

# An Exploratory Study of Neurohormonal Responses of Healthy Men to Massage

DEBRA BELLO, Ph.D., R.N.,<sup>1</sup> ROSEMARY WHITE-TRAUT, Ph.D., R.N., F.A.A.N.,<sup>2</sup>  
DORIE SCHWERTZ, Ph.D., R.N., F.A.A.N., F.A.H.A.,<sup>2</sup>  
HOSSEIN POURNAJAFI-NAZARLOO, M.D., Ph.D.,<sup>3</sup> and C. SUE CARTER, Ph.D.<sup>3</sup>

## ABSTRACT

**Objective:** This research examined the relationship between plasma oxytocin (OT), arginine vasopressin (AVP), cortisol, and anxiety before, during, and after a massage in healthy adult men.

**Design:** A randomized, controlled, crossover, repeated-measures, prospective experimental design with subjects acting as their own controls was used.

**Setting:** The research was conducted at a Midwestern University.

**Subjects:** Fourteen (14) healthy men between the ages of 19 and 45 years of age were randomly assigned to the order of two conditions: a 20-minute massage (experimental condition) or a 20-minute reading period (control condition).

**Methods:** Blood samples were collected at time intervals during each data collection session. Plasma OT, AVP, and cortisol levels were evaluated by enzyme immunoassay (EIA). The Spielberger State Anxiety Inventory (SAI) and autonomic measures were recorded pre- and postcondition.

**Results:** Both experimental (massage) and control (reading) conditions elicited a significant increase in plasma OT levels ( $p < 0.05$ ) and a decrease in SAI score ( $p < 0.05$ ) from pre- to postintervention. A significant positive correlation was detected between plasma AVP and plasma cortisol ( $r = 0.63$ ,  $n = 24$ ,  $p = 0.001$ ) in the massage group, whereas a significant positive correlation between plasma AVP and the SAI ( $r = 0.47$ ,  $n = 25$ ,  $p = 0.016$ ) was observed in the reading group. No significant differences were observed for the autonomic measures between conditions.

**Conclusions:** The finding that plasma OT levels increased in both the massage and reading groups, suggests that tactile stimulus is not necessary for OT release. The results suggest that another unknown factor associated with reduction of anxiety may be involved.

## INTRODUCTION

### *Role of oxytocin, arginine vasopressin, and cortisol*

The role of oxytocin (OT) is well known in relation to the onset and maintenance of labor and lactation. There is an expanding body of animal and human research that implicates OT as a neuropeptide involved in sociality,<sup>1,2</sup> and

the management of stressful experiences.<sup>3</sup> Arginine vasopressin (AVP) is a closely related neuropeptide that also has been implicated in social behavior, but which tends to be associated with increases in stressful activity and activation of the hypothalamic–pituitary–adrenal (HPA) axis. Oxytocin and AVP are components of a complex interneuronal communication that is only beginning to be understood.<sup>4</sup>

---

<sup>1</sup>Baxter Healthcare Corporation, Deerfield, IL.

<sup>2</sup>College of Nursing, University of Illinois at Chicago, Chicago, IL.

<sup>3</sup>College of Medicine and the Brain Body Center, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL.

Noxious or arousing stimuli activate the HPA axis, tending to result in elevations in adrenal hormones, including cortisol. In animals and humans, the relationship between OT, AVP, and the stress response is complex. In some conditions, such as lactation, increases in OT activity have been associated with reductions in reactivity to stressors or perceived stress.<sup>5</sup> However, correlational studies in older women found that higher plasma OT levels were related to relationship stress and elevated HPA activity at baseline, and the OT levels did not change in response to stress nor were significantly associated with blood pressure or cortisol reactivity or recovery from stress tasks.<sup>6</sup>

Heinrichs and colleagues<sup>7</sup> surmised that OT might have a role in an underlying biologic mechanism for stress-protective effects of positive social interactions. OT release during positive social interactions may buffer the response to stressors and reduce autonomic nervous system reactivity, thereby reducing heart rate and blood pressure.<sup>3,8</sup> AVP may also modulate the stress response by balancing active versus passive coping strategies, depending on the mode of release in different areas of the brain.<sup>4</sup>

Many animal and human behaviors associated with intense tactile stimulation and infant (pup) caretaking are also associated with an increase in OT levels. Positive benefits of tactile stimulation such as reduced tension and positive emotion also have been reported in the research conducted with adults.<sup>9,10</sup> After tactile stimulation, increased weight gain, improvement in mother–infant interaction, and changes in behavior from sleep to a quiet alert state are some of the benefits observed in premature infants.<sup>11–15</sup> However, the specific underlying mechanisms contributing to these benefits are still unknown.

