Relation of Oxytocin to Psychological Stress Responses and Hypothalamic-Pituitary-Adrenocortical Axis Activity in Older Women

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Objective: Animal research suggests that oxytocin (OT) plays a role in stress responses and that in females, this role is modulated by estrogen. Yet little is known about the relation of OT to human stress responses. This study was conducted to examine the relations between estrogen activity and OT, identify stressors distinctively associated with elevations in OT, and investigate whether OT is related to cardiovascular and hypothalamic-pituitary-adrenocortical (HPA) activity in a laboratory challenge paradigm. **Methods:** Seventy-three postmenopausal women who were on hormone therapy (HT) or not completed questionnaires assessing psychological distress and social relationships and then participated in a laboratory stress challenge (Trier Social Stress Task), during which OT, cortisol, and blood pressure were assessed. **Results:** HT was significantly associated with higher plasma OT. Controlling for HT, elevated plasma OT was significantly associated with gaps in social relationships, with less positive relationships with a primary partner, and with elevated cortisol levels. OT was not associated with stress reactivity or recovery. **Conclusion:** In women, plasma OT signals relationship stress and is associated with elevated cortisol; it does not appear to significantly affect cortisol or blood pressure responses to acute stress. **Key words:** oxytocin, stress, cortisol, hypothalamic adrenocortical axis, hormone therapy.

OT = oxytocin; **HPA** = hypothalamic-pituitary-adrenocortical; **HT** = hormone therapy; **TSST** = Trier Social Stress Test; **CAD** = coronary artery disease; **CHF** = coronary heart failure; **CRC** = UCLA Clinical Research Center; **BP** = blood pressure; **SCL-90** = Brief Symptom Inventory; **PANAS** = Positive and Negative Affect Schedule; **RPM** = rotations per minute; **HLM** = hierarchical linear modeling; **GCA** = growth curve analysis.

INTRODUCTION

Oxytocin (OT) is a hypothalamic neuropeptide, implicated in human and animal stress responses, although its exact role in these processes is unknown (1–3). The present investigation had three objectives: to examine the relations between estrogen activity and OT; to identify whether OT levels in human females are reflective of stress and, if so, what kind; and to examine whether OT is related to cardiovascular and hypothalamic-pituitary-adrenocortical (HPA) activity in a laboratory stress challenge paradigm.

Psychological Concomitants of OT

Research supports two quite different hypotheses concerning the relation of OT to stress, one suggesting that higher OT reduces stress responses, the other suggesting that elevated OT may be an indicator of at least some kinds of stress.

Related to the first hypothesis, substantial experimental research has tied OT to a relaxed, calm psychological state (1). Animal studies have related the exogenous administration of OT to sedation and relaxation (2) and to behavioral signs of reduced fearfulness in female rodents (1,2). In human experimental studies and studies of lactating mothers, OT has been related to relaxation and low anxiety as well (3,4). These anxiolytic effects of OT may facilitate social encounters (1). For example, exogenous administration of OT increases maternal behavior in several species (5,6) and affiliative behaviors (such as grooming) (5,6).

Other research, however, implies a role for OT as a potential stress indicator. In an investigation of the relation of OT to psychological and social states in young women (7), baseline plasma OT was associated with relationship stress, including anxiety in relationships, perceived coldness or intrusiveness in relationships, and not being in a primary (romantic) relationship. As a hormone that prompts affiliative activity, OT may act as an indicator of relationship distress and, potentially, as an impetus to social interaction to reduce that distress (7,8). The present study investigated these hypotheses by examining the psychological and social correlates of natural individual variation in OT.

OT and Responses to Acute Stress

OT levels increase in response to at least some stressors, and OT appears to reduce biological responses to stress. For example, in experimental studies, OT has been tied to reduced sympathetic and HPA axis responses to acute stress. In animal studies, exogenous administration of OT has been found to decrease sympathetic reactivity, blood pressure (BP), and corticosterone levels (1,2). The stress-reducing properties of OT are less well documented in humans, but exogenous administration of OT can produce decreases in sympathetic activity and inhibit the secretion of cortisol (3). As such, OT may be part of the system that helps to restore biological homeostasis following stress, at least in females. However, the relation of plasma OT to SNS or HPA stress responses in humans has not been examined.

Hormone Therapy (HT) and OT

Estrogen greatly enhances the effects of OT, and a common paradigm for studying OT in animal studies is to observe its effects in estrogen-treated females (1). HT for the treatment of postmenopausal symptoms provides a naturalistic human analog to this paradigm. Women who are postmenopausal have

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low levels of estrogen, whereas those on HT receive a daily exogenous dose of estrogen. If HT facilitates secretion of OT, then a sample of older women on HT (or not) may provide sufficient variability in OT to examine its relation to stress responses. A second rationale for focusing on older women is that they may be especially vulnerable to stress. Compared with age-matched men and younger women, women who are postmenopausal exhibit increased HPA axis reactivity (9,10) that may be lessened among women on HT (11,12).

