trapezoidal method.

Anxiety and Depressive Symptom Assessment

The STAI is a well-validated, reliable instrument for assessing anxiety symptoms. The state scale assesses how subjects feel "right now, at this moment," and the trait scale assesses how they feel "generally." Based on normative data, scores of > 46 on the state scale and > 45 on the trait scale (1 SD > mean) were considered abnormal.[17,19] The BDI-II is a validated, reliable questionnaire for assessing symptoms of depression. The BDI-II assesses the severity of depression over the prior 2 weeks, using *DSM-IV* criteria. The reference range is 0–13 minimal, 14–19 mild, 20–28 moderate, and 29–63 severe symptoms.[18]

Data Analysis

JMP Statistical Discoveries (version 9.0; SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses.

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Table 1. Subject Characteristics and Hormone Levels in Subjects With Active Anorexia Nervosa (AN), Subjects With Weight-Recovered Anorexia Nervosa (ANWR), and Healthy Controls (HC)[a]

				P Value[b]			
	AN	ANWR	HC	AN vs ANWR	AN vs HC	ANWR vs HC	Overall ANOVA
Subject characteristics							
Age, y	21.7 ± 0.7	23.2 ± 0.8	22.0 ± 0.4	…	…	…	NS
Weight, kg	48.2 ± 1.1	58.4 ± 2.0	62.0 ± 1.7	**<.0001**	**<.0001**	NS	**<.0001**
Body mass index (kg/m^2)	17.7 ± 0.3	22.1 ± 0.7	22.5 ± 0.4	**<.0001**	**<.0001**	NS	**<.0001**
% of ideal body weight	80.6 ± 1.3	98.3 ± 3.8	97.2 ± 1.7	**<.0001**	**<.0001**	NS	**<.0001**
Hours of exercise/wk	7.8 ± 1.7	3.8 ± 0.8	4.1 ± 0.7	…	…	…	.054
No. of alcoholic drinks/wk	0.8 ± 0.4	2.8 ± 0.7	3.1 ± 0.8	**.038**	**.011**	NS	**.023**
Hours of sleep previous night	6.0 ± 0.3	6.7 ± 0.5	6.1 ± 0.3	…		…	NS
Hours since last oral intake	13.9 ± 0.4	13.9 ± 0.2	14.1 ± 0.2	…		…	NS
Breakfast nutritional intake							
Calories consumed	378.5 ± 16.2	408.5 ± 6.4	405.8 ± 2.0	…		…	NS
Protein, g	18.3 ± 0.7	19.4 ± 0.6	19.4 ± 0.2	…		…	NS
Fat, g	9.4 ± 0.8	10.4 ± 0.6	10.6 ± 0.3	…		…	NS
Carbohydrates, g	58.2 ± 2.0	62.1 ± 1.4	61.5 ± 0.5	…		…	NS
Hormone levels							
Oxytocin							
Fasting (immediately premeal), pg/mL	15.8 ± 1.1	8.1 ± 0.6	16.4 ± 2.3	**.0003**	NS	**.0006**	**.0005**
30 min postmeal, pg/mL	17.6 ± 2.5	9.3 ± 1.1	15.4 ± 1.9	**.004**	NS	**.024**	**.012**
60 min postmeal, pg/mL	16.6 ± 2.3	9.0 ± 1.0	12.3 ± 1.9	**.003**	**.049**	NS	**.009**
120 min postmeal, pg/mL	19.1 ± 3.7	7.7 ± 0.4	12.0 ± 1.2	**<.0001**	**.009**	**.018**	**<.0001**
Area under the curve	2,086 ± 195	1,040 ± 96	1,621 ± 125	**<.0001**	**.041**	**.002**	**<.0001**
Postprandial nadir, pg/mL	13.5 ± 1.1	7.7 ± 0.4	9.0 ± 0.7	**<.0001**	**.0002**	NS	**<.0001**
Postprandial peak, pg/mL	23.4 ± 4.0	9.9 ± 3.2	18.9 ± 1.8	**.0001**	NS	**.001**	**.0004**
Cortisol							
Fasting (immediately premeal), µg/dL	15.9 ± 1.4	12.7 ± 1.1	11.7 ± 1.1	NS	**.014**	NS	**.042**
30 min postmeal, µg/dL	15.1 ± 1.6	11.3 ± 1.0	11.7 ± 0.8	…	…	…	.089
60 min postmeal, µg/dL	13.3 ± 1.5	11.5 ± 0.7	10.9 ± 0.8	…	…	…	NS
120 min postmeal, µg/dL	12.9 ± 1.3	11.1 ± 0.8	8.8 ± 0.7	NS	**.006**	0.067	**.019**
Area under the curve	1,679 ± 159	1,383 ± 83	1,280 ± 73	…	…	…	.084
Leptin							
Fasting (immediately premeal), ng/mL	3.2 ± 0.4	9.3 ± 1.4	10.9 ± 1.3	**<.0001**	**<.0001**	NS	**<.0001**
30 min postmeal, ng/mL	2.9 ± 0.4	8.4 ± 1.3	9.7 ± 1.2	**<.0001**	**<.0001**	NS	**<.0001**
60 min postmeal, ng/mL	2.9 ± 0.4	8.7 ± 1.3	10.3 ± 1.2	**<.0001**	**<.0001**	NS	**<.0001**
120 min postmeal, ng/mL	2.8 ± 0.4	8.3 ± 1.3	9.5 ± 1.1	**<.0001**	**<.0001**	NS	**<.0001**
Area under the curve	347 ± 48	1,034 ± 159	1,203 ± 140	**<.0001**	**<.0001**	NS	**<.0001**

