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13. ABSTRACT (Maximum 200) The purpose of this study was examine the behavioral and physiological responses of lactating versus nonlactating females to stressors, such as those that might be encountered in military life and to analyze in animal models the possible mechanisms that might account for differences between lactating and nonlactating females. Studies of basal cortisol levels, cognitive performance and reactivity to stressors were conducted in human subjects during late pregnancy and immediately postpartum in women that were lactating or bottle-feeding their infants. Analyses of blood and behavior from the human subjects revealed that lactating women had increased lymphocyte proliferation in response to a mitogenic challenge, but were less likely to respond to psychological stress. Research in rats revealed that lactating female rats show less fear behavior and are less hormonally reactive to stress than nonlactating females. Lactation did not affect acoustic startle responses in rats. Lactating rats have also had enhanced lymphocyte proliferation responses to mitogens. Studies with a new rodent model (prairie voles) have revealed that oxytocin (a principle hormone of lactation), but not vasopressin, is capable of inhibiting the HPA axis.			
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FOREWORD

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C Sue Carter 11-13-98
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INTRODUCTION

Women have become increasingly important to the military. For example, during Operations Desert Shield and Desert Storm, 40,000 women were deployed to southwest Asia (Hines, 1993). Military women are commonly of reproductive age (between 17 and 35), pregnancy is no longer discouraged within the military and about 10 percent of women in this age group might be expected to be pregnant or lactating at any one time. In one recent military hospital study (Madlon-Kay and Carr, 1988), 41-42% of female soldiers nursed their infants, continuing to do so for a period of approximately 2 months.

Breast feeding is a normal component of human reproduction. There is consensus among pediatricians that breast feeding normally benefits the infant (reviewed Carter, 1988). Modern women often feel intense social pressure to breast feed, to the point that they may be labelled a "bad mother" if they do not do so. However, remarkably little is known regarding the physiological or behavioral effects for the mother of lactation. Even in animals, research into the consequences of lactation is rare, and many fundamental questions remain unexplored.

The decision to breast feed or to bottle feed can have profound consequences for female physiology. In military life decisions regarding breast feeding may be influenced by the demands of the military, including assignments that expose the mother to potentially stressful or harmful stimuli, or separate the mother and infant. The research proposed here tested hypotheses regarding the biological and behavioral consequences of lactation to the mother and sought to explore hormonal mechanisms for the effects that we have described.

Lactation and human behavior.

Lactation is the defining property of mammalian existence, and until modern times was essential to mammalian reproduction. It has been found that lactating women interact more positively with their babies, directing more touching and smiling toward their infants than do bottle-feeding mothers. It also is reported that nursing, versus bottle-feeding, mothers are more likely to describe positive mood states (reviewed Carter, 1988). Successful lactation involves the nervous system, and neuroendocrine adaptations of the HPA and gonadal axes. **The research sponsored by this grant extends our understanding of the importance of lactation and hormones associated with lactation in the regulation of behavior and physiology.**

Lactation inhibits reactivity to stressful experiences.

In general, neuroendocrine reactivity of the adrenal axis is reduced during lactation (Carter and Altemus, 1997). Wiesenfeld and associates (1986) measured reduced autonomic reactivity in response to infant cries in lactating women. Both skin conductance and heart rate showed indications of lower levels of sympathetic arousal in lactating versus nonlactating mothers. The reduced responsivity to stressful experiences associated with lactation may be viewed as an adaptive response which protects a nursing female from overreacting to stressful stimuli and promotes successful lactation.

Lactation also influences the activity of other neural systems that have been implicated in the management of psychological stress. For example, catecholamine responses to stress are reduced in lactating rats. Suckling also increases central production of gamma amino butyric acid (GABA) in rats and sheep. GABA is an inhibitory neurotransmitter, known to play an important role in the regulation of anxiety and behavioral reactivity. Lactating females do not show the expected neuronal activation in cortical neurons following exposure to an excitatory amino acid, suggesting that the functional modifications associated with lactation extend beyond the hypothalamus to include cortical functions (Altemus, 1997 and in press).

Peptides, human behavior and physiology.