The present investigation had three purposes: (1) to assess the relation of HT to OT levels; (2) to identify whether higher levels of OT are associated with positive social experiences or with social distress indicative of a need for social contact (7,8); and (3) to examine the relation of plasma OT to cardiovascular and HPA axis responses to stress.

METHODS

Participants and Screening Procedures

Seventy-three healthy postmenopausal women were recruited from two existing pools of postmenopausal research volunteers maintained by one of the investigators (G.A.G.). Eligibility criteria included (1) age 56 to 75, (2) at least 1 year since last menstrual period, (3) no HT within past 12 months for non-HT users/12 months minimum use for HT-users, (4) English speaking, and (5) 8+ years of education and no evidence of existing cognitive deficits. Exclusionary criteria for safety reasons included active coronary artery disease (CAD), significant arrhythmia, or uncontrolled hypertension; current insulin-dependent diabetes; use of β-blockers, inhaled β-agonists, or oral or parenteral corticosteroids within 3 months of study; reported hot flashes within past 6 months (hot flashes may increase cortisol); CESD Depression score $\geq$16; history of stroke or other neurologic disorder likely to affect cognition, reported use of psychotropic medication within past 8 weeks, or psychiatric hospitalization within the past year. HT users indicated the regimen they were using, which was confirmed via medical records. Twenty women were taking unopposed estrogen, and 19 were taking a combined estrogen/progesterone regimen.

Women who met eligibility criteria and provided verbal consent reported to the UCLA Clinical Research Center (CRC) at 2 PM on the day of their testing session. All participants were fasted after lunch at noon and instructed to cease smoking and alcohol consumption. On arrival at the UCLA-CRC, each woman was further screened by a physician for (1) BP $<$ 140/90 mm Hg, (2) resting pulse 60 to 100, (3) normal lung auscultation, and (4) normal cardiac examination (no evidence of significant coronary heart failure [CHF] or arrythmia). She was then fitted with an indwelling intravenous catheter for collection of blood samples from the antecubital vein during the protocol. To control for the circadian rhythm of cortisol (9), all challenge sessions began at 4 PM.

Prechallenge Measures

While she acclimated to the laboratory, each woman completed several questionnaires. We first assessed age, education, ethnicity, self-rated health status, income, height, weight, exercise, smoking history, and alcohol consumption.

Questionnaires designed to assess social support, social distress, and psychological distress were next administered. Participants completed the SCL-90 Brief Symptom Inventory (13), a standardized measure with good reliability and validity that assesses symptoms of psychological distress, and the Rosenberg self-esteem scale (14). They next rated their interpersonal interactions as to overall quality, perceived closeness to others, cooperation with others, and conflict with others (7-point scales with labeled endpoints).

Next, participants indicated the amount of social contact they had with children, grandchildren, spouse or partner, mother, other family, friends, coworkers, and social groups to which they belonged. Using a measure derived from Schuster et al. (15), they then rated each source: how much they appreciate you, how much they understand the way you feel about things, how much you can rely on them for help if you have a serious problem, and how much you can open up to them if you need to talk about your worries. These items were combined into an index of support for each contact. They also rated these: how often they make too many demands on you, how often they criticize you, how often they let you down when you are counting on them, and how often they get on your nerves (on 7-point scales). These items were combined into an index of negativity for each contact. For partner relationship only, participants rated the overall quality of the marriage and the amount of physically affectionate contact. Each woman then underwent a neuropsychological assessment that addressed another purpose of the study. Subjects then relaxed until the challenge protocol began.

Challenge Protocol

The Trier Social Stress Test (TSST) was used as the laboratory challenge. It reliably elicits significant increases in heart rate, BP, and salivary cortisol (16). Subjects were given 10 minutes to prepare a 5-minute speech about their suitability as a classroom assistant. Following the speech, subjects completed a serial subtraction task (counting backwards as rapidly as possible by 13s from 2,053). The standard TSST is a social stressor that employs an evaluative panel. In the present study, 55 of the 73 subjects completed the TSST with a panel present, and 18 completed the TSST with no panel present. Because OT is tied to social behavior under stress, we randomly assigned some participants to the smaller control group without a panel present to examine whether our results would be different for a social versus nonsocial stressor. Following the TSST, participants relaxed for 90 minutes.

Emotion Measures

Immediately preceding and following the TSST, participants completed the standardized Positive and Negative Affect Schedule (PANAS) (17), using a scale from 1 (very slightly/not at all) to 5 (extremely). Two subscales were calculated. The first scale, known as the positive affectivity scale, included interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active (pre $\alpha = 0.88$, post $\alpha = 0.89$).

The second scale, known as the negative affectivity scale, included distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid (pre $\alpha = 0.78$, post $\alpha = 0.78$).