Determining the relationship between plasma OT, AVP, and cortisol in response to specific tactile and nontactile behavioral interventions may provide new information regarding the role of these potential biological stress mediators and provide evidence to support clinical applications. The purpose of the current research was to examine the relationship between plasma OT, AVP, cortisol, and anxiety before, during, and after a 20-minute massage (experimental condition) and a 20-minute reading period (control condition) in adult males. We hypothesized that after the administration of massage, but not reading, plasma OT levels would increase and AVP and cortisol levels would decrease concomitantly with a reduction in anxiety.

## METHODS

### *Setting*

The research was conducted at a midwestern university in the College of Nursing that offered quiet separate preparatory and massage rooms that were free of interruptions. The Institutional Review Board at the university approved the

research protocol. The investigator obtained informed consent prior to enrollment.

### *Subjects*

A total of 14 males were recruited and completed the study. Inclusion criteria included healthy males between 19 and 45 years of age who reported a positive experience with massage and were willing to complete two separate data collection sessions. Healthy males were selected to avoid potential female menstrual influence on OT, AVP, and cortisol levels.

Subjects were excluded if they had worked the 11 PM to 7 AM shift the day prior to the data collection session (to control for alteration in circadian rhythm) or consumed recreational drugs, over-the-counter medicine, physician-prescribed medications, or alcoholic beverages within 48 hours prior to the data collection session (e.g., antidepressants, steroids, diuretics, or hormonal therapy). Subjects were nonsmokers and were not taking medications for a psychiatric illness. Since sexual satiety in animals has been associated with an increase in OT levels,<sup>16–18</sup> subjects agreed not to have sexual relations at least 8 hours prior to arriving at the study site. Subjects also abstained from food and liquids other than water for 2 hours prior to the initiation of the study since ingestion of food may affect OT levels.<sup>8</sup> Finally, for their own safety, subjects were also not included in the study if they had known health restrictions or chronic illnesses such as diabetes or heart disease.

### *Conditions*

Research subjects were randomly assigned to the order of two conditions: massage or a reading period. The control condition consisted of reading a National Geographic periodical (without sexual connotation) for a 20-minute period and the experimental condition consisted of a 20-minute shoulder massage administered by a certified massage therapist. A 15–20-minute massage has been previously shown to evoke a neuroendocrine response in infants and adult women.<sup>9,14,19,20</sup> In adult women, an overall increase in OT was noted after a 15-minute massage and levels returned to baseline 30 minutes postmassage.<sup>9</sup> For the control (reading) condition, the subject was seated in a “Relax The Back” chair in a semireclining position with legs elevated and was alone where no conversation took place. During the experimental (massage) condition, the subject was prone on a padded massage table and the massage therapist administered the same massage to each subject. The massage occurred in the following progression: shoulders, upper arms, neck, upper back, and along the spine. Conversation during the massage was at the discretion of the subject based on their comfort level. All subjects initiated conversation with the massage therapist during their massage.

### *Protocol/procedure*

The order of experimental and control conditions was randomized prior to the initiation of the study and the subjects were sequentially assigned to the randomized schedule. Data were collected on 2 days, 6–7 days apart. Each data collection session lasted approximately 90 minutes. A 20-gauge intravenous catheter was inserted peripherally in the vein of the hand or arm for drawing the blood samples at the designated times. Patency of the catheter was maintained with 0.9% normal saline.

After catheter insertion, the subject was escorted to the massage room for a 30-minute waiting period in the “Relax The Back” chair. During the control condition, the subjects remained in the “Relax The Back” chair. Vital signs were recorded while the subjects sat in the chair. For massage, the subjects were positioned prone on a padded massage table and vital signs were taken in that position pre- and postintervention.

A baseline blood sample was collected prior to the start of each condition, placed on ice, and then prepared for storage. Blood samples were also collected 15 and 30 minutes after initiation of the intervention. After each condition, vital signs were recorded and the six-item Spielberger State Anxiety Inventory (SAI) was completed. Upon completion of the data collection session, the intravenous catheter was removed. Blood samples were collected in purple-top ethylenediaminetetraacetic-containing 5 mL tubes (Becton Dickinson, Franklin Lakes, NJ). Plasma was separated by centrifugation (1600g for 15 minutes at 5°C) within 15 minutes of collection and then stored at –70°C for no longer than 8 months. Each sample was aliquoted into three 2-mL polypropylene vials.