The neuropeptides, oxytocin and vasopressin, participate in important reproductive functions, such as parturition and lactation, and homeostatic responses, including modulation of the HPA axis. Oxytocin plays an essential role in milk-let down. The study of human lactation, in conjunction with animal research, provides an opportunity to begin to develop viable hypotheses regarding the behavioral effects of oxytocin. Oxytocin also plays a pivotal role in the integration of the behavioral and physiological processes unique to female physiology (Carter and Altemus, 1997; McCarthy and Altemus, 1997). Based primarily on research with animals we speculate that oxytocin and vasopressin, and interactions between these hormones and steroid hormones regulate dynamic behavioral states, including the capacity of an individual to respond to both social and physical challenges.

It has been known since the early 1970's that lactating female rodents showed reduced adrenal reactivity, often indexed by reduced corticosterone secretion, following exposure to stressors such as ether, surgical trauma and electric shock (reviewed Carter and Altemus, 1997). In rats, injections of hypertonic saline normally are considered stressful and are expected to release glucocorticoids. However, during lactation there is a selective inhibition of normal hypothalamic stress responses. In women, both adrenocorticotropin hormone (ACTH) and cortisol levels fall during a bout of breast feeding. There also is evidence that peripheral injections of oxytocin can inhibit ACTH and cortisol release in both men and women. In addition, oxytocin injections can inhibit the release of ACTH and/or glucocorticoids, which normally follow treatments with corticotropin-releasing hormone (CRH), vasopressin plus CRH, or exercise.

Clinical research also indicates that biological changes associated with pregnancy and lactation may protect some women from mental disorders. In women with a history of panic disorder, panic symptoms tend to decline in pregnancy and remain low during the lactation period (Altemus, 1997 and in press). These results suggest that patterns of infant feeding may influence a mother's mental health and thus her ability to deal with the demands of child rearing or other environmental challenges, such as those encountered in military service.

Peptide hormones, including oxytocin and vasopressin, do not readily cross the blood-brain barrier, and must be administered centrally (intracerebroventricularly, ICV) to reach the brain. Nasal sprays have been used to promote milk let down, and have been used in a few behavioral studies, but the extent to which such compounds reach the brain is not known. Therefore, virtually nothing is known regarding the effects in humans of centrally-administered oxytocin.

Naturally-occurring changes in peptides. Two aspects of mammalian life, birth and breast feeding, are clearly associated with the release of oxytocin. The naturally occurring changes in peptides associated with birth and lactation offer opportunities to correlate behavioral and hormonal events. Among the neuroendocrine adaptations that accompany both birth and subsequent lactation are hormonal changes that may promote selective social interactions, including maternal behaviors and high levels of physical contact. Positive social behaviors in turn may foster good health.

Birth and breast-feeding. Birth is a hormonally complex event that is hard to study. In addition, very strong social attachments between adults and children can occur in the absence of birth. However, it is possible that birth plays a role in the particularly strong form of social bonding that is recognized as "mother love." Studies in sheep have demonstrated, at least for that species, a major role for oxytocin in maternal bonding. Although, the experiences associated with birth may play a role in maternal bonding in humans, studies of the physiology of mother-infant interactions are at present primarily correlational.

BODY**Research sponsored totally or part by this grant.****Aim 1. Human research: cognitive performance.**

Recruitment, screening and cognitive testing of 20 control subjects, 20 pregnant subjects, 20 postpartum lactating subjects, and 20 postpartum nonlactating subjects was completed using both the selective attention and the implicit/explicit memory paradigms outlined in the original proposal. Data analysis has been completed for the selective attentional test and the implicit/explicit memory paradigm, and showed no difference between any of the 4 subject groups on either test. A manuscript is now being completed for publication.

An additional study was completed which was not outlined in the original grant proposal. The response to acoustic startle was compared between 24 postpartum lactating women and 25 postpartum nonlactating women. Background data relevant to this study were indirectly supported by the present grant (Altemus, et al., 1997). Lactating women had enhanced eyeblink responses to acoustic startle, which we interpret as further evidence of reduced cognitive arousal and anxiety during lactation. This new finding parallels findings from our laboratory of reduced acoustic startle responses in patients with obsessive-compulsive disorder and increased responses after treatment with the antidepressant/anxiety agent fluoxetine (Altemus, et al., in press, JCP). We also took advantage of a collaborative opportunity to examine the relationship between personality traits and levels of oxytocin, and other hormones, in women. These studies revealed a negative relationship between oxytocin pulses and a tendency toward depression, further implicating oxytocin in human behavior (Turner, et al., under review).