[a]Values expressed as mean ± SEM unless otherwise noted. [b]Boldface indicates significance.
Abbreviations: ANOVA = analysis of variance, NS = nonsignificant. Symbol: ... = not applicable/no analysis conducted.

Hormones were not normally distributed and were therefore log-transformed prior to analyses. Clinical characteristics, hormone levels, and psychiatric scores were compared using overall analysis of variance; variables that were significantly different were then compared by Fisher least significant difference test. Linear regression analyses were used to investigate associations between oxytocin levels and psychiatric symptoms. Multivariate least-squares analyses were constructed to control for cortisol and leptin levels. Stepwise regression analyses were performed to further investigate determinants of psychiatric symptoms (forward direction, $P < .1$ to enter and leave). Statistical significance was defined as a 2-tailed P value ≤ .05. Data are reported as mean ± SEM.

RESULTS

Subjects

Table 1 presents subject characteristics. Mean age was 22.2 ± 0.4 years and did not differ between groups. Weight, BMI, and percentage of ideal body weight were low in AN, but did not differ between ANWR and HC, as per design. For AN, mean percentage of ideal body weight was 80.6 ± 1.3, and time since diagnosis was 52.7 ± 11.2 months. ANWR had a mean percentage of ideal body weight of 98.3 ± 3.8 and reported weight stability for at least 12 months and regular menstrual cycles for at least 14 months. ANWR had recovered weight and menses a mean of 44.4 ± 12.0 and 47.0 ± 17.4 months prior to the study, respectively. Comorbid Axis I diagnoses in AN included current generalized anxiety disorder in 3 subjects; current attention-deficit/hyperactivity disorder (ADHD) not otherwise specified (NOS) in 1 subject; current generalized anxiety disorder and history of bipolar I disorder, ADHD-NOS, and posttraumatic stress disorder in 1 subject; history of major depressive disorder in 2 subjects; and history of depressive disorder NOS in 1 subject. Comorbid Axis I diagnoses in ANWR included a past history of major depressive disorder and social phobia in 1 subject and a past history of major depressive disorder in 2 subjects. Five AN were taking psychotropic medications: 2 were taking venlafaxine, 1 was taking fluoxetine, 1 was taking a low dose of amphetamine/dextroamphetamine (5 mg 24 hours prior to the scan), and 1 was taking escitalopram and aripiprazole. One ANWR was taking a psychotropic medication: fluoxetine. Subjects in each group reported