The following controls were included in the study design to minimize extraneous variables. The study was conducted between the hours of 1:30 PM and 9:00 PM and each subject participated at approximately the same time and experienced the same order of procedures for each of their two data collection sessions. The same registered nurse, certified in adult infusion therapy, inserted all peripheral catheters to minimize the stress related to catheter insertion and the same massage therapist administered the massage to each subject to minimize variability in the independent measure. One laboratory was designated to analyze the OT, AVP, and cortisol samples.

### *Outcome measures*

*Enzyme immunoassay of OT, AVP, and cortisol.* Plasma OT, AVP, and cortisol were measured at each time point (see Protocol/procedure) using an enzyme immunoassay (EIA) purchased from Assay Designs, Inc. (Ann Arbor, MI). The assays were performed according to the manufacturer’s instructions. For each of the three assays, precision was assessed by the variability between high and low controls, interassay and intra-assay coefficient of variation (CV), and intra-assay CV within known standards. Tests of accuracy

resulted in a high correlation between expected and observed values. The EIAs are reported by the manufacturer to be highly sensitive (minimal detection rate = 4.68 pg/mL OT, 3.39 pg/mL AVP, and 56.72 pg/mL cortisol) with very little antibody cross-reactivity for other neuropeptides or other steroid hormones. For the OT and AVP EIA kits, the cross-reactivity between OT and AVP was <0.04%.

*State anxiety.* The six-item SAI was used to establish a baseline anxiety level 30 minutes post intravenous (IV) insertion and to test the hypothesis that anxiety would change as a function of massage versus the control condition since OT has been associated with anxiolytic effects.<sup>21,22</sup> The SAI is a reliable and sensitive measure of current (state) feelings of anxiety.<sup>23</sup> Correlation coefficients greater than 0.90 were obtained using 4 and 6 items from the 40-item State-Trait Anxiety Index, and the reliability coefficient of the 6-item SAI was  $\alpha = 0.82$ . The comparability of prorated scores from the 6 items with the use of the full 40 items was used to determine concurrent validity of the short-form of the SAI.<sup>23</sup>

*Autonomic measures.* Autonomic measures consisting of tympanic temperature, heart rate (HR), respiratory rate, and blood pressure (BP) were obtained to establish a baseline prior to the two conditions and to identify any changes post intervention. OT and AVP have been implicated in central regulation of autonomic activity as reflected by cardiovascular function.<sup>24</sup>

*Statistical analysis.* Demographic data were summarized with descriptive statistics. Analysis of variance with repeated measures (ANOVA) was used to test for differences between the two conditions. The factors in the model were the two interventions (massage/experimental and reading/control), timing of sample collection (pre, post), and the interaction of the control or experimental condition and the time of sample. For each of the independent, dependent, and miscellaneous variables the following analyses were conducted: simple summary statistics of the variables, simple summary statistics on the change from baseline of the variables, the *p* values from the ANOVA model, and estimates (least-square means) from the ANOVA model. Pearson’s correlation coefficient was calculated to examine the correlation between plasma OT, AVP, cortisol, SAI, and the control and experimental conditions. All analyses were conducted using SAS (version 9.1.3; Cary, NC). An  $\alpha$  of 0.05 was used to determine whether any significant differences existed.

## RESULTS

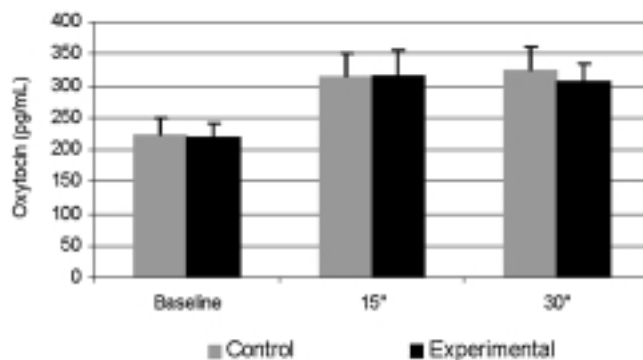
Fourteen (14) healthy males were enrolled and completed both data collection sessions. Subjects were inclusive of three races: white (11), Hispanic (2), and Korean (1) and ranged in age from 23 to 45 years.