Biological Assessments

Two baseline, two challenge, and four recovery samples of saliva for the assessment of cortisol levels were taken, and BP was also taken at these time points. Three blood samples to provide assessments of plasma OT were also collected (at baseline, following the challenge, and 60 minutes into recovery).

Whole blood samples for OT assays were immediately placed in chilled vaccutainers containing EDTA. Tubes immediately were placed on ice and then were centrifuged (1500*g*) for 15 minutes at 4°C. Approximately 3 ml of aliquotted plasma per sample was frozen at −80°C in separate microtubes for later neuroendocrine assessment. Frozen samples were batched and shipped overnight on dry ice to a CLIA-certified analytical laboratory (Salimetrics, LLC, State College, PA).

Assay Procedures

Salivary cortisol levels were assayed by the Clinical Laboratory of the Cleveland-GCRC in duplicate by radioimmunoassay using the HS-cortisol High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit (Salimetrics LLC). All samples were tested in a single assay batch. Sensitivity of the assay is 0.007 μg/dl. Intra-assay coefficients of variation are 3.88%, 6.22%, and 7.12% at high (mean = 0.897 μg/dl), medium (mean = 0.51 μg/dl), and lower (mean = 0.14 μg/dl) levels, respectively. Interassay coefficient of variation is 6.8%.

On the day of testing, blood samples were thawed at room temperature for 2 hours, centrifuged at 3200 rotations per minute (RPM) for 10 minutes, and pipetted into appropriate test wells. All samples were assayed for OT using a commercially available enzyme immunoassay (Assay Design, Ann Arbor, MI, 1990). The test uses 100 μl of sample (for singlet determinations), has a lower limit of sensitivity of 4.68 pg/μl, and has a range of sensitivity to 1000 pg/μl. External controls representing low and high OT plasma levels were

TABLE 1. Relation of Plasma OT to Social Contact Measures[a]

Psychological/Social Functioning	Oxytocin Baseline (Mean)	Oxytocin Controlling for HT Baseline (Mean)
Amount of Contact		
Mother (n = 23)	−0.36* (−0.43**)	−0.39* (−0.47**)
Friends (n = 37)	−0.25 (−0.29*)	−0.30* (−0.35**)
Pets (n = 40)	−0.30* (−0.29*)	−0.32* (−0.29*)
Social groups (n = 28)	−0.38** (−0.39**)	−0.39** (−0.40**)
Relationships		
Overall quality (n = 72)	−0.30** (−0.31***)	−0.24** (−0.25**)
Marriage quality (n = 36)	−0.28 (−0.32*)	−0.20 (−0.34**)
Physically affectionate contact (n = 33)	−0.25 (−0.31*)	−0.26 (−0.33*)
Positive partner relations (n = 36) (index)	−0.33** (−0.39**)	−0.32* (−0.37**)
Partner understand	−0.36** (−0.37**)	−0.38** (−0.41**)
Partner appreciate	−0.30* (−0.34**)	−0.27 (−0.32*)
Open up to partner	−0.34** (−0.40**)	−0.30* (−0.37**)

* $p < .10$, ** $p < .05$, *** $p < .01$.

[a] Varying degrees of freedom reflect the numbers of women with each contact. All results are partial correlations controlling for HT status. All significance tests are two-tailed.

included in each assay. All plasma samples were tested in duplicate; values that varied by more than 5% were subject to repeat testing. To minimize variability, all samples from each participant were assayed on the same plate. Average intra- and interassay coefficients of variation, method accuracy, precision, and linearity were within guidelines from the National Committee for Clinical Laboratory Standards Evaluation Protocols (18,19).

RESULTS

Preliminary Analyses

Preliminary analyses examined the relation of baseline cortisol, OT, and HT status to all demographic, health, and mental health measures. The only significant effects were that baseline cortisol was positively associated with weight ($r(n = 72) = 0.43$, $p < .01$), and baseline OT was negatively associated with exercise ($r(n = 71) = -0.34$, $p < .01$). There were significant differences among the HT groups in weight ($F(2,68) = 5.65$, $p < .01$). Women on the combined estrogen/progesterone HT regimen (M = 134.37, SD = 5.80) weighed significantly less than women not on HT (M = 158.78, SD = 4.47, $t(49) = 3.21$, $p < .01$), but neither group differed significantly from women on an estrogen only regimen (M = 147.00, SD = 5.65). Self-esteem and SCL-90 scores were unrelated to OT, HT, or cortisol.