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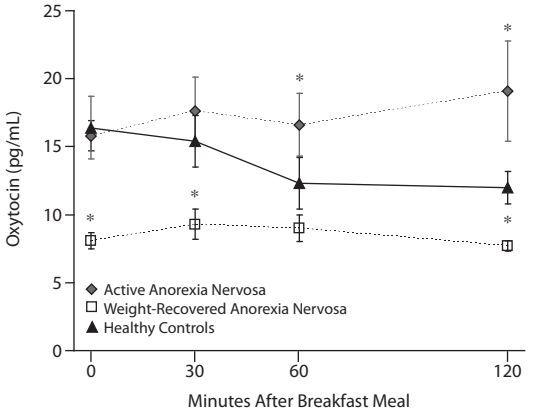
Figure 1. Oxytocin Levels Fasting and After a Mixed Meal[a]



[a]Mixed meal was a 400-kcal breakfast meal standardized for nutrient content (approximately 20% calories from protein, 20% fat, and 60% carbohydrates). Oxytocin levels were high in subjects with active anorexia nervosa compared to healthy controls at 60 and 120 minutes after the meal and low in those with weight-recovered anorexia nervosa compared to healthy controls fasting and 30 and 120 minutes after the meal.
*$P < .05$ compared to healthy controls.

similar mean hours of sleep and hours since last oral intake. No subjects consumed alcohol within 24 hours or caffeine within 12 hours of the study. No subjects smoked cigarettes on the morning of the study. Three AN, 1 ANWR, and 3 HC failed to consume the entire meal. Caloric content consumed at the meal did not differ between groups.

Hormones

Table 1 and Figure 1 present hormone levels. Oxytocin, cortisol, and leptin levels at specific timepoints and AUC were previously reported.[4] Mean fasting levels of oxytocin were comparable in AN and HC, but lower in ANWR. Mean oxytocin levels were higher in AN than in HC at 60 and 120 minutes and were lower in ANWR than in HC at 30 and 120 minutes and in AN at all timepoints. Mean oxytocin AUC was highest in AN, intermediate in HC, and lowest in ANWR. The change in oxytocin levels at 30, 60, and 120 minutes from baseline did not significantly differ between groups. To explore oxytocin secretory dynamics more fully here, we analyzed differences in nadir and peak oxytocin levels. The mean postprandial nadir oxytocin level was higher in AN than in ANWR or HC. The mean postprandial peak oxytocin level did not differ between AN and HC, but was lower in ANWR than in AN or HC. To take into account possible effects of antidepressant medications, we then excluded subjects receiving antidepressants, and the results were similar. Mean leptin levels at every timepoint and AUC were lower in AN than in ANWR or HC. Mean cortisol levels at 0 and 120 minutes and AUC were higher in AN than HC. The mean cortisol AUC differences between AN, ANWR, and HC did not reach statistical significance. In AN and ANWR, there were negative relationships between leptin AUC and oxytocin AUC ($r = -0.42$, $P = .053$), nadir ($r = -0.44$, $P = .042$), and peak ($r = -0.35$, $P = .11$); relationships between cortisol AUC and oxytocin secretion were positive but nonsignificant.

Psychiatric Symptoms

Anxiety state premeal and postmeal, anxiety trait, and depressive symptoms were higher in AN than in ANWR and HC (Table 2). Sixty-two percent (8/13) of AN, 22% (2/9) of ANWR, and no (0/13) HC had clinically significant STAI trait scores. Forty-six percent (6/13) of AN, 33% (3/9) of ANWR, and 8% (1/13) of HC had an increase in anxiety symptoms following the meal. Sixty-two percent (8/13) of AN, 11% (1/9) of ANWR, and no (0/13) HC had more than minimal depressive symptoms.