### OT, AVP, and cortisol plasma levels

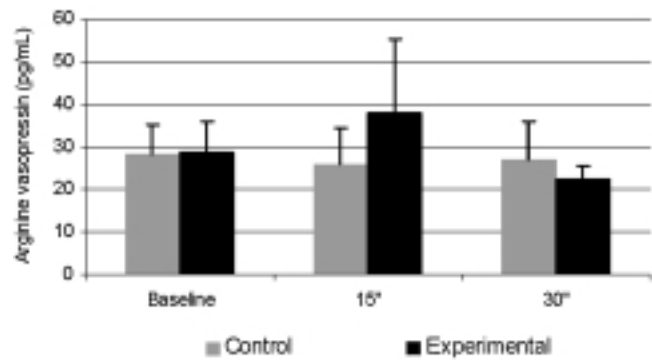
Mean plasma OT, AVP, and cortisol levels are shown in Figures 1–3. Plasma OT baseline values ranged from 99.7 pg/mL to 420.6 pg/mL in the control, reading condition and from 96.0 pg/mL to 373.2 pg/mL in the experimental, massage condition. Variability was noted between different subjects for the baseline plasma OT levels. Overall, the plasma OT increases observed during each intervention in each subject remained within a range of two times their baseline level with the exception of 1 subject. During the experimental condition, this subject had a baseline value of 179.9 pg/mL that then increased to 748.8 pg/mL at the 15-minute time interval that possibly corresponded to obtaining the sample during a pulse release of OT. The subsequent plasma OT level at the 30-minute time interval decreased to 228.1 pg/mL.

Plasma AVP baseline levels ranged from 2.3 pg/mL to 75.3 pg/mL in the control condition and from 2.4 pg/mL to 96.6 pg/mL in the experimental condition. An extreme maximum value of 243.8 pg/mL was reported in 1 subject at the 15-minute time interval during the experimental condition. Plasma cortisol levels ranged from 106.6 ng/mL to 146.3 ng/mL in the control condition and from 100.3 ng/mL to 154.5 ng/mL in the experimental condition. One sample was lost in the control condition at the 30-minute time interval due to laboratory error. One additional sample in the control condition at baseline (a different subject) and the three samples in the experimental condition (also a different subject) were out of detection range for the AVP assay and no value was obtained. Analysis was conducted without values at these timepoints. There were no significant differences in plasma OT, AVP, and cortisol levels between the control and experimental conditions.

The least-square means and confidence intervals were calculated to estimate the mean change in plasma OT, AVP, and cortisol levels from baseline to the 15-minute and 30-minute time points (Table 1). Significant mean changes in plasma OT levels ( $p < 0.05$ ) were associated with both the reading and massage conditions as indicated by the increases from baseline to the 15-minute and 30-minute time inter-



**FIG. 1.** Mean plasma oxytocin levels by condition.



**FIG. 2.** Mean plasma arginine vasopressin (AVP) by condition. AVP measured by enzyme immunoassay.

vals. No significant mean changes in plasma AVP levels were observed. However, plasma cortisol levels increased significantly from baseline to the 15-minute time point ( $p < 0.05$ ). This significant increase in plasma cortisol did not impact the overall  $p$  values when assessing the interaction of the time intervals in both conditions.

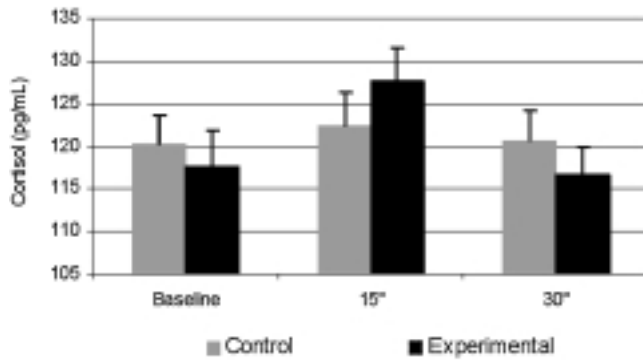
### State anxiety

Table 2 summarizes the SAI scores. In both conditions, the SAI overall score decreased from pre- to post-intervention ( $p < 0.05$ ), indicating that the subjects were less anxious after the control or experimental intervention. However, no significant differences between the control and experimental conditions were identified. When both conditions were combined, a significant difference existed ( $p < 0.05$ ) between pre- and post-SAI scores for the items “I feel calm” and “I am relaxed.” A significant difference ( $p < 0.05$ ) between the control and experimental conditions for the items “I feel calm” and “I am worried” was observed. However, there were no significant interactions between pre- and post-SAI scores and both conditions for each of the six individual items.