Relation of HT to OT

We examined whether HT condition was related to plasma OT level, using a 3 × 3 mixed-factor analysis of variance with HT status (no HT, estrogen only, estrogen/progesterone) as a between-subjects factor and time (baseline, postchallenge, recovery) as a within-subjects factor. The interaction was not significant ($F(4,134) = 1.40$, ns), and there was no main effect of time ($F(2,134) = 0.99$, ns), but there was a main effect of HT (2, 67) = 3.22, $p < .05$).[1] Pairwise tests showed that women on unopposed estrogen (M = 251.77, SD = 138.42) had significantly higher levels of OT than women not on HT (M = 160.27, SD = 103.04, $t(52) = 2.74$, $p < .01$). The difference in mean OT levels between women on estrogen/progesterone (M = 221.59, SD = 161.78) and those not on HT was in the predicted direction but not statistically significant, suggesting that the estrogen-enhanced levels of OT may be somewhat attenuated by progesterone (20).

Relation of OT to Psychological and Social Measures

OT levels were highly intercorrelated across the 3 time points (range of correlations is 0.86–0.90), and mean levels of OT across the 3 time points did not differ significantly (mean values ranged from 0.192 to 0.201) ($F(2,144) = 1.14$, ns). Accordingly, in the analyses of the psychological and social measures that follow, we report both basal and mean levels of OT because mean levels provide a more stable indicator than the single baseline measurement point.

OT has been variously associated with a calm, positive psychological state or as a hormone that may reflect interpersonal distress. To test between these hypotheses, we computed partial correlations controlling for HT status between basal and mean OT levels with ratings of relationship quality, amount of contact with each source of support, and the composite measures of support and negativity for each source.

Supporting the characterization of OT as an indicator of interpersonal distress, plasma OT levels were associated with significantly lower overall quality of interactions with others (see Table 1). Women with higher OT levels also reported gaps in their social contacts, specifically, less contact with their mothers, their best friend (marginally), a pet (marginally), and the social groups to which they belonged. Contacts with children, grandchildren, and coworkers were not associated with baseline OT. (Most of the women were not working, and no woman had children or grandchildren at home).

OT was also significantly associated with (absence of) positive partner relations, as Table 1 indicates. To explore this

[1] The degrees of freedom are reduced because three women were missing OT levels at the second blood collection. n sizes vary slightly in different analyses presented due to missing data.

TABLE 2. Means and Standard Deviations of Cortisol and Blood Pressure (n = 73)

	Time of Assessment							
	15 min Pre-TSST	10 min Pre-TSST	Post-TSST Prep	Immediately Post-TSST	15 min Post-TSST	30 min Post-TSST	60 min Post-TSST	90 min Post-TSST
Oxytocin								
Mean	199.92			200.61			196.32	
SD	135.72			137.53			141.35	
Cortisol								
Mean	0.1465	0.1174	0.1161	0.1371	0.1760	0.1551	0.1195	0.1043
SD	0.0955	0.0689	0.0737	0.1060	0.1442	0.1225	0.0708	0.0512
Systolic BP								
Mean	128.08	128.73	142.52	147.24	140.90	137.78	137.25	139.04
SD	20.70	19.88	20.61	21.49	20.74	19.99	20.49	21.60
Diastolic BP								
Mean	70.14	70.55	73.05	75.00	72.71	74.08	72.15	73.98
SD	11.89	11.46	11.68	14.26	11.98	11.45	11.15	11.05

TSST = Trier Social Stress Test.

difference more fully, we examined the individual items that composed this index. Women with higher levels of OT reported that their husband was less likely to understand the way they felt about things, that he was less likely to appreciate them, and that they could not open up to him if they needed to talk about their problems. The overall quality of the marital relationship and the frequency of affectionate contact were marginally negatively associated with OT as well (see Table 1).

We also examined whether OT was associated with general psychological distress or only with social distress. OT was not correlated with the SCL-90, (baseline OT $r(70) = 0.13$, mean OT $r(70) = 0.15$, both ns) or with self esteem (baseline OT $r(70) = -0.06$ mean OT $r(70) = -0.06$, both ns) after controlling for HT, indicating discriminant validity.

Relation of OT to BP and Cortisol

We used growth curve analysis (GCA) to analyze the relationship of OT to BP and cortisol. GCA is a two-level approach to examining continuous change in a dependent measure. At level 1, change is modeled for each individual. We modeled how BP and cortisol changed in each individual subject. At level 2, the parameters of change for each individual are used as dependent measures to be explained by between-subjects variables, in this case, basal levels of OT. Thus, GCA allowed us to determine if basal OT levels predicted individual change in BP and cortisol. To conduct the GCA analysis, we used the Hierarchical Linear Model (HLM) 5.05 computer program (21).[2]

