Regulation of anxiety during the postpartum period

Joseph S. Lonstein *

Neuroscience Program & Department of Psychology, Gillman Hall, Michigan State University, East Lansing, MI 48824, USA

Available online 2 June 2007

Abstract

Healthy mother–infant interactions are critical for the physical, cognitive, and psychological development of offspring. Such interactions rely on numerous factors, including a positive maternal emotional state. However, many postpartum women experience emotional dysregulation, often involving elevated anxiety. Neuroendocrine factors contributing to the onset of postpartum anxiety symptoms are mostly unknown, but irregularities in hypothalamic–pituitary–adrenal axis function, reduced prolactin and oxytocin signaling, or parturitional withdrawal of ovarian, placental and neural steroids could contribute to anxiety in susceptible women. Although the causes of initial onset are unclear, postpartum anxiety can be mitigated by recent contact with infants. Numerous neurochemical systems, including oxytocin, prolactin, GABA, and norepinephrine mediate this anxiolytic effect of infant contact. Insight into the etiology of postpartum anxiety disorders, and how contact with infants helps counter existing anxiety dysregulation, will surely facilitate the diagnosis and treatment of postpartum women at risk for, or experiencing, an anxiety disorder.

Keywords: Anxiety disorder; Breastfeeding; Hormones; Lactation; Maternal behavior; Neuropeptides; Nursing; Postpartum depression; Psychopathology; Stress; Suckling

1. Introduction

The prospect of becoming a mother for the first time, or re-experiencing the joys of a newborn baby, elicits pleasant anticipation and great exhilaration in many women. Indeed, becoming a mother is considered by some to be the most significant and rewarding of human experiences, and most women show stable or increased levels of positive mood during late pregnancy and the early postpartum period. In many cases, this positive change in mood includes decreased anxiety [12,54,94,128,152,170,227,234,241,386,396,451]. This same life event, however, has tremendous potential to be physically and psychologically distressing [209]. Issues regarding personal appearance and health, health of the fetus and infant, increased demands on time and energy, maintenance of interpersonal relationships, and the ability to adequately care for the neonate are frequent concerns [151,214,149,208,300,316]. Such concerns are normal, but for some women lead to a postpartum mood disorder that often involves elevated anxiety.

The goals of this review are to provide an overview of the literature on the neural, endocrine, and neuroendocrine factors influencing postpartum anxiety in women and laboratory rodents. The neurochemical events precipitating increased anxiety after parturition are virtually unknown, although there are many likely contributors. Nonetheless, females are provided a natural stimulus that can help prevent such increases—the infant. Contact with infants is anxiolytic in both women and laboratory rats, and understanding the biological factors contributing to this phenomenon is a primary goal of our research.

This review will focus on postpartum anxiety, with the realization that there is greater colloquial acknowledgement of postpartum depression, even though postpartum women are more likely to be anxious than depressed [465]. Even while considering postpartum depression, it is critical to recognize that it is rarely a unidimensional disorder and is frequently associated with elevated anxiety [29,31,36,201,369,412,465]. In fact, peripartum anxiety is a very strong predictor of later postpartum depression.
and anxiety accounts for much of the variance on the widely used Edinburgh Postnatal Depression Scale [63,369,426,427]. It is reasonable to believe that a better understanding of postpartum anxiety could help prevent a trajectory toward postpartum depression for some women. Readers specifically interested in the etiology and treatment of postpartum depression, and how it is influenced by infant contact and lactation, are referred to other recent sources [43,106–108,153,195,222,223,235,291,295,296,346,353,366,385,470,488].

2. Frequency and effects of postpartum anxiety dysregulation

Accurately determining the rate of anxiety disorders in postpartum women is problematic. Numerous studies indicate that anxiety disorders afflict parturient women at a rate quite similar to the one-month or one-year incidence found for non-parturient women (~5–12%) [16,29,85,92,255,288,318,360,367,369,370,412,449]. Furthermore, high postpartum anxiety can often be predicted by a woman’s prepartum history of anxiety disorders, low psychological resiliency, and socioeconomic disadvantage [54,62,204,449,465]. These factors also predict anxiety in non-postpartum people [see 62,263], so one might conclude that there are no triggers for anxiety dysregulation specific to the postpartum period. That is, a woman’s predisposition for high trait anxiety and low resiliency leads to increased likelihood of high anxiety whenever life stress is high, as is typically the case when caring for an infant. In this scenario, anxiety disorders during the postpartum period might have similar biological underpinnings as anxiety disorders during any other time of a woman’s life.

This view of postpartum anxiety is probably incorrect. Numerous studies report the onset of some types of anxiety disorders during the postpartum period in women with no previous history of such disorders [11,62,204,279,370,391,393,465]. Furthermore, the rate of anxiety dysregulation at clinical or sub-clinical levels in postpartum women is probably much higher than the general population because the likelihood of detecting elevated anxiety in postpartum women is very low [85]. Additionally, elevated anxiety is particularly prevalent in women who experienced pregnancy complications, gave birth prematurely, delivered a low birthweight infant, or are caring for an infant with a birth defect [61,135,205,231,249,350,469,485]. These women may not only be less willing to participate in studies of postpartum emotional regulation, but are sometimes purposely excluded from them. They give birth to approximately 10% of the 4 million infants born each year in the United States [100,286], further indicating that the reported rate of elevated anxiety or diagnosable anxiety disorders in postpartum women is significantly underestimated. In fact, the actual rate may be greater than 20–25% [61,85,275].

Understanding the factors underlying postpartum anxiety is critical because increased anxiety in mothers, even at sub-clinical levels and independent of comorbidity for depression, has highly detrimental and long-term [166] effects on their children. Anxiety is higher in mothers at risk for or already abusing their infants [103,320,466], and is associated with reduced likelihood of breastfeeding [31,84,108,156,164,397], delayed physical growth [31,334], delayed cognitive [86,165] and social development [165], reduced touching and speaking to the infant [485], irregularities in mother–child interactions and attachment [5,31,282,314,444,477], and increased propensity for anxiety and other psychiatric disorders in the children of mothers with elevated anxiety [32,207,294,335,476]. Given the high incidence rate of postpartum anxiety and its negative effects on child development, many researchers have concluded that increased attention to this type of postpartum emotional disorder is desperately needed [201,288,370,391,465,485].