Aim 2. Human research: Endocrine and immune effects of psychological stress.

Although lactating versus nonlactating women show differential responses to stressors, their basal production of adrenal steroids measured acutely in serum appeared comparatively similar (Altemus, et al., 1995). However, it is been suggested that pregnancy, which is a period of sustained hypercortisolism, may be followed by transient hypocortisolism. To examine this hypothesis we measured 24 hour urinary free cortisol (UFC) as an index of integrate hypothalamic-pituitary-adrenal (HPA) axis activity in lactating versus bottle feeding women during the third trimester of pregnancy, and at 5 days, 6 weeks, 16 weeks and one year postpartum (Altemus, et al., under review). UFC levels fell significantly from the third trimester of pregnancy to 5 days postpartum and again from 5 days postpartum to 6 weeks postpartum. There was a much smaller but significant reduction in UFC from 6 weeks to one year postpartum. There were no differences in UFC between breast feeding and bottle feeding women at 6 or 16 weeks postpartum. These results suggest that integrated 24 hour UFC secretion is not affected by lactation and that despite sustained elevations in UFC during pregnancy, the HPA axis is not hypoactive postpartum.

We have examined the effects of physical stress in lactating versus recently delivered, bottle-feeding women (Altemus, et al., 1995). In that study women were given treadmill exercise to 90% of their VO₂ max. The two groups were matched in age, and weeks postpartum. The peak blood lactate level, a measure of exercise intensity, was similar in both groups, and lactating and nonlactating subjects had similar basal levels of ACTH and cortisol. ACTH, cortisol and vasopressin increased following exercise in bottle feeding women, as would be expected in normal controls. However, the magnitude of the increase in ACTH, cortisol and vasopressin in response to exercise stress was blunted in the lactating women. Thus, lactating women show a marked inhibition

of stress hormone secretion in response to exercise, which was not seen in postpartum women who bottle fed their infants.

These studies lead to the following investigations which examined the effects of psychological stress. Recruitment, screening and testing of 15 control subjects, 23 lactating, and 15 postpartum nonlactating women was completed. Psychological stress testing was performed as described in the original proposal using the Trier Social Stress Test.

Data analysis has been completed for the endocrine and physiological data. In response to the stress interview, all three groups of subjects showed significant increases in anxiety, heart rate, systolic and diastolic blood pressure, and ACTH and cortisol secretion. No differences were found in the hormonal (ACTH and cortisol) or anxiety responses to psychological stress among the three conditions. However, blood pressure and heart rate at baseline and during stress were significantly elevated in the postpartum, nonlactating women compared to controls and lactating women. In addition, vagal tone was reduced in postpartum nonlactating women compared to controls and lactating women. This manuscript has been completed and is under review.

Since oxytocin and lactation can alter adrenal function and glucocorticoid secretion, it is to be expected that this might have immunological consequences. In general, research on the effects of lactation on immunological parameters is uncommon in animals or humans. Among the few studies available is research indicating that lactation is associated with enhanced inflammatory reactions to endotoxin and ozone in rats. We found that the responses of lymphocytes (an important component of the immune system) to mitogen stimulation is altered in lactating women and rats.

Several changes in immune function were noted in postpartum women, both at baseline and in response to stress. Compared to control women, both lactating and nonlactating postpartum women had increased lymphocyte proliferation to a T-cell mitogen (PHA) at baseline and throughout the psychological stress test. In contrast, the baseline response to the B-cell mitogen (pokeweed) was reduced in both groups of postpartum women. In addition, postpartum women did not show the usual decrease in proliferation to either the B-cell or T-cell mitogen during stress. In addition, postpartum, nonlactating women had elevated total white blood cell counts with a normal distribution of white cell subpopulations. Data analysis and a manuscript describing this study have been completed and the final draft of that manuscript is now being refined for submission for publication (Redwine, et al., ms in prep).