Oxytocin and Anxiety Symptoms in Anorexia Nervosa

We investigated the relationship between oxytocin secretion—as defined by oxytocin AUC, postprandial nadir, and postprandial peak—and the severity of psychiatric symptoms in subjects with anorexia nervosa (AN and ANWR) (Table 3, Figure 2). Oxytocin AUC and nadir and peak levels were positively associated with anxiety trait and premeal and postmeal anxiety state scores; these relationships remained significant after controlling for cortisol AUC and leptin AUC. The results were similar when we excluded subjects taking antidepressants. We entered oxytocin AUC, cortisol AUC, and leptin AUC into a stepwise regression. Oxytocin AUC explained 51% of the variance in STAI trait scores. When oxytocin nadir was substituted for oxytocin AUC, oxytocin accounted for 46% of the variance in STAI trait scores. When oxytocin peak was used as the measure of oxytocin secretion, oxytocin explained 45% of the variance of STAI trait scores. The effects of cortisol AUC and leptin AUC were not significant in any of these models.

Oxytocin in Patients With Anorexia and Anxiety Symptoms

Figure 3A shows oxytocin levels in AN and ANWR with and without anxiety symptoms. Ten of the 22 women had elevated STAI trait scores, indicating clinically significant baseline anxiety symptoms. Compared with subjects who had normal scores (ie, no anxiety symptoms), those with elevated STAI trait scores (ie, clinically relevant anxiety symptoms) had higher mean oxytocin AUC ($2,135 \pm 235$ vs $1,260 \pm 158$, $P = .002$), nadir levels (12.8 ± 1.2 vs 9.8 ± 1.2 pg/mL, $P = .042$), and peak levels (25.2 ± 4.9 vs 11.8 ± 1.7 pg/mL, $P = .002$), independent of cortisol AUC and leptin AUC.

Oxytocin and Depressive Symptoms in Anorexia Nervosa

Table 3 shows the associations between oxytocin secretion and depressive symptoms. Oxytocin AUC and severity of depressive symptoms were positively correlated, independent of cortisol AUC. There was also a significant positive relationship between oxytocin nadir levels and severity of depressive symptoms. After controlling for cortisol AUC and leptin AUC, this relationship remained significant. These results were similar when subjects on antidepressants were excluded from the analysis. In a stepwise regression model including oxytocin AUC, cortisol AUC, and leptin AUC, oxytocin explained 19% of the variance in BDI-II scores.

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Table 2. Symptoms of Anxiety and Depression in Subjects With Active Anorexia Nervosa (AN), Subjects With Weight-Recovered Anorexia Nervosa (ANWR), and Healthy Controls (HC)[a]

				P Value[b]			
Assessment	AN	ANWR	HC	AN vs ANWR	AN vs HC	ANWR vs HC	Overall ANOVA
State-Trait Anxiety Inventory							
Trait score	53.2 ± 3.7	33.7 ± 3.7	28.0 ± 1.5	**<.0001**	**<.0001**	NS	**<.0001**
State score, premeal	48.8 ± 2.3	30.0 ± 3.5	25.9 ± 1.3	**<.0001**	**<.0001**	NS	**<.0001**
State score, postmeal	50.0 ± 3.4	28.6 ± 2.4	24.6 ± 1.2	**<.0001**	**<.0001**	NS	**<.0001**
Beck Depression Inventory II	16.8 ± 3.3	6.3 ± 1.9	0.8 ± 0.4	**.004**	**<.0001**	NS	**.0004**

[a]Values expressed as mean ± SEM unless otherwise noted. [b]Boldface indicates significance.
Abbreviations: ANOVA = analysis of variance, NS = nonsignificant.

When oxytocin nadir and peak were substituted for oxytocin AUC, oxytocin accounted for 24% and 16% of the variance in BDI-II scores, respectively. The effects of cortisol AUC and leptin AUC were not significant in these models. Peak oxytocin levels were positively associated with the degree of suicidal ideation, as assessed by the BDI-II, independent of cortisol AUC ($r = 0.44$, $P = .039$). In a stepwise regression model that included peak oxytocin, cortisol AUC, and leptin AUC, oxytocin accounted for 20% of the variance in suicidal ideation, while cortisol AUC and leptin AUC did not have significant effects.