Pearson correlation coefficients were conducted to determine the relationships between the control and experimental conditions and OT, AVP, and cortisol levels. In the control condition, whether or not the aforementioned outliers were removed, there was a significant positive correlation between plasma AVP and the SAI ( $r = 0.47$ ,  $n = 25$ ,  $p = 0.016$ ). In the experimental condition, a significant positive correlation was observed between plasma AVP and plasma cortisol ( $r = 0.63$ ,  $n = 24$ ,  $p = 0.001$ ).

### Autonomic responses

The autonomic measures consisting of tympanic temperature, heart rate, respiratory rate, systolic and diastolic BP were obtained 30 minutes post IV insertion to establish a baseline prior to the two conditions and to identify any changes postintervention. No significant differences were



**FIG. 3.** Mean cortisol levels by condition. Cortisol measured by enzyme immunoassay.

observed between the control and experimental conditions for each of the autonomic measures. Although this was a small sample, the subject lying prone during the massage condition and sitting in a chair during the reading condition did not impact the autonomic measures in this study.

## DISCUSSION

Regardless of the intervention (control/reading or experimental/massage), plasma OT levels increased significantly from baseline to the 15- and 30-minute time point in healthy men. This finding did not support the original hypothesis that the tactile stimulation via massage, but not the reading intervention, would elicit an increase in peripheral OT levels. It is unknown why similar increases in plasma OT levels occurred whether the subjects were reading or receiving massage. How-

ever, both conditions may have reduced stressful environmental stimuli and stress reactivity as suggested by the decrease in anxiety as indicated by the SAI scores. The reduction in stress could further influence OT levels. Bastani and colleagues<sup>25</sup> studied relaxation training as a function of reducing anxiety among pregnant women using the Spielberger State Trait Anxiety Inventory and reported reduced anxiety with specific relaxation techniques. The neuroendocrine effects of relaxing quietly are not known; however, one could speculate that a 20-minute relaxation period with minimal movement, in a supine position, while reading a nonthreatening periodical may be an effective means to reduce anxiety. The results of our study do support the biologic validity of EIA measurement of OT. However, additional research is needed to better understand potential mechanisms responsible for the increased plasma OT levels.

Previous research, using radioimmunoassay (RIA), to measure plasma OT generally reported basal levels in men and women to be less than 10 pg/mL.<sup>26–28</sup> Utilizing EIA, the baseline mean plasma OT levels in our current study were 223 pg/mL in the control condition and 217 pg/mL in the experimental condition. These levels were similar to the plasma OT levels we measured in our pilot studies using EIA. Our values for plasma OT measured via EIA are also similar to those found by two other investigators. Zak and colleagues\* demonstrated that the receipt of a signal of trust was associated with increased plasma OT levels ranging between 200 and 350 pg/mL. Taylor and colleagues<sup>6</sup> reported that plasma OT levels in postmenopausal women did not change as a function of a social stressor, the Trier Social Stress Test. Their plasma OT levels ranged between 195 and 220 pg/mL, consistent with the baseline plasma OT levels in our study.

TABLE 1. ESTIMATE OF THE MEAN CHANGE FROM BASELINE FOR PLASMA OXYTOCIN, ARGININE VASOPRESSIN, AND CORTISOL LEVELS BY CONDITION

	Condition	Sample	Estimate	95% CI		p-value*	
				Lower	Upper		
OT pg/mL	Control	15"	92.3	37.3	147.2	0.003	
		30"	101.7	46.7	156.6	0.002	
	Experimental	15"	97.2	42.3	152.2	0.002	
		30"	88.2	33.3	143.2	0.004	
AVP pg/mL	Control	15"	-0.6	-17.4	16.1	0.934	
		30"	-0.2	-17.6	17.3	0.985	
	Experimental	15"	9.5	-7.3	26.2	0.236	
		30"	-6.4	-23.2	10.3	0.411	
	Cortisol ng/mL	Control	15"	3.5	-4.4	11.5	0.351
			30"	1.7	-6.5	9.9	0.661
Experimental		15"	8.9	1.0	16.9	0.031	
		30"	-2.2	-10.1	5.8	0.566	

\*Test that change from baseline for massage-no massage = 0.

Change from baseline = Conc-Baseline.

Oxytocin (OT), arginine vasopressin (AVP), and cortisol measured by enzyme immunoassay.

CI, confidence interval.