3. Neurochemical contributions to high postpartum anxiety

The neurobiology underlying why millions of women experience elevated anxiety after giving birth is poorly understood. Although it is only broad indication, a literature search of Medline-indexed, non-review articles on humans published over the past 38 years using the keyword “anxiety” with either “postpartum” or “lactation” reveals only approximately 500 articles. In contrast, the number of articles indexed on Medline with the keywords “anxiety” and “men” exceed 41,000. The rodent literature is even more scant, with fewer than 55 Medline-indexed articles using the keywords “anxiety” and “rat” with either “postpartum” or “lactation”. Nonetheless, some possibly unique neuroendocrine contributors to elevated anxiety during the peripartum period are proposed below. The relative importance or degree of independence among them are not suggested, as a psychological phenomenon as complex as postpartum anxiety dysregulation surely has a large number of interacting and overlapping determinants.

3.1. Prolactin and oxytocin

High prolactinergic or oxytocinergic activity is stress relieving and anxiolytic in non-postpartum animals and humans [14,28,117,158,199,284,293,364,435,447,472,473]. Considering that one of the hallmarks of lactation is increased pituitary gland release of the peptides prolactin (PRL) and oxytocin (OT), which are necessary for milk production and letdown, it is not unexpected that numerous studies have attempted to correlate levels of these peptides with anxiety in parturient women. Indeed, low plasma PRL [21,182,330,464] and OT [330,448; although see 200] titers are associated with higher anxiety in lactating and even non-lactating women, as is irregularity in peptide synthesis and breakdown [275].

A potential problem interpreting these and other data correlating plasma peptide levels with anxiety is only between 1% and 5% of many peptides circulating in blood plasma cross the blood–brain-barrier [130,131]. Plasma PRL enters the central nervous system via transporter...
proteins [136,460], resulting in cerebrospinal fluid levels that are positively correlated with plasma levels [9,22,23,285; however, see 349]. Levels found in individual brain sites, however, are neither correlated with plasma levels nor affected by hypophysectomy, at least in laboratory rats [127,433]. Oxytocin does not readily cross into the brain [130,131] and, needless to say, blood levels often do not correlate well with brain levels [9,13,15,422]. There is no evidence that the blood–brain-barrier is weakened by pregnancy and lactation [341,421], so measuring peripheral PRL and OT, and probably most other peptides, may not readily contribute to our understanding of how peptides affect the neural networks regulating anxiety.

PRL and OT are released not only from the pituitary gland into the general circulation, but also intracerebrally from PRL- and OT-synthesizing neurons of the hypothalamus that project to widespread areas of the brain [82,163,347,392,401,418,487]. Activity of these central projections is probably far more important for anxiety than peripheral peptide release. Central PRL or OT levels in postpartum women are unknown, but CSF measures of OT do not differ between late-pregnant and non-pregnant women [9,421], while PRL is elevated during late pregnancy [9]. In any case, unless samples are taken both before and after the onset of postpartum anxiety symptoms, it would be very difficult to ascertain whether low basal levels of OT or PRL could be a cause or effect of women’s anxiety. It is also reasonable to consider that abnormal peripartum fluctuations in PRL or OT, rather than only basal levels of these peptides, could be responsible for elevated anxiety.

3.2. Hypothalamic–pituitary–adrenal hormones

Hypo- or hyper-activity of the hypothalamic–pituitary–adrenal (HPA) axis has received considerable attention for a causitive role in emotional dysregulation in peripartum and non-peripartum women [76,210,222,287,295,324,325,365]. Women’s HPA axis response to stressors is suppressed during late pregnancy [111,222], which is partly due to high placental release of corticotropin-releasing hormone (CRH) dampening maternal CRH release [287]. This suppression may continue during the early postpartum period [277], but the lack of such HPA suppression could lead to postpartum hyperarousal and anxiety [3,20,441]. Further hyperarousal could result from HPA activation reducing the anxiety-eliciting effects of other neurochemicals, such as ovarian steroids [454].

Studies exploring the association between peripheral measures of HPA responsiveness and anxiety symptoms in lactating and non-lactating postpartum women have been inconsistent, though [8,60,115,123,182]. There are also discrepancies in whether the HPA axis during the early postpartum period is suppressed [198,200,443]. It would be more insightful, but clearly more difficult in humans, to evaluate CRH projections that could directly influencing neural sites mediating anxiety, independent of an influence on the HPA axis [20,225]. Even if this was possible, CRH antagonists do not universally inhibit anxiety-related behaviors in laboratory rats, and CRH effects on anxiety may be specific to the intensity, context, and innately anxietyogenic properties of a stimulus [303]. If the same is true for women, postpartum anxiety disorders associated with particular triggering stimuli or experiences—such as phobias, panic, or post-traumatic stress disorder—might be the most affected by intracerebral CRH activity [365].

3.3. Estrogens, progestins, and neurosteroids

Ovarian and placental steroids fluctuate dramatically during the peripartum period in women, with estrogens and progestogens high during late pregnancy, and then precipitously falling at parturition [264,402]. Steroid hormones of peripheral origin readily enter the brain and have the capacity to affect postpartum mood by directly affecting cellular activity and function [161,178,437,455], and indirectly by influencing neurotransmitters systems modulating anxiety, including serotonin, norepinephrine, dopamine, and GABA [e.g., 17,37,38112,133,206,244,343].