Within-Subject Analyses: Modeling Individual Changes in Cortisol and BP

Means for OT, cortisol, and BP are shown in Table 2. A piecewise analysis that simultaneously modeled linear changes in cortisol at baseline (saliva samples 1–3), reactivity (saliva samples 4–5), and recovery (saliva samples 5–8) was used to model change in cortisol (e.g., 23). The level 1 function was as follows:

$$\text{Cortisol} = \beta_{0j} + \beta_{1j}(\text{baseline}) + \beta_{2j}(\text{reactivity}) + \beta_{3j}(\text{recovery}) + r_{ij}$$

where β_{0j} represents the intercept of cortisol for participant j, β_{1j} represents the baseline slope of cortisol for participant j, β_{2j} represents the reactivity slope of cortisol for participant j, β_{3j} represents the recovery slope of cortisol for participant j, and r_{ij} is the residual variance in repeated measurements for individual j. As shown in Table 3, the average intercept, baseline, reactivity, and recovery coefficients were all signif-

TABLE 3. Mean Trajectories of Cortisol and Blood Pressure (n = 73)[a]

	Mean	SE	t (n)	χ^2
Cortisol				
Intercept	0.138	0.010	13.37 (72)***	396.03***
Baseline (linear)	−0.131	0.038	−3.43 (72)***	130.73***
Reactivity (linear)	0.117	0.028	4.17 (72)***	389.06***
Recovery (linear)	−0.039	0.009	−4.50 (72)***	278.75***
Systolic				
Intercept	127.88	2.28	56.04 (72)***	491.02***
Reactivity (linear)	41.61	4.09	10.16 (72)***	96.80*
Recovery (linear)	−4.64	0.98	−4.75 (72)***	95.33*
Diastolic				
Intercept	70.13	1.25	56.17 (72)***	299.07***
Reactivity (linear)	9.50	2.37	4.00 (72)***	66.22
Recovery (linear)	−0.56	0.63	−0.89 (72)	80.29

* $p < .05$. ** $p < .01$. *** $p < .001$.

[a] Entries reflect the intercept, baseline, reactivity, and recovery coefficients for cortisol and the intercept, reactivity, and recovery coefficients for BP (column 1), the standard errors of these coefficients (column 2), the statistics testing differences of these coefficients from zero (column 3), and the χ^2 indicating significant variance among the coefficients of each individual to be explained at level 2 (column 4).

[2]For a discussion of the advantages of multilevel models and HLM in general see Raudenbush and Bryn (22), and for biological responses in particular, see Llabre et al. (23). More details about the estimation of the models are available from the authors.

icant, and each had sufficient random effects variance. To model BP, we used a piecewise analysis that simultaneously modeled linear change in reactivity (measurements 1–4) and recovery (measurements 4–8). The level 1 function was as follows:

$$BP = \beta_{0j} + \beta_{1j}(\text{reactivity}) + \beta_{2j}(\text{recovery}) + r_{ij}$$

where β_{0j} represents the intercept of BP for participant j, β_{1j} represents the reactivity slope of BP for participant j, β_{2j} represents the recovery slope of BP for participant j, and r_{ij} is the residual variance in repeated measurements for individual j. As shown in Table 3, the linear model produced significant intercept, reactivity, and recovery coefficients for systolic BP, and there was significant random effects variance. However, this model did not fit the diastolic BP data very well; only the intercept and reactivity coefficients were significant, and there was significant random effects variance for only the intercept. We also attempted to fit quadratic models to systolic and diastolic reactivity and recovery. These models fit the data more poorly than the linear models.

Relation of OT to Changes in Cortisol

We specified the following models at level 2 to test the value of OT in predicting individuals' parameters of change: Intercept: $\beta_{0j} = \gamma_{00} + \gamma_{01}$ (panel status) + γ_{02} (baseline OT levels) + μ_{0j}

Baseline: $\beta_{1j} = \gamma_{10} + \gamma_{11}$ (panel status) + γ_{12} (baseline OT levels) + μ_{1j}

Reactivity: $\beta_{2j} = \gamma_{20} + \gamma_{21}$ (panel status) + γ_{22} (baseline OT levels) + μ_{2j}

Recovery: $\beta_{2j} = \gamma_{30} + \gamma_{31}$ (panel status) + γ_{32} (baseline OT levels) + μ_{3j}

Because our interests centered around the effect of OT and not panel presence on cortisol response, we centered the panel presence variable before entering it into the equation. This has the effect of showing the effect of OT on the "average" participant rather than in each panel group separately. γ_{00} Is the initial intercept parameter (i.e., in this model, the intercept represents participants' baseline level of cortisol); γ_{10}, γ_{20}, γ_{30} are the initial baseline, reactivity, recovery slope parameters j; γ_{01}, γ_{11}, γ_{21}, and γ_{31} represent the mean intercept, baseline, reactivity, and recovery coefficients, respectively, for the effect of panel presence; γ_{02}, γ_{12}, γ_{22}, and γ_{32} represent the change in intercept, baseline, reactivity, and recovery, respectively, for women per unit of change in baseline levels of OT; and μ_{0j}, μ_{1j}, μ_{2j}, and μ_{3j} represent the residual scores for the intercept, baseline, reactivity, and recovery, respectively, in individual j. The OT coefficients represent the value of OT in predicting cortisol after controlling for panel presence.