TABLE 2. SUMMARY STATISTICS OF SPIELBERGER STATE ANXIETY INVENTORY (SAI)—INDIVIDUAL ITEMS AND OVERALL SCORE BY CONDITION

SAI	Condition	Pre Post	n	Mean	Standard error	Minimum	Median	Maximum
"I feel calm."	Control	Pre	14	2.9	0.2	2.0	3.0	4.0
		Post	14	3.3	0.2	2.0	3.0	4.0
	Experimental	Pre	14	3.1	0.1	2.0	3.0	4.0
		Post	14	3.9	0.1	2.0	4.0	4.0
"I am tense."	Control	Pre	14	1.5	0.2	1.0	1.0	3.0
		Post	14	1.4	0.2	1.0	1.0	4.0
	Experimental	Pre	14	1.5	0.1	1.0	1.5	2.0
		Post	14	1.2	0.1	1.0	1.0	2.0
"I feel upset."	Control	Pre	14	1.1	0.1	1.0	1.0	2.0
		Post	14	1.0	0.0	1.0	1.0	1.0
	Experimental	Pre	14	1.1	0.1	1.0	1.0	2.0
		Post	14	1.1	0.1	1.0	1.0	2.0
"I am relaxed."	Control	Pre	14	2.9	0.3	1.0	3.0	4.0
		Post	14	3.2	0.2	1.0	3.0	4.0
	Experimental	Pre	14	3.1	0.2	2.0	3.0	4.0
		Post	14	3.6	0.2	2.0	4.0	4.0
"I feel content."	Control	Pre	14	2.9	0.3	1.0	3.0	4.0
		Post	14	3.1	0.3	1.0	3.0	4.0
	Experimental	Pre	14	3.0	0.2	1.0	3.0	4.0
		Post	14	3.4	0.2	1.0	4.0	4.0
"I am worried."	Control	Pre	14	1.3	0.1	1.0	1.0	2.0
		Post	14	1.1	0.1	1.0	1.0	2.0
	Experimental	Pre	14	1.0	0.0	1.0	1.0	1.0
		Post	14	1.0	0.0	1.0	1.0	1.0
Overall Score	Control	Pre	14	10.1	0.8	6.0	9.5	15.0
		Post	14	8.8	0.6	6.0	9.0	14.0
	Experimental	Pre	14	9.4	0.5	6.0	9.5	12.0
		Post	14	7.4	0.5	6.0	7.0	13.0

This is the first study to measure plasma AVP in relation to a massage in human subjects. Several of the known behavioral and autonomic consequences of AVP are opposite to those of OT;<sup>3</sup> however, in this study no correlation between OT and AVP was identified. Additionally, there were no significant differences observed between the control and experimental conditions for plasma AVP or plasma cortisol.

Results of previous animal and human research suggest that the relationship between OT and the stress response is complex. The influence of OT on the HPA axis has been studied less in humans and has been associated with different levels of HPA axis reactivity.<sup>5,6,30,31</sup> As observed in the findings reported here and in earlier human research, an increase in plasma OT levels is not always associated with lower HPA axis reactivity.<sup>6,32</sup>

Interestingly, massage in healthy adult men was not correlated with a decrease in plasma cortisol as reported in previous research with premature infants.<sup>19</sup> White-Traut and colleagues\* observed that full-term infants who received a tactile-only stimulation in the form of massage or no stimulation experienced an increase in salivary cortisol levels,

while infants who received a multisensory intervention consisting of talking to the infant, massage, eye contact, and rocking showed a steady decline in salivary cortisol levels. In the findings presented here, the research subject was alone during the control condition and engaged in conversation with the massage therapist during the experimental condition. It could be speculated that the perception of tactile and other stimuli could be interpreted differently by infants and adults, thereby influencing stress, anxiety, and relaxation differently, resulting in different neurohormonal responses. It is useful to note that the cortisol values measured here by EIA, when converted into similar units (12.0  $\mu\text{g}/\text{dL}$  and 11.8  $\mu\text{g}/\text{dL}$  in the control and experimental conditions, respectively), are consistent with previous levels (8.81  $\mu\text{g}/\text{dL}$ ) reported for healthy men between 20 and 49 years of age, using the RIA method of analysis.<sup>33</sup>

Turner et al.<sup>9</sup> suggested that peripheral secretion of OT in response to emotional stimuli is associated with the individual's own circumstances. In addition to anxiety, other emotions and circumstances may have influenced the SAI scores found in the present study. A significant change existed from pre- to post-SAI scores in both conditions for the combined individual items of "I feel calm" and "I am relaxed." Furthermore, a significant difference existed between the two conditions for the individual items of "I feel

\*White-Traut R, Schweitz D, McFaulin B, et al. Salivary cortisol responses of full term infants of moderate touch tactile-only and auditory-tactile-visual-vestibular stimulation. Submitted.

calm” and “I am worried,” with the experimental condition having lower anxiety scores. However, no significant interactions were observed between the two conditions and the pre- and post-SAI scores for each of the six individual items.