Surprisingly, there is little evidence for the involvement of ovarian hormones in the etiology of persistent postpartum anxiety. Progesterone has been reported to be inversely related to anxiety [464], but many other studies report no significant correlations between circulating progestosterone or estrogens and either anxiety or other mood states after the first few postpartum days [21,65,194,197,201,331,337,338,371]. Steroid hormones readily cross the blood–brain-barrier, but similar to peripheral peptides, plasma levels do not necessarily reflect what is bioavailable to the central nervous system. Steroid hormone binding proteins in plasma and cerebrospinal fluid render steroids inactive, and these binding proteins are influenced by reproductive state in human and non-human primates, with levels of the estrogen-sequestering α-fetoprotein and other steroid-binding proteins particularly high during late pregnancy and at parturition [230,237,240,446]. Furthermore, steroid hormone binding protein levels are lower in CSF than plasma [134], so even if total hormone levels were similar in each compartment, bioactive hormone levels might not. Correlations between unbound levels in plasma and cerebrospinal fluid also depend on women’s reproductive state, at least for progesterone [99]. It seems that measuring total levels of peripheral hormones, rather than unbound levels, and correlating them with mood states across different reproductive states in women is limiting [337,338].

Rather than basal hormone levels, the magnitude of change in ovarian hormones across late pregnancy and the early postpartum period may instead be crucial for mothers’ anxiety [193,331,337,338]. Some women are particularly susceptible to the mood-altering effects of hormone fluctuations across the menstrual cycle [42], and Rubinow and Schmidt suggest that their susceptibility could be due to differences in the expression in
polymorphisms for genes controlling steroid hormone receptor expression and function [374]. Whether this is directly relevant to recently parturient women is unknown because they experience months of elevated progesterone and estradiol followed by their decline, compared to the relatively short duration of high steroid levels and declines across a menstrual cycle. In any case, a relationship between the magnitude of steroid hormone change across the peripartum period and women’s depressive symptom has sometimes been found [169,331,337,338,380], but as far as I am aware, a relationship with their anxiety has not.

Even if the magnitude of change in ovarian hormones across the peripartum period is found to intensify anxiety, using a naturally pregnant and parturient rat model to study its cellular or molecular causes would be problematic because the endocrine profile of parturient rats differs from that of parturient women. Unlike women, rats undergo a postpartum estrus, during which previously low estradiol levels sharply rise [91]. To avoid this surge in estradiol, which itself is anxiolytic [161,437], some laboratories have examined anxiety after withdrawal of hormones from steroid-treated virgin rats or after ovariectomizing pseudopregnant females [41,399,472]. Another endocrine dissimilarity between postpartum women and rats is that progesterone levels remain low in parturient women for weeks or months, particularly if the infant is regularly breastfeeding [298], whereas suckling by rat pups increases maternal progesterone within 3 days after parturition to levels as high as those found during late pregnancy [183,425,432]. Because ovariectomy soon after parturition virtually eliminates circulating progesterone, but does not alter anxiety in female rats [188,265], this particular endocrinological difference may not be as problematic.

Steroid hormones released from peripheral endocrine glands are not the only source of steroids that could eventually be found to contribute to the onset of postpartum anxiety disorders. Steroids synthesized within the brain either de novo or from peripheral substrates (i.e., neurosteroids) have been implicated in numerous psychiatric disorders, including some types of anxiety disorders [for reviews see 35,118,411] and in women’s perimenstrual mood swings [159,175,313,358,416,461; however, 381]. Plasma, hippocampal, and cortical levels of 3α-hydroxy-5α-pregn-20-one (3α,5α-THP or allopregnanolone), a reduced metabolite of progesterone and a positive allosteric modulator of the GABA_A receptor, dramatically drops within 3 days after parturition in rats [90,162], and plasma levels in women remain low for at least 6 months after giving birth [129]. Plasma and cortical levels of another reduced metabolite of progesterone, 3α,21-dihydroxy-5α-pregn-20-one (allo-tetrahydrodeoxycorticosterone, THDOC), also fall at parturition in rats [90]. Sudden withdrawal of neurosteroids, and subsequent absence of their enhancement of GABA_A receptor function, could dramatically increase neural excitability and lead to hyperarousal and anxiety.

It is unexpected, then, that the drop in allopregnanolone in parturient women is unrelated to of their emotional state [129], and that parturition increases depressive-like behaviors [162], but not anxiety-like behaviors in rats. The apparent lack of effects of neurosteroid withdrawal on anxiety in women may be because they all experience the withdrawal, but only some are susceptible to its effects on mood.

In parturient rats, Kellogg and Barratt [226] hypothesized that anxiety-related behaviors do not increase in parturient rats because suckling by pups elicits high progesterone release in mothers [183,425,432], thereby protecting them from the anxiogenic effects of withdrawal of progesterone and its neuroactive metabolites. This is inconsistent with the reduction in anxiety during lactation, however, because anxiety is highest during late lactation when maternal plasma progesterone is also at its highest [265,352]. It is also inconsistent with Kellogg and Barratt’s findings that conversion of progesterone into its reduced metabolities was lower in lactating rats compared to virgins, that levels of reduced progesterone metabolites did not correlate well with anxiety behaviors, and that administration of a 5α-reductase inhibitor further reduced anxiety in lactating females instead of increased it. Conversely, 5α-reductase inhibition does increase anxiety-related behaviors in pregnant rats [283], hinting at differences between virgin, pregnant, and lactating rats in how progesterone and its metabolites influence anxiety.

Nonetheless, studies examining anxiety in non-parturient models reveal that terminating pseudopregnancy in rats by ovariectomy increases anxiety-related behaviors in the elevated plus-maze [41,399]. This is due to the rapid withdrawal of progesterone’s reduced metabolites acting on the GABA_A receptor, as well as changes in GABA_A receptor subunit configuration that render the receptor less sensitive to positive modulators [40,167,399]. As noted above, estradiol levels sharply increase to produce a postpartum estrus in naturally parturient rats, and as discussed in detail below, interactions with pups release many non-steroidal neurochemicals that reduce anxiety. Withdrawal of neurosteroids after pregnancy or pseudopregnancy has the potential to increase anxiety in rats, but this is apparently counteracted by the anxiolytic effects of dams’ rising estradiol levels and the physical contact dams have with infants during and after parturition.

Even if neurosteroid levels are not associated with postpartum anxiety in susceptible women, some cell-surface receptors affected by neurosteroids, including those for GABA [89,280], NMDA [2,184], dopamine [25], and opioids [114,186,187], are upregulated or downregulated across pregnancy and lactation. Peripartum modulation at the receptor level could contribute to heightened or blunted neurosteroid sensitivity. Data from pregnant and early postpartum rats indicate no such changes in GABA_A receptor sensitivity to 5α-reduced steroids, at least in the cortex [226].