We did not control for HT status in this analysis because the reason for using the HT paradigm is to increase OT levels. Thus, controlling for HT would restrict the range of the OT variable. However, we repeated the HLM analysis, adding HT to the model predicting cortisol. We centered HT status before we entered it into the equation, as we had with panel presence. In order to center, we grouped all women on an HT regimen (unopposed estrogen and estrogen/progesterone) together and compared them to the women who were not on HT. HT was related to the cortisol intercept only. However, including it in the model did not substantially alter the effects of panel presence or OT (see Table 4, bottom row of each cell in parentheses, for these results).

As Table 4 indicates, baseline levels of OT significantly predicted the intercept and baseline slope of cortisol, but not the reactivity or recovery slopes. Those women high in OT had higher initial levels of cortisol and a steeper decline in cortisol across baseline. The effect of OT at baseline and on the intercept remained significant when controlling for both HT and panel presence. For illustrative purposes, Figure 1 portrays these relations for women in the top and bottom quarters of the OT distribution. The means of these groups were approximately 1 SD above and below the mean for basal OT levels and thus approximate the HLM analysis.

Panel presence was significantly related to the reactivity and recovery slopes such that women in the panel condition had a steeper reactivity slope and a steeper recovery slope. HT status, when it was added to the model, was related only to the cortisol intercept such that women not on HT had higher initial levels of cortisol than women on HT.

TABLE 4. Predicting Cortisol Levels From Panel Presence (HT Status), and Baseline Oxytocin Levels ($n = 73$)[a]

	Panel Presence		HT Status		Oxytocin (OT)	
	Coefficient (SE)	*t* (Effect Size)	Coefficient (SE)	*t* (Effect Size)	Coefficient (SE)	*t* (Effect Size)
Intercept	−0.026 (0.026)	−0.98 (0.013)			0.030 (0.010)**	3.07 (0.118)
	(−0.026 (0.22))	(−1.15 (0.018))	(−0.043 (0.020)*)	(−2.15 (0.060))	(0.036 (0.010)**)	(3.50 (0.145))
Baseline	−0.095 (0.117)	−0.82 (0.002)			−0.092 (0.031)**	−3.00 (0.114)
	(−0.094 (0.087))	(−1.09 (0.016))	(0.098 (0.076))	(1.29 (0.022))	(−0.105 (0.039)**)	(−2.71 (0.093))
Reactivity	0.175 (0.040)**	4.41 (0.199)			0.002 (0.029)	0.08 (<0.001)
	(0.175 (0.065)**)	(2.69 (0.091))	(0.068 (0.057))	(1.19 (0.019))	(−0.007 (0.029))	(−0.22 (0.001))
Recovery	−0.041 (0.014)**	−2.90 (0.108)			0.004 (0.009)	0.041 (0.002)
	(−0.041 (0.021)*)	(−1.98 (0.051))	(−0.010 (0.018))	(−0.55 (0.004))	(0.005 (0.009))	(0.54 (0.004))

* $p < .05$. ** $p < .01$.

[a] Table entries are coefficients, standard errors, and *t* tests results for HLM analyses. Analyses for OT control for panel presence (top row) and for both panel presence and HT status in the bottom row. Effect sizes are in r^2.