Table 3. Relationship Between Oxytocin Secretion and Psychiatric Symptoms in Subjects With Active or Weight-Recovered Anorexia Nervosa

	Oxytocin AUC		Oxytocin Nadir		Oxytocin Peak	
Assessment	*r*	*P*[a]	*r*	*P*[a]	*r*	*P*[a]
State-Trait Anxiety Inventory						
Trait score	0.72	**.0002**[b,c]	0.68	**.0005**[b,c]	0.67	**.0007**[b,c]
State score, premeal	0.63	**.002**[b,c]	0.63	**.002**[b,c]	0.58	**.005**[b,c]
State score, postmeal	0.66	**.0008**[b,c]	0.74	**<.0001**[b,c]	0.58	**.004**[b,c]
Beck Depression Inventory II	0.44	**.043**[c]	0.49	**.021**[b,c]	0.40	.069[c]

[a]Boldface indicates significance. [b]$P < .05$ after controlling for leptin AUC.
[c]$P < .05$ after controlling for cortisol AUC.
Abbreviation: AUC = area under the curve.

Oxytocin in Patients With Anorexia and Depressive Symptoms

Figure 3B shows oxytocin levels in AN and ANWR with and without symptoms of depression. Nine of the 22 subjects had more than minimal symptoms of depression, based on BDI-II scores. Subjects with more than minimal symptoms of depression had higher oxytocin AUC (2,014 ± 199 vs 1,218 ± 117, $P = .002$) than those who did not; this difference remained significant after controlling for cortisol AUC ($P = .009$) and leptin AUC ($P = .041$). Subjects with more than minimal symptoms of depression also had higher nadir oxytocin levels (13.3 ± 1.6 vs 9.7 ± 0.9 pg/mL, $P = .041$) compared to those who did not; this difference remained significant after controlling for cortisol AUC ($P = .035$) and became a trend after controlling for leptin AUC ($P = .070$). Peak oxytocin levels were also higher in subjects with more than minimal symptoms of depression compared to those without (23.9 ± 5.1 vs 13.7 ± 2.6 pg/mL, $P = .018$); this remained significant after controlling for cortisol AUC ($P = .006$) and leptin AUC ($P = .032$).

DISCUSSION

This is the first report linking altered secretion of oxytocin to anxiety and depressive symptoms in anorexia nervosa. Oxytocin secretion in response to a food-related paradigm, whether assessed using AUC, peak levels, or nadir levels, was strongly associated with anxiety and depressive symptoms in women with active and weight-recovered anorexia nervosa. In stepwise regression models that included other hormones with effects on mood and behavior, up to 51% of anxiety and 24% of depressive symptom variance was attributable to oxytocin secretion. Postprandial oxytocin levels were higher in women with elevated symptoms of anxiety and depression than those without symptoms. The higher postprandial oxytocin levels in AN may represent a response to the stress induced by food. Although women with active or weight-recovered anorexia nervosa seem to have an altered setpoint for oxytocin secretion compared to healthy controls, the endogenous oxytocin secretion in women with anorexia nervosa is directly related to the severity of anxiety and depressive symptoms and may reflect a physiologic response geared toward reduction of these symptoms.

Oxytocin knockout mice display increased anxiety-like behaviors and corticosterone response to stress.[20,21] Oxytocin administration reduces anxiety-like behaviors and blunts the hypothalamic-pituitary-adrenal stress response in animal models of anxiety.[6–8,20,22] In mice, administration of an oxytocin antagonist blocks the anxiolytic effects of oxytocin.[8,20] Several human studies have shown that oxytocin administration reduces anxiety related to psychosocial stress.[23,24] Although the exact mechanisms of oxytocin-mediated anxiolysis have not been defined, key pathways and brain regions have been identified. In vitro data indicate that oxytocin, similar to benzodiazepines, promotes inhibitory neurotransmission in the central amygdala, suggesting that oxytocin in this limbic region may dampen anxiety.[25] Interestingly, generalized anxiety disorder patients display heightened fMRI amygdala activation, and administration of oxytocin in these patients results in normalization of amygdala activation in response to viewing fearful faces.[26] Consistent with these data, we previously reported lower preprandial and postprandial amygdalar activation using a food-related fMRI paradigm in AN than in controls, associated with differences in oxytocin secretion.[4]