In sum, sufficient data do not yet exist to confidently support a role for neurosteroids in mediating the onset of
postpartum anxiety. There is ample evidence from non-
postpartum models, however, suggesting that some partu-
rrent women could be more susceptible to the anxiogenic
effects of abnormal basal levels of neurosteroids [52], fluc-
tuations in these levels across the peripartum period, or
reproductive state-specific changes in neurosteroid affinity
at the level of their receptors [389].

4. Animal models of postpartum anxiety

Given the detrimental effects of postpartum anxiety on
mothers and their children, understanding the underlying
neurobiology in an animal model would be greatly benefi-
cial. Similar to the reduced anxiety experienced by the
majority of postpartum women, most postpartum rats also
show decreased anxiety compared to non-parturient
females. Also similar to women, reduced anxiety in post-
partum rats has been proposed to affect their ability to care
for their offspring [150,192], and differences in the maternal
parturient rats has been proposed to affect their ability to care
females. Also similar to women, reduced anxiety in post-
partum rats has been proposed to affect their ability to care
for their offspring [150,192], and differences in the maternal
behaviors displayed by presumed low-anxiety and high-
anxiety mother rats have dramatic effects on the later phys-
iology and behavior of offspring [71,73,80]. At least two
complimentary and mutually informative paths of investi-
gation have contributed to our understanding of postpart-
umanxiety states in laboratory rodents. First, studying
the neurobiology responsible for why anxiety is reduced
in most postpartum rats can provide insight into what
could be awry in cases of elevated postpartum anxiety. Sec-
ond, it has also proven useful to study cases of aberrantly
high-anxiety in rats, which one could do by comparing
behavior and neurochemistry of the most anxious and least
anxious subjects within a larger sample of animals, or by
selectively breeding for high and low anxiety [47,327].

One of the first reports suggesting reduced anxiety in
postpartum rats demonstrated that parturient females
would traverse an unfamiliar T-maze to retrieve pups,
but that virgin females induced to act maternally due to
continuous exposure to pups (i.e., maternally sensitized)
would not [57,59]. Although this could suggest that lactat-
ing rats were less anxious or fearful of the T-maze, it could
alternatively suggest that they were simply more responsive
than virgins to the sensory cues emanating from pups that
elicit retrieval. Indeed, sensitized virgins are as likely as lac-
tating rats to leave the home cage and enter the T-maze
[407], but are less likely to then examine the two terminal
arms that may contain pups [59,407]. Degree of maternal
motivation is not only critical for how females respond to
pups [see 267], but also how they respond to anxiogenic
stimuli, as the presence of pups can override the effects of
an anxiogenic stimulus if mothers are sufficiently motivated
to contact infants [351]. A similar complication arises for
interpreting the now “classic” study of postpartum anxiety
by Hard and Hansen [192], in which they reported that lac-
tating rats showed less freezing than virgins in response to
a sudden acoustic stimulus. In this study, lactating rats
only showed less freezing if their pups were also in the star-
tle chamber. This leads one to wonder if this result reflects
reduced fear or anxiety, but instead, reduced attention to
or perception of the startle stimulus because dams were dis-
tracted while they interacted with the pups. Other studies
where pups are present in the apparatus during testing
might be open to similar interpretations [140,141,188,
346], but alternatively, could reveal how dams might
respond when the litter is also directly under threat
[109,474].

Maternal motivation and perception of the anxiogenic
stimuli could be important factors contributing to mothers’
anxiety state, but postpartum rats and mice are also less
anxious than virgins in many paradigms even when pups
are not present during testing. These include acoustic start-
tle [438], the open field [150,438], elevated plus-maze
[39,226,265], defensive burying of a electrified probe
[352], punished drinking [140], and the light–dark box con-
flict test [276,308]. It is important to point out that numer-
ous studies have not found reduced fear or anxiety in
lactating rats [44,138–140,326,328,345,352,394,405,482,
489]. Most, but not necessarily all, of these discrepancies
are probably due to procedural details. For example, our
laboratory has found that the amount of ambient light is
critical for detecting the effects of reproductive state on
behavior in the light–dark box. Differences between lactat-
ing and diestrous females are found only under medium or
high-light conditions (~600–1400 lux in white chamber),
but not under lower light conditions (~15 lux in white
chamber). This seems to be because diestrous females find
the white chamber aversive only when it is intensely illumi-
nated, while lactating rats do not find it aversive under any
of our light conditions [308]. Other discrepancies probably
result because different behavioral paradigms reveal differ-
ent aspects of anxiety [307,345], some of which may be
more sensitive than others to the effects of reproductive
state. The timing of testing is also critical, as anxiety is
not reduced throughout all of lactation in rats, but only
within the first few days or weeks [265,352]. Another
important issue is whether dams had recent contact with
pups before testing, as removal of the litter prior to testing
increases anxiety [265,325]. It is hopefully clear that, even
though numerous studies have not been able to demon-
strate that postpartum state reduces anxiety, changes in
emotional state might be more readily observed when par-
ticular methodological details are considered.

In addition to current motherhood reducing anxiety,
there are long-term effects of parity on anxiety-related
behaviors in rats. Females are less anxious in an elevated
plus-maze and open field after giving birth and weaning a
litter compared to inexperienced, virgin females [69,463].
Interestingly, these effects in the plus-maze were only found
when young, experienced females were tested during proes-
trus, when ovarian hormones levels are relatively high
[69,70]. Age of the females is also a factor, because older,
primiparous, experienced females in constant estrus are
more anxious than older, nulliparous ones [69], although
the opposite effect of age has also been reported [271]. In
the latter study, aged females were repeatedly tested in
the elevated plus-maze, which may explain this discrepancy because different trials in this paradigm measure different emotional states [147]. In any case, the effects of prior parity and motherhood on anxiety are due to ovarian hormones because they are eliminated by ovariectomy [69]. Given that ovarian hormones can be anxiolytic [161,437], this result is surprising because these hormones are lower in young reproductively experienced females, not higher [58,69]. Even in light of lower circulating ovarian hormones, neural anxiety networks could be more sensitive because of increased steroid hormone receptor expression [58], thereby leading to reduced anxiety in reproductively experienced females.