During the experimental condition, an increase in plasma AVP levels was correlated with an increase in plasma cortisol levels. This correlation is consistent with research in the animal model where AVP is associated with an increase in the sympathetic nervous system functions associated with behaviors such as enhanced arousal, attention, or aggression, and the HPA axis responds to arousing or noxious stimuli increasing the levels of HPA hormones such as cortisol.<sup>33</sup> A negative correlation between plasma OT and plasma AVP and plasma OT and plasma cortisol was expected but was not observed in this study. Little is known about the underlying biochemical effects of positive tactile stimulation on neuropeptides, and the effects on humans may be very different than in animal models.

This study was limited by the small sample size. A wide range between the lower and upper confidence intervals existed; therefore, a larger sample size may assist in decreasing the variability between subjects and facilitate interpretation of the data. These results provide promising advancements for future research, and a larger sample size may provide further interpretation and direction from the correlations calculated in our study. Plasma OT, AVP, and cortisol levels may have been influenced by the interruption of the massage. Sampling times of blood were designed to be minimally intrusive during the experimental condition so as not to dilute the effects of the massage. However, inserting an intravenous catheter could have influenced anxiety levels of the subjects even though there was a 30-minute rest period post IV insertion. Collecting plasma OT samples is further complicated by the pulsatile secretion and short half-life of OT. Optimal methods and time to collect peripheral plasma OT samples warrant further research.

### RECOMMENDATIONS FOR FUTURE STUDIES

The majority of studies examining neuropeptides and social behavior have used animal models, and it is not known whether similar results would be found in human subjects. The need for improved sensitivity and assay technology to study neuropeptides in humans still remains.<sup>3</sup> In addition, establishing an appropriate, neutral (nonrelaxing but non-stressful) control condition presents a challenge. Plasma OT levels may have increased due to general relaxation and reduction of anxiety that were unrelated to the massage. In future studies, it may be beneficial to consider a floor effect and introduce a stressor or include a stressed subject population. Additional research is warranted to expand our understanding of the relationship of OT, AVP, and cortisol lev-

els in humans with positive social interactions and its impact on health and illness.

### ACKNOWLEDGMENTS

The authors gratefully acknowledge the subjects who gave of their time to participate in this research. The authors acknowledge Nancy Peterson, Massage Therapist for administration of the massages, and Ken Story, Statistician, Baxter Healthcare Corporation, for statistical analysis of the study.

### REFERENCES

1. Carter CS. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology* 1998;23:779–818.
2. Insel TR, Young LJ. The neurobiology of attachment. *Nat Rev Neurosci* 2001;2:129–136.
3. Carter CS, Pournajafi-Nazarloo H, Kramer KM, et al. Behavioral Associations and Potential as a Salivary Biomarker. New York: New York Academy of Sciences, 2007.
4. Landgraf R, Neumann ID. Vasopressin and oxytocin release within the brain: A dynamic concept of multiple and variable modes of neuropeptide communication. *Front Neuroendocrinol* 2004;25:150–176.
5. Altemus M, Deuster PA, Galliven E, et al. Suppression of hypothalamic-pituitary-adrenal axis responses to stress in lactating women. *J Clin Endocrinol Metab* 1995;80:2954–2959.
6. Taylor SE, Gonzaga GC, Klein LC, et al. Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. *Psychosom Med* 2006;68:238–245.
7. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry* 2003;54:1389–1398.
8. Stock S, Uvnas-Moberg K. Increased plasma levels of oxytocin in response to afferent electrical stimulation of the sciatic and vagal nerves and in response to touch and pinch in anaesthetized rats. *Acta Physiol Scand* 1988;132:29–34.
9. Turner RA, Altemus SM, Enos T, et al. Preliminary research on plasma oxytocin in normal cycling women: Investigating emotion and interpersonal distress. *Psychiatry* 1999;62:97–113.
10. Wikstrom S, Gunnarsson T, Nordin C. Tactile stimulus and neurohormonal response: A pilot study. *Int J Neurosci* 2003;113:787–793.
11. Field TM, Schanberg SN, Scafidi F, et al. Tactile/kinesthetic stimulation effects on preterm neonates. *Pediatrics* 1986;77:654–658.
12. White-Traut RC, Pate CM. Modulating infant state in premature infants. *J Pediatr Nurs* 1987;2:96–101.
13. White-Traut RC, Nelson MN. Maternally administered tactile, auditory, visual, and vestibular stimulation: Relationship to later interactions between mothers and premature infants. *Res Nurs Health* 1988;11:31–39.