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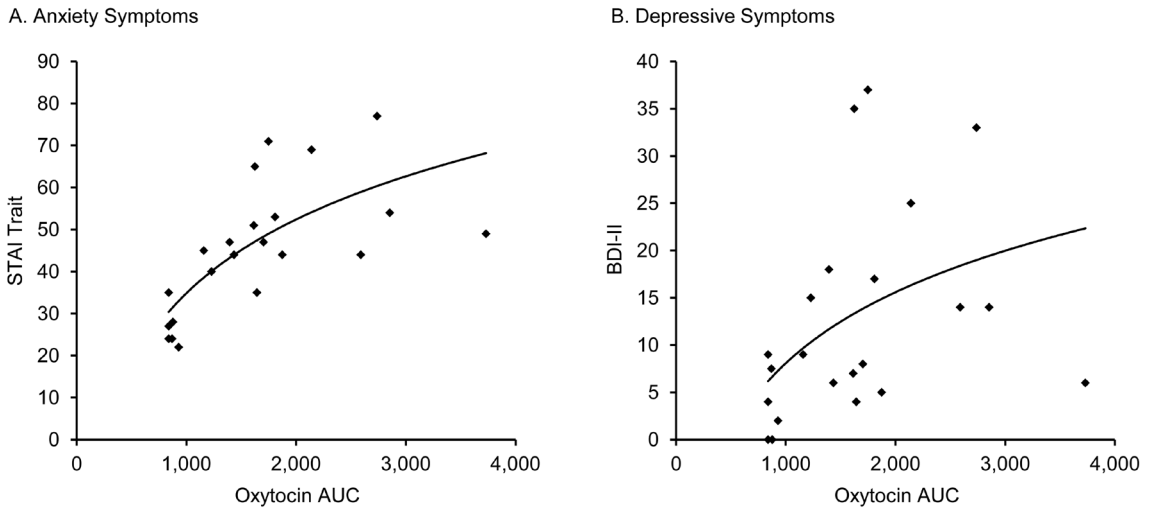
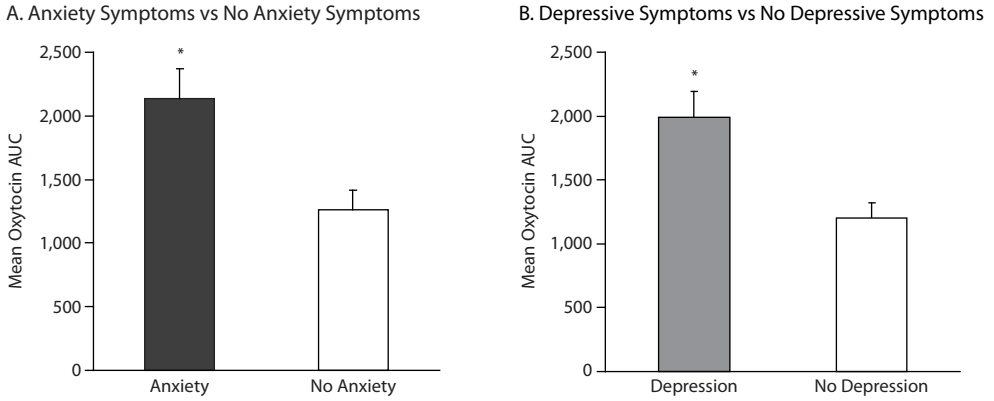
Figure 2. Relationship Between Oxytocin Secretion and Symptoms of (A) Anxiety and (B) Depression in Subjects With Active or Weight-Recovered Anorexia Nervosa[a]



[a]Oxytocin AUC was significantly associated with (A) STAI trait ($r = 0.72$, $P = .0002$) and (B) BDI-II ($r = 0.44$, $P = .043$) scores.
Abbreviations: AUC = area under the curve, BDI-II = Beck Depression Inventory II, STAI = State-Trait Anxiety Inventory.