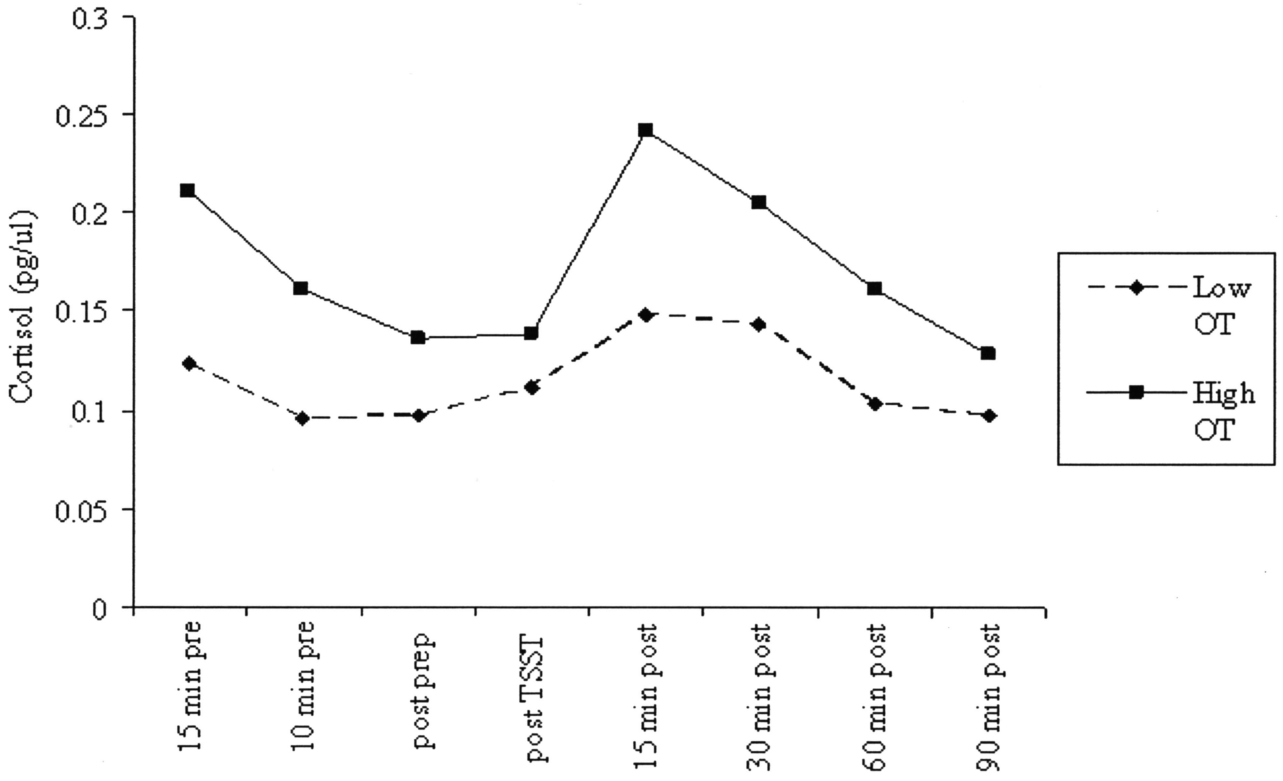

Figure 1. Cortisol levels for high and low OT groups (upper and lower quartiles).

Relation of OT to Systolic and Diastolic BP

We specified the following model at level 2 to test the value of OT in predicting individuals' parameters of change in both systolic and diastolic BP than women on HT.

Intercept: $\beta_{0j} = \gamma_{00} + \gamma_{01}$ (panel status) $+ \gamma_{02}$ (basal OT levels) $+ \mu_{0j}$

Reactivity: $\beta_{1j} = \gamma_{10} + \gamma_{11}$ (panel status) $+ \gamma_{12}$ (basal OT levels) $+ \mu_{1j}$

Recovery: $\beta_{2j} = \gamma_{20} + \gamma_{21}$ (panel status) $+ \gamma_{22}$ (basal OT levels) $+ \mu_{2j}$

The coefficients represent the same parameters outlined in the cortisol analysis above. OT was not a significant or close to significant predictor of the intercept, reactivity, or recovery coefficients for either systolic or diastolic BP. Panel presence significantly predicted systolic BP reactivity ($\gamma_{11} = 31.61$, SE = 8.53, $t(70) = 3.71$, $p < .001$) and recovery ($\gamma_{11} = -6.34$, SE = 1.89, $t(70) = -3.35$, $p < .001$). When added to the equation, HT did not predict BP intercept, reactivity, or recovery.

Relation of OT to Emotion Reports

Partial correlations between pre- and postpositive emotion measures and OT, controlling for panel presence, revealed that OT level was related to lower pre-TSST positive emotion (mean $r(70) = -0.24$ $p < .05$, baseline $r(70) = -0.20$, $p < .09$) and to lower post-TSST positive emotion (mean $r(70) = -0.28$, $p < .05$, baseline $r(70) = -0.24$, $p < .05$). OT was uncorrelated with pre- and postnegative emotion.

DISCUSSION

The present study found that higher plasma OT in older women was associated with relationship stress and with elevated HPA activity at baseline. OT levels did not change in response to stress, nor was OT significantly associated with BP or cortisol reactivity or recovery from the stress tasks.

OT and Social Distress

We tested between two hypotheses regarding the relation of OT to psychological and social functioning. The first hypothesis draws on extensive animal and some human research indicating that OT increases in response to stress and exerts a countervailing influence on stress responses by inducing a calm, relaxed physiologic and psychological state, as may occur in conjunction with affiliation (1–4). An alternative hypothesis is that OT signals gaps or problems in social relationships and may provide an impetus for social affiliation to reduce social distress (7,8). Consistent with the second viewpoint, OT was significantly associated with gaps in and dissatisfaction with social relationships.

OT was elevated in women experiencing chronic problems in their social relationships, including decreased contact with friends and family and an unrewarding partner relationship. These findings are consistent with Turner and colleagues (7), who found plasma OT levels in young women to be associated with relationship distress. The consistency of this pattern across two quite different samples suggests that elevated plasma OT levels may be a marker of relationship stress, at

least in women. Whether this pattern generalizes to men is not yet known. Potentially, OT acts as an impetus to seek out positive social contacts, as has been documented in animal studies (1,6,7). However, the present study did not test this latter point.