The diversity of behavioral paradigms detecting anxiety differences between mother and virgin rats greatly strengthens the validity of the anxiolytic effects of motherhood, and helps justify the use of laboratory rats as a model to study its underlying biology. It seems unclear, however, how animal behavior in these paradigms corresponds to human anxiety disorders. As noted in a recent discussion of this issue [388], most animal models of anxiety involve conflict or threat, which has high face validity for almost all types of anxiety disorders in humans. Mapping animal models onto specific symptoms particular to different types of human anxiety disorders, though, can be more difficult [388]. Postpartum women are most likely to experience symptoms of obsessive–compulsive disorder (OCD; ∼20% of postpartum women), panic disorder (∼10% of postpartum women), and generalized anxiety disorder (∼6% of postpartum women) [370]. Paradigms that model aspects of these disorders in animals could be the most valuable for understanding anxiety in postpartum women.

Numerous animal models of obsessive–compulsive disorder have been developed, and include animals with genetically or pharmacologically altered dopaminergic or serotonergic activity, and several behavioral models [for review see 220]. One simple behavioral model used is rats’ repetitive burying of innocuous marbles placed in the home cage, which is sensitive to pharmacological agents known to treat general anxiety or OCD. Another model is the signal attenuation model, in which rats are first trained to barpress for food in the presence of a specific stimulus. After this training, the stimulus is repeatedly presented without the opportunity for rats to barpress to obtain food. When the levers and signaling stimulus are presented together again, but still without the possibility of obtaining food, rats will compulsively barpress. According to Joel [220], this model has high face, construct, and predictive ability for OCD. Neither the marble-burying nor the signal attenuation paradigms seem to have been used with lactating rodents.

The elevated T-maze paradigm is designed to address specific symptoms of human panic and generalized anxiety disorders. The elevated T-maze is similar to an elevated plus-maze, with the exception that there is one closed arm and two open arms, instead of two arms of each type [181]. The advantage of this paradigm is that one can examine both the rats’ latency to escape after being placed on the open arm, suggested to model panic, and their avoidance of the open arms after repeatedly being placed into closed arms, suggested to model generalized anxiety [181]. Stage of the estrous cycle affects female rats’ generalized anxiety-like behaviors (but not panic-like behaviors) in the elevated T-maze [180], demonstrating that this paradigm is sensitive enough to detect endocrine and neuroendocrine factors influencing anxiety, but it has yet to be utilized with postpartum rats.

5. Infant contact reduces anxiety in mothers

Given the importance of infant contact on almost all aspects of postpartum physiology and behavior in mammals, it seems intuitive that infants would be intimately involved in regulating their mother’s anxiety. The human literature suggests that breastfeeding reduces anxiety and increases positive mood in recently parturient women [4,182,196,200,305,448,452], implicitly or explicitly implicating suckling and its hormonal and other neurochemical concomitants in this reduction. Interpreting this literature can be problematic for numerous reasons. First, not all studies consistently report a relationship between breastfeeding and anxiety [7,10,224,309,447,464,465,467], even if breastfeeding affects other measures of mood. Second, some studies do not include a postpartum, but non-breastfeeding, control group that would really be necessary to make such a claim; they instead use non-mothers as controls [196,304,448]. It cannot be determined if giving birth and caring for an infant, rather than breastfeeding and lactation, are the critical factors in these studies. One often-cited study that does include a non-breastfeeding control group reports only marginally significant effects of breastfeeding on anxiety, possibly due to very high variability in bottlefeeding group [452]. Lastly, breastfeeding involves both skin-to-skin contact with the infant and sucking inputs to the nipples. Bottlefeeding typically involves neither. Without a control group controlling for the recent physical contact with the infant, the relative importance of physical contact versus infant suckling remains unknown. This is an important consideration, as both suckling and non-suckling tactile stimulation from infants increase neuropeptide and hormone release in women [289,299]. In fact, one study that did include mothers who simply held their infants on their laps before anxiety testing reported that their anxiety was similar to mothers who just breastfed their infants [200]. Another problematic issue is that anxious women are less likely to breastfeed [88,344], leading one to wonder if higher anxiety in some bottlefeeding women is a cause or effect of their feeding method.

Using a clever design, two studies examined mood in women who were both bottlefeeding and breastfeeding, during or after these women fed their infant using one of the methods. Modahl and Newton [309] reported that anxiety was the same when these women breastfed as when
they had not recently fed their infant, but that anxiety in both cases was non-significantly lower than non-postpartum women. Mezzakappa and Katkin [305] found that a bout of breastfeeding decreased negative mood (as measured with the Positive and Negative Affect Scale; PANAS), but had no effect on positive mood, while bottle-feeding decreased positive mood, but did not affect negative mood. It remains unknown if the decrease in negative mood after breastfeeding is specifically related to decreased anxiety or other dimensions of negative mood detected by the PANAS (e.g., depression).

It seems that, although many studies report that most new mothers are less anxious than non-mothers, the sensory underpinnings and cause-and-effect relationships remain unclear. Our laboratory has recently been investigating the fundamental sensory determinants of reduced anxiety during lactation in laboratory rats [265]. Given the gist of the human literature, we originally hypothesized that suckling and consequent pituitary and ovarian hormone release were necessary for reduced anxiety in postpartum rats. We found that this was not the case. As assessed with an elevated plus-maze, one of the most frequently used and pharmacologically reliable paradigms to examine anxiety in rodents, we found that postpartum mothers did not show reduced anxiety throughout all of lactation, but only during the first week after giving birth. By day 14 postpartum, their anxiety-related behaviors were similar to diestrous virgins [265]. Lactation and continual suckling by pups, therefore, seemed to be insufficient for reduced anxiety. We also found that dams separated from their pups for as little as 4 h before testing showed greatly elevated anxiety [Fig. 1], indicating that the anxiolytic effects of infant contact are relatively transient. This was consistent with data from the Neumann laboratory [noted in 325] indicating that separation from pups for 2 h before testing increased anxiety in the elevated plus-maze and holeboard tests. Also in apparent support of a role for pup suckling in their mother’s anxiety, dams did not show reduced anxiety if, for the 4 h before testing, their pups were encased in a wire mesh box that allowed transmission of just olfactory, visual, and auditory cues. Only if dams could physically contact the pups did they show reduced anxiety.