Figure 3. Oxytocin Secretion in Subjects With Active or Weight-Recovered Anorexia Nervosa With Versus Without (A) Anxiety and (B) Depressive Symptoms[a]



[a]Among women with active or weight-recovered anorexia nervosa, mean oxytocin AUC was high in those with (A) anxiety and (B) more than minimal depressive symptoms compared to those without.
*$P = .002$ vs those without symptoms.
Abbreviation: AUC = area under the curve.

There is also evidence that oxytocin may modulate anxiety through activation of neurons that release serotonin. Serotonergic neurons in the raphe nuclei of mice express oxytocin receptors; oxytocin administration increases serotonin release and inhibits anxiety-like behaviors.[11] Furthermore, administration of a serotonin-2A/2C antagonist blocks the anxiolytic effects of oxytocin, indicating that serotonergic neurons mediate oxytocin effects on anxiety.

We demonstrated a positive correlation between oxytocin secretion and anxiety symptoms, independent of cortisol or leptin—hormones implicated in anxiety in anorexia nervosa. In stepwise regression models that included cortisol and leptin, oxytocin secretion accounted for more than 50% of the variability in anxiety trait scores. Our findings support the preclinical literature linking oxytocin to anxiety symptoms. Although we cannot infer causality, a possible explanation is that anxiety in women with anorexia nervosa induces increased oxytocin secretion in an effort to reduce these symptoms.

Arletti and Bertolini[9] first showed that oxytocin had an antidepressant effect similar to or better than that of the tricyclic antidepressant imipramine in mouse models of depression. In male mice, mating has an antidepressant effect. The typical antidepressant effects of mating are absent in male oxytocin receptor knockout mice, and an oxytocin receptor antagonist blocks the expected antidepressant effects of mating in wild-type mice.[10] We found that postprandial oxytocin secretion was associated with the severity of depressive symptoms, independent of cortisol, and in a stepwise regression model that included cortisol and leptin,

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postprandial oxytocin secretion accounted for one-quarter of the variability in depressive symptoms. Furthermore, subjects who had more than minimal symptoms of depression had higher postprandial oxytocin secretion. Postprandial oxytocin secretion was also positively associated with the degree of suicidality. In a stepwise regression model that included cortisol and leptin, postprandial oxytocin secretion accounted for 20% of the variance in suicidal ideation.

Limitations of this study include its cross-sectional design and small sample size. Although we do not know the relationship between oxytocin secretion in the brain and serum, the robust associations between peripheral oxytocin secretion and psychiatric symptoms suggest that they are linked. Methods for the quantitative measurement of oxytocin in peripheral blood are not standardized, and results are method-specific. We selected a commercially available ELISA with extraction, a method that is useful in examining relative differences in oxytocin levels.[27] Finally, although we cannot rule out the possibility that social interactions during the study visit affected oxytocin levels, procedures and exposure to research staff were similar across groups.

In summary, we found that increased postprandial oxytocin secretion is associated with severity of anxiety and depressive symptoms in anorexia nervosa. This finding supports preclinical data linking oxytocin pathways to anxiety and depressive symptoms and raises the question of whether abnormal postprandial oxytocin dynamics in part represent a response to food-induced stress in these patients. Further research will be important to investigate this. Studies administering centrally acting oxytocin or oxytocin agonists will also be critical in determining whether modulation of this pathway may be useful in the treatment of anxiety and/or depression.

Drug names: aripiprazole (Abilify), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), venlafaxine (Effexor and others).

Author affiliations: Neuroendocrine Unit (Drs Lawson and Klibanski and Mss Santin, DeSanti, and Meenaghan) and Department of Psychiatry (Drs Eddy and Herzog), Massachusetts General Hospital and Harvard Medical School; and Division of Women's Health, Department of Medicine, and Department of Psychiatry, Brigham & Women's Hospital and Harvard Medical School (Drs Holsen and Goldstein), Boston.

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