OT was distinctively related to relationship stress and not to psychological distress more generally, as assessed by the SCL-90 and a self-esteem measure. These findings help to establish the discriminant validity of social distress as a concept and suggest that plasma OT is a biological marker of it. The important protective role that social support plays with respect to mental and physical health (24) suggests that social distress, in conjunction with elevated plasma OT, merits continued investigation.

The present findings, coupled with earlier research (7), suggest that OT does not have a reliable affective substrate. Why, then, has OT been associated with calm, companionable feelings? A possibility is that plasma OT reflects social distress, but that OT pulsatility is associated with calm and companionable feelings (7). OT pulsatility, as induced exogenously or in conjunction with affiliation, may produce the anxiolytic effects of OT documented in the experimental animal literature (1,2) and in some human studies (3,4). However, naturally occurring elevations in plasma OT do not appear to have these stress-protective effects. These differences indicate that a combination of experimental and naturalistic evidence may be needed to elucidate fully the stress-related concomitants of OT.

OT, Cortisol, and BP

Plasma OT was significantly associated with elevated cortisol at the beginning of the challenge protocol. In response to the stress tasks, women with both high and low levels of plasma OT showed the expected increase in cortisol followed by a decline in cortisol levels during recovery (see Figure 1); however, this pattern was not significantly related to plasma OT levels. This pattern appears contrary to a large experimental animal literature and a modest human literature relating OT to lower HPA axis activity (1–3). A possible reconciliation of these divergent findings stems from the fact that past research has not consistently disentangled the effects of OT from the effects of affiliative contact or its anticipation. The reduced stress responses attributed to OT may be due instead to its affiliative consequences and/or to OT's impact on other aspects of the affiliative neurocircuitry; for example, modulation of pathways implicating reward, such as the mesolimbic dopamine and opioid systems (25,26). Positive social contact or its anticipation may activate these aspects of the affiliative neurocircuitry (26), producing the stress-reducing effects that have been attributed to OT. Merely having elevated OT levels does not appear to be protective against cortisol or BP responses to stress, an important qualification to the literature that has documented the stress-protective effects of OT.

An HT paradigm was used to increase the range of OT values, and the results show that it did. HT was unrelated to BP, emotion ratings, and gaps in relationships. Women not on HT, however, had significantly elevated baseline cortisol levels.

We had included a group with no panel present to see if stress responses are elevated under conditions of higher social stress. The panel-present group had a somewhat steeper rise in cortisol and systolic BP during the TSST. This pattern is consistent with work showing a stronger cortisol response to social versus nonsocial stress (27).

Limitations

Several limitations should be noted. First, the data are correlational, precluding statements of causality. Possibly women with high levels of OT are prone to experiencing social relationships as distressing. Some evidence is inconsistent with this alternative. First, only some relationship gaps were associated with OT, suggesting that OT is not uniformly associated with the perception of relationships as lacking or disappointing. Second, high levels of OT were associated with decreased contact with one's mother and, marginally, with a pet, usually due to death or significant deterioration. There is no reason why women high in OT would be especially likely to experience the death or deterioration of their mother or a pet. Rather, it seems more likely that OT was elevated in response to these relationship gaps.

A second limitation is that we assessed circulating OT, and the relation of plasma OT levels to central OT activity is not known. The fact that the present study demonstrated relations of OT to relationship stress, to emotions, and to cortisol suggests that OT release peripherally is related to oxytocinergic activity in the brain. However, the fact that plasma OT levels and exogenously administered OT relate differently to psychological and biologic stress responses suggests that both experimental and nonexperimental research is needed to understand the relations of OT to HPA axis activity.

A third limitation is that women self-selected into HT condition. Baseline analyses revealed few differences among the groups, and analyses that examined and controlled for HT effects on the study outcome variables found no relations. However, these controls do not entirely eliminate concerns over unmeasured variables that may have contributed to the associations between OT and HT and, potentially, to the relation between OT and other study variables.

A fourth limitation is that only women were included as participants, and so it is unknown whether these findings generalize to men. Heinrichs and colleagues (3) found OT to be associated with lower cortisol responses in men to the TSST; however, because they exogenously administered OT, the results indicated that OT can have stress-reducing effects in men but not that it necessarily does. Because OT secretion is strongly enhanced by estrogen and antagonized by androgen, at least in some species (1,28), OT levels may not typically be high enough in men to have reliable effects on cortisol. Women's consistently stronger affiliative response to stress, compared with men (29), is also potentially consistent with a greater role for OT in women's than men's stress

responses. However, this point is speculative, and sex differences clearly merit investigation.

Conclusions and Future Directions

OT appears to be a biomarker of relationship stress in women that is associated with greater HPA axis activity. High levels of plasma OT do not appear to exert a protective effect on responses to acute stress, however, as has been found for exogenous or manipulated increases in OT. The relation of OT to social stress merits continued investigation.

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