14. Dieter JN, Field T, Hernandez-Reif N, et al. Stable preterm infants gain more weight and sleep less after five days of massage therapy. *J Pediatr Psychol* 2003;28:403–411.
15. White-Traut R. Providing a nurturing environment for infants in adverse situations: Multisensory strategies for newborn care. *J Midwifery Womens Health* 2004;49(4 suppl 1):36–41.
16. Witt DM, Carter CS, Walton DM. Central and peripheral effects of oxytocin administration in prairie voles (*Microtus ochrogaster*). *Pharmacol Biochem Behav* 1990;37:63–69.
17. Witt DM, Insel TR. A selective oxytocin antagonist attenuates progesterone facilitation of female sexual behavior. *Endocrinology* 1991;128:3269–3276.
18. Carter CS. Oxytocin and sexual behavior. *Neurosci Biobehav Rev* 1992;16:131–144.
19. Acolet D, Modi N, Giannakouloupoulos X, et al. Changes in plasma cortisol and catecholamine concentrations in response to massage in preterm infants. *Arch Dis Child* 1993;68(1 spec no):29–31.
20. White-Traut RC, Nelson MN, Silvestri JM, et al. Effect of auditory, tactile, visual, and vestibular intervention on length of stay, alertness, and feeding progression in preterm infants. *Dev Med Child Neurol* 2002;44:91–97.
21. Uvnäs-Moberg K, Ahlenius S, Hillegaard V, Alster P. High doses of oxytocin cause sedation and low doses cause an anxiolytic-like effect in male rats. *Pharmacol Biochem Behav* 1994;49:101–106.
22. Ring RH, Malbery JE, Potestio L, et al. Anxiolytic-like activity of oxytocin in male mice: Behavioral and autonomic evidence, therapeutic implications. *Psychopharmacology (Berl)* 2006;185:218–225.
23. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *Br J Clin Psychol* 1992;31(Pt 3):301–306.
24. Gutkowska J, Jankowski M, Mukaddam-Daher S, McCann SM. Oxytocin is a cardiovascular hormone. *Braz J Med Biol Res* 2000;33:625–633.
25. Bastani F, Hidarnia A, Kazemnejad A, et al. A randomized controlled trial of the effects of applied relaxation training on reducing anxiety and perceived stress in pregnant women. *J Midwifery Womens Health* 2005;50:e36–e40.
26. Light KC, et al. Oxytocinergic activity is linked to lower blood pressure and vascular resistance during stress in postmenopausal women on estrogen replacement. *Horm Behav* 2005;47:540–548.
27. Landgraf R. Plasma oxytocin concentrations in man after different routes of administration of synthetic oxytocin. *Exp Clin Endocrinol* 1985;85:245–248.
28. Amico JA, Robinson AG. Oxytocin: Clinical and laboratory studies. Proceedings of the Second International Conference on Oxytocin, Lac Beauport, Quebec, Canada, June 29 to July 1, 1984. International congress series; no. 666. 1985. Amsterdam; New York: Excerpta Medica; New York, NY, USA: Sole distributors for the USA and Canada, Elsevier Science Pub. Co., xxv, 444 p.
29. Zak PJ, Kurzban R, Matzner WT. Oxytocin is associated with human trustworthiness. *Horm Behav* 2005;48:522–527.
30. Amico JA, Johnston JM, Vagnucci AH. Suckling-induced attenuation of plasma cortisol concentrations in postpartum lactating women. *Endocr Res* 1994;20:79–87.
31. Chiodera P, Salvarani C, Bacchi-Modena A, et al. Relationship between plasma profiles of oxytocin and adrenocorticotrophic hormone during suckling or breast stimulation in women. *Horm Res* 1991;35:119–123.
32. Grewen KM, Girdler SS, Amico J, Light KC. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. *Psychosom Med* 2005;67:531–538.
33. Carter CS, Altemus M. Integrative functions of lactational hormones in social behavior and stress management. *Ann N Y Acad Sci* 1997;807:164–174.

Address reprint requests to:

*Debra Bello, Ph.D., R.N.*  
*Baxter Healthcare Corporation*  
*Deerfield, IL 60015*

*E-mail: debra\_bello@baxter.com*