A critical experiment was necessary before we could appropriately interpret these results. We needed to examine the effects of physical contact with pups in the absence of suckling. Surgical removal of the 12 teats (i.e., thelectomy) is a relatively non-invasive procedure that eliminates suckling by infants, but not other ventral somatosensory inputs they provide. Thelectomy had previously been used to demonstrate that physical contact with pups, but not suckling, can maintain essentially normal maternal behavior and maternal aggression in lactating rats [290,406]. We found that thelectomy 24 h prior to testing, or even prior to mating, had no effect on elevated plus-maze behavior in postpartum dams [265, Fig. 2]. This conclusively demonstrated that recent physical contact with pups was necessary for reduced anxiety in mother rats, but suckling was not. This differs notably from the reduced responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis to stressors during lactation [200], which clearly requires suckling by infants [442]. We do not yet know what types of non-suckling somatosensory inputs are required for reduced anxiety in postpartum rats. Rooting in their dam’s ventrum while searching for a nipple does have physiological consequences for the mother [269,270,310,408], but perioral stimulation that dams receive during interactions with pups may also be sufficient to reduce anxiety [315].

This series of experiments lead us to conclude that suckling was not the critical sensory factor reducing anxiety in postpartum rats. Instead, physical interaction with infants alone was sufficient to produce a temporary anxiolytic effect in mother rats. Our data are consistent with studies

![Fig. 1. A 4-h separation (Sep.) from the litter increases dams’ anxiety-related behaviors in the elevated plus-maze (i.e., reduces the percentage of time spent in the open arms of the maze) to levels found in diestrous virgins. Different letters above bars indicates statistically significant differences between groups (p < 0.05). Modified from [265].](image1)

![Fig. 2. Thelectomy (removal of the teats) has no effect on anxiety-related behavior in dams. Thelectomized and sham-operated dams spend a similarly greater percentage of time in the open arms of the elevated plus-maze compared to diestrous virgins. Different letters above bars indicates significant differences between groups (p < 0.05). Modified from [265].](image2)
showing that virgin female rats induced to be maternal through contact with pups are less anxious, even though they are neither parturient nor lactating [141,351; but see 407]. This is also conceptually similar to the study noted above where simply holding an infant was associated with reduced anxiety in postpartum women [200], indicating that general somatosensory inputs from infants may be an effective modulator of anxiety in many mammals. "Kangaroo care", which promotes holding neonates on the mother’s chest or regularly carrying older infants in a harness on the mother’s chest (even if infants are not breastfed), increases skin-to-skin and non-skin-to-skin contact between mothers and infants. It promotes mother–infant bonding, infant physical development [18,81], and possibly reduces anxiety in new mothers [68,390]. It is interesting to note that the mother–infant dyad is not the only context where somatosensation reduces anxiety, and massage is well-known to reduce anxiety in non-lactating humans [48,105,142–146,297].

6. Infant contact modulates neurochemistry to reduce postpartum anxiety

Many neurochemical systems mediate how recent physical contact with infants prevents high-anxiety in postpartum rats. Many of these are the same as those indicated above as possible precipitants of anxiety disorders in parturient women, suggesting that perturbations of these systems could contribute to the onset of anxiety disorders, but that contact with infants can retune maternal neurochemistry to help reduce her anxiety.

6.1. Prolactin and oxytocin

Empirical data from laboratory rats support both PRL and OT in how infants modulate their mother’s anxiety. The critical source of these peptides must be from central origin, as we found that surgical removal of the pituitary gland during late pregnancy does not affect the ability of pups to later reduce mothers’ anxiety-related behaviors in the elevated plus-maze [265], similar to the lack of effects of hypophysectomy on maternal behavior [132,251,265] and maternal aggression [132].

As mentioned above, the anti-stress effects of PRL in lactating and non-lactating rats have long been recognized [117,379], but PRL effects on anxiety-related behaviors have been only recently examined. Torner and colleagues demonstrated that intracerebroventricular infusion of PRL is anxiolytic in virgin female and male rats, while conversely, infusion of antisense oligonucleotides targeting the long form of the PRL receptor was anxiogenic [435]. The anxiogenic effects of central administration of PRL receptor antisense was later extended to lactating rats [434]. Torner and colleagues also showed that interaction with pups increases PRL mRNA expression and release specifically within the paraventricular nucleus of the hypothalamus (PVN) and preoptic area (POA) [433]. These sites modulate anxiety [179,445], and are two of probably many brain areas where infant contact increases intracerebral PRLergic and reduces anxiety.

High central OTergic activity is also anxiolytic in laboratory rats and mice [28,293,364,472,473]. The recently developed OT-knockout mouse lends support for an important role for OT in anxiety states, as virgin female OT knockouts are more anxious than wild-type females, an effect that can be reversed with intracerebral infusion of OT [14,284]. Regulation at the level of the OT receptor is also relevant, with virgin female rats with low-anxiety having higher OT receptor binding in the central amygdala and bed nucleus of the stria terminalis (BST), areas of the traditional fear and anxiety networks [459], compared to females with higher anxiety [158]. A negative relationship between plasma OT and anxiety is not always found in female rats [326,327,329], reinforcing a more critical role for central, rather than peripheral, OT.

The effects of OT on anxiety in male are less clear. Anxiety is reduced after intranasal infusion of OT in men [199] and after peripheral injection in male rats [447], but it is also reduced in male OT-knockout mice [284,475; although see 110]. Furthermore, plasma levels of OT and OT synthesis in the hypothalamus are not correlated with anxiety in male rats [247,468]. This apparent sex difference in the effects of OT on anxiety may be related the fact that OT release and receptor expression in many sites are sensitive to circulating estradiol [292,355], which is typically greater in females than males.