In a separate *ex vivo* study, lipopolysaccharide stimulated cytokine (IL-1 and Il-6) release was resistant to dexamethasone suppression in lactating women compared to controls. Data analysis for this study is in progress. Estrogen and progesterone levels were similar in lactating women and controls, suggesting that lactational hormones such as oxytocin and prolactin underlie these changes, rather than suppression of gonadal steroids. In addition, comparisons of results from the same paradigm in women in the early follicular and midluteal phases of the menstrual cycle indicate that suppression of estrogen and progesterone in the early follicular phase is also associated with resistance to dexamethasone suppression. Thus lactating women may have resistance due to additive effects of both suppression of gonadal steroids and other lactational hormones (Altemus, et al., 1997, Neuropsychol.).

Aim 3. Animal research: The behavioral effects of lactation.

We have refined the testing paradigm for conditioned freezing in our laboratory and found a reduction in conditioned freezing behavior and in the ACTH and corticosterone responses to conditioned freezing in lactating rats. We also established the plus maze testing paradigm and found increased exploration of the open arms of the maze in lactating rats. We also examined the response to acoustic startle in lactating versus nonlactating rats; acoustic startle did not differ between these two groups. These studies also are being prepared for publication.

Aim 4. Animal research: Possible mechanisms for the behavioral and physiological effects of lactational hormones - new animal models.

Oxytocin reduces HPA axis activity. Oxytocin has been shown to reduce HPA axis activity in humans and there are now several reports that lactation has similar effects (Altemus, et al., 1995). However, oxytocin does not produce an acute decline in corticosterone production in rats. *Thus, rats have not proven useful as an animal model for examining the hypothesis that oxytocin plays a major role in regulating HPA axis activity* (reviewed Carter and Altemus, 1997). For this reason, we elected to examine the effects of oxytocin in a rodent model that is more analogous to humans (Carter, 1998).

Prairie voles are highly social rodents with several behavioral features that are similar to human behavior including the formation of social bonds, which in turn reduce stress as indexed by a reduction in the activities of the HPA axis (DeVries, et al., 1995; 1996; Taymans, et al., 1997; Carter, et al., 1995; 1997; Carter, 1998). Social bond formation is regulated by oxytocin and vasopressin (Cho, et al., under review). Injections of oxytocin (ICV) (but not vasopressin) inhibit corticosterone secretion in female and male prairie vole. CRH (corticotropin releasing hormone) increased corticosterone secretion as expected. The effects of oxytocin on both social bonding and HPA axis inhibition are reversed by a selective oxytocin receptor antagonist (OTA) (DeVries, et al., ms in prep). In addition, pairing no longer reduces glucocorticoid levels if males or females are first pretreated with OTA. The capacity of oxytocin to inhibit HPA axis activity supports the hypothesis that this hormone is a component of the mechanism through which lactation as well as positive social behaviors, are capable of regulating the activity of the HPA axis. Steroid hormones, including estrogen, progesterone and glucocorticoids, vary as a function of reproductive state, and are capable of affecting the response to oxytocin. The outcome of these studies has stimulated Dr. Altemus to initiate a research program aimed at examining in more detail the role of gonadal steroids as modulators of stress responses in female mammals.

CONCLUSIONS.

Taken together these studies suggest that lactation can reduce physiological reactivity to various physical and psychological stressors. Measures of lymphocyte proliferation suggest that lactating women may actually be more reactive to certain kinds of mitogens, possibly explaining the increased incidence of autoimmune disease associated with gestation-lactation. However, other measures of immune function, including some of the work reported here, support the hypothesis that women are less reactive to psychological stressors.

These studies lead us to investigate the role of steroids, of both adrenal and gonadal origins, in the regulation of the behavioral effects of oxytocin (reviewed Carter, 1998; Altemus, in press; Carter and DeVries, in press). These findings also suggest that positive social behaviors, perhaps mediated through a central oxytocinergic system, may modulate the activity of the HPA axis and the autonomic nervous system, accounting for health benefits that are attributed to social bonds (Carter, et al., 1997; Carter, 1998; Carter and Altemus, 1997; Altemus, 1997; McCarthy and Altemus, 1997). Although, these findings go beyond the scope of the proposed research, we suggest that understanding the behavioral effects of oxytocin (released by either lactation or positive social experiences) may be important in understanding the regulation of responses to stressful experiences in humans and animals. These studies support the hypothesis that the consequences (often benefits) of both positive social environments and lactation may be modulated by the neuropeptide oxytocin, and indirectly modulated by steroid hormones (Carter, 1998).

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