OT levels in the cerebrospinal fluid, preoptic area, and BST are elevated when sheep and rats interact with their offspring [228,229,323], but this does not occur everywhere in the postpartum brain. Bosch and colleagues [45] found that basal OT levels do not differ between lactating and virgin female rats in the PVN, central amygdala, or lateral septum. They also found [46] that rat dams selectively bred to have high or low anxiety do not differ in their basal OT levels within the PVN and central amygdala, and that highly anxious dams show greater OT release in these sites when exposed to a stressful and anxiogenic aggressive interaction than do low-anxiety dams. One might have expected low-anxiety dams to have greater OTergic tone in these sites, but this could indicate that elevated OT receptor expression in these sites is more important than the amount of OT released for females’ anxiety. However, virgin and early postpartum rats do not differ in their OT receptor expression in some sites traditionally involved in generating anxiety, including the ventromedial hypothalamus, central amygdala, and ventral subiculum [157,215,216,483]. If examined very soon after parturition, though, OT receptor mRNA and binding levels are very high in the ventromedial hypothalamus, lateral septum, central amygdala, and dorsal BST [215,216,483]. Because OT receptor levels do not remain elevated throughout early lactation, its relevance for reduced anxiety of mother rats is unclear, and it may instead be related to the onset of maternal behavior at parturition. Nevertheless, in the only study...
to directly examine the relationship between OT and the postpartum performance of anxiety-related behaviors, Neumann and colleagues [328] demonstrated that intracerebroventricular infusion of a highly specific OT receptor antagonist decreased the percentage of time spent in the open arms of an elevated plus-maze, indicating increased anxiety, without affecting general activity. In contrast, OT receptor antagonism had no effects on elevated plus-maze behavior in virgin females.

Areas of the brain where disruption of OT receptor activity produces anxiogenic effects in lactating rats are probably widespread. Work in our laboratory has implicated the midbrain periaqueductal gray (PAG) as one such site. The PAG is necessary for a myriad of behavioral and physiological processes [30]. It receives descending projections from many sites involved in anxiety, and acts as a supraspinal “final common pathway” for anxiety- and fear-related behaviors in animals [53]. Electrical stimulation of the PAG elicits feelings of anxiety and panic in rodents and humans [217,319,378], and functional MRI reveals that the PAG is activated when people feel anxious [120]. Conversely, lesions of the PAG are anxiolytic [232,253,450] and manipulating a number of neurochemical systems in the PAG reduces anxiety [53,302]. The PAG contains OTergic terminals [66], expresses OT receptors [481], and exhibits electrophysiological responses to iontophoretically applied OT [336].

In lactating female rats, the ventrocaudal PAG (cPAGv) is uniquely sensitive to somatosensory inputs from pups [269,270]. Lonstein and Stern found that this sensitivity was relevant for dams’ nursing behavior [269,270], and also their anxiety. When the cPAGv was lesioned, there was a further decrease in anxiety-related behavior in lactating rats [268]. At least part of the cPAGv’s function in modulating anxiety in dams is mediated through OTergic mechanisms. Similar to the demonstration by Neumann et al. [328] that OT receptor antagonism increases anxiety in lactating rats when infused ICV, we found that infusion of this same highly specific antagonist directly into the cPAGv (but not the dorsal cPAG) also increases anxiety in dams to the levels typically found in virgin females [Figueira, Peabody and Lonstein, in preparation; Fig. 3]. Midbrain infusions that missed the cPAGv did not affect anxiety. Importantly, infusion of the OT antagonist into the cPAGv of diestrous virgin females had no effects on plus-maze behavior, suggesting that OT’s effects are specific to mother rats. Conversely, we have also found that in mothers that were more anxious because their pups were taken from them before testing, infusion of OT itself into the cPAGv reduced anxiety back to low levels. This was also specific to postpartum state, as OT infused into the cPAGv of diestrous virgins did not reduce their anxiety.

Possibly analogous to the rooting and probing that pups do in their dam’s ventrum, repeated stroking-like somatosensory stimulation of the ventrum increases OT content in the PAG of male rats [274], and this increase might also occur in lactating females while they interact with pups.

There may also be transient upregulation of OT receptor expression in the cPAGv when mothers are with their infants, as changes in OT receptor content can occur relatively quickly [87,382]. The source of OTergic input to the cPAGv is unknown, as no retrograde-tracing studies from the cPAGv have been performed in conjunction with dual labeling for OT. One would expect that it arises from intracerebrally projecting parvocellular OTergic cells of the medial paraventricular nucleus. Interactions with pups during the early postpartum period elicits immediate early gene expression in some magnocellular OTergic cells [260,261], and perhaps also in parvocellular OTergic cells. Novel populations of OT-immunoreactive cells are found, however, in areas outside the PVN during lactation [219]. These might be unique sources of OTergic input to the cPAGv and elsewhere to regulate anxiety and other behaviors during lactation. Indeed, excitotoxic lesions encompassing much of the parvocellular PVN affect neither exploration or defecation in a novel chamber, nor freezing in response to an acoustic startle stimulus [339]. This could mean that the source of OT modulating dams’ anxiety is not the PVN, or that there are redundencies in the neural systems modulating anxiety, such that infant contact sufficiently affects other systems to be anxiolytic even without a contribution from the parvocellular PVN.

6.2. Corticotropin-releasing hormone

High central CRH signaling is anxiogenic, and its reduction anxiolytic, in non-lactating rats [27,210,246,381]. Some CRH systems are downregulated during lactation in rats [96,97,148,436,456,457,471,473], and this downregulation is necessary for milk letdown [6], maternal aggression [168], and hyporesponsiveness to stress [116,258,324].
Similar to the downregulation discussed above that might help prevent the onset of postpartum anxiety, continued downregulation of CRH systems in response to infants might help maintain decreased anxiety. At the moment, however, there does not seem to be sufficient data supporting this. Only one study directly suggests this to be the case in lactating rats, with CRH unable to enhance their startle responding, as it does in virgin [436]. Because this was examined in dams on day 14 postpartum, when anxiety as measured in the elevated plus-maze and defensive burying has reverted back to virgin levels [265,353], it is unknown if downregulation of CRH systems contributes to the decrease in anxiety during early lactation. It may not, because CRH mRNA is highest in PVN, POA, and central amygdala during the first few days postpartum when anxiety is at its lowest [97,109]. Additionally, basal CRH-1 receptor mRNA expression, at least in the PVN, is not affected by reproductive state [97]. Corticosterone feeding back onto the brain also does not seem critical, as adrenalectomy does not prevent high rates of punished drinking in dams [188].

Data from our laboratory also suggest that CRH is not involved in how infant contact reduces anxiety during early lactation. We found that Fos expression within the dense populations of CRH-synthesizing cells of the PVN, dorsal BST, and central amygdala [420] does not differ between dams that were separated or not separated from their pups before exposure to an elevated plus-maze [398]. That is, there seems to be no “recruitment” of CRH-synthesizing cells when highly anxious dams who had their pups removed prior to testing are exposed to an anxiogenic situation. Instead of the number of cells being affected, it could be the amount of CRH produced or released is rapidly increased in anxious dams, although this also may be unlikely because increased CRH signaling necessary for resumption of stress responsiveness after removal of the litter is not rapid, but rather, takes at least 24–72 h to occur [259,406,457]. I have previously highlighted the numerous dissociations between activity of the HPA axis and anxiety-related behaviors in lactating rats [266], but detailed and direct examination of how central CRH influences postpartum anxiety in a variety of behavioral paradigms is still required. Even if the central CRH systems influencing the HPA axis and anxiety behaviors partly overlap, how the postpartum suppression of the HPA axis in rats pertains to postpartum women can be unclear because, as discussed above, the HPA axis in women does not seem to be chronically downregulated and its activity is also not consistently correlated with anxiety [8,10,200,224, 277,443].

6.3. Estradiol, progesterone, and neurosteroids

Estradiol and progesterone, and activation of their receptors, modulate anxiety in virgin female rodents [161,437,465]. Circulating levels of these hormones are not responsible, however, for how infant contact reduces anxiety in postpartum rats. First, late-pregnant rats with high circulating levels of progesterone and increasing levels of estradiol are more anxious than females tested at other times of the reproductive cycle when hormone levels are lower [326,489]. Second, administering exogenous hormones or inducing pseudopregnancy to mimic the hormonal patterns of pregnancy do not reduce anxiety in female rats [41,409], unless females interact with pups during or after treatment [57,189,407]. Third, the greatest reduction in anxiety is found during early lactation [265,352], when ovarian hormone levels are relatively low in rats nursing a full litter of pups [183,425,432]. Finally, and most importantly, postpartum ovariec-tomy has no effect on dams’ elevated plus-maze behavior [265] or punished drinking [188]. These results are not completely unexpected, because even ovariec-tomized virgin female rats induced to be maternal just through contact with pups show somewhat reduced anxiety [141,351], suggesting that some of the anxiolytic effects of infant contact do not require prior or current exposure to ovarian hormones.

Even if ovarian steroids are not responsible for how litter contact reduces anxiety, neurosteroids remain a possibility. Even in maternal rats that are not naturally parturient, infant contact has neuroendocrine consequences [413,428], and at least one other form of tactile input (vaginocervical stimulation, with last injection four hours before testing) leads to changes in neurosteroid levels in female rats [160]. In an initial examination of this possibility, we subcutaneously administered the steroidogenesis inhibitor, aminoglutethimide, to dams twice per day during postpartum days 5–7 (100 mg/injection, with last injection four hours before testing), and found that it had no effect on their elevated plus-maze behavior [Cavanaugh and Lonstein, unpublished data]. This supports the work detailed above by Kellogg and Barrett [226], showing that inhibition of just the 5α-reduced products of progesterone does not affect dams’ anxiety. Nonetheless, the effect of more chronic treatments and additional doses of aminoglutethimide or other steroidogenesis inhibitors need to be examined before a role for neurosteroids in postpartum anxiety can be excluded.

6.4. GABA

The postpartum period introduces an entire array of neurochemicals, including PRL and OT, which are released in unique patterns and quantities to potentially influence anxiety. The relative degree that these unique factors contribute to postpartum anxiety state is unknown, but it makes sense that the fundamental neurochemistry regulating anxiety in non-postpartum animals is still pertinent in postpartum ones. The inhibitory neurotransmitter, GABA, is well-known to influence anxiety states in both humans and laboratory rodents. This is largely based on the anxiolytic effects of GABA receptor activation, with the GABAA receptor subtype particularly well studied [307,321]. Sedative and anxiolytic agents including benzodiazepines, barbiturates, and steroids have binding sites on the GABAA receptor and facilitate negative chloride ion influx and hyperpolarization of neurons. Mice with genetic mutations...
of the GABA<sub>A</sub> receptor show increased anxiety [93,272], and female rats with higher anxiety have lower benzodiazepine receptor expression in many areas of the brain [71]. In humans with some types of anxiety disorders, GABA<sub>A</sub> and benzodiazepine receptor expression are reduced [55,281]. The GABA<sub>B</sub> receptor subtype is not completely irrelevant, and mice with a genetic mutation leading to non-functional GABA<sub>B</sub> receptors are also more anxious [312]. Additionally, human panic disorder can be alleviated with baclofen, a GABA<sub>B</sub>-receptor agonist [56].

Given this, it is surprising that very few studies find a negative correlation between plasma or cerebrospinal fluid (CSF) GABA with anxiety in humans [50], and most find no association [176,177,212,363,372,373], or even a positive association [173]. CSF GABA levels also do not change after treatment with anxiolytics and alleviation of anxiety symptoms [363]. Instead of examining GABA levels in plasma or CSF, examining it site-specifically in the brain may be more fruitful [129,176], as would determining GABA’s effectiveness at its receptors [55,185,430].

Little is known about changes in central GABA systems in postpartum women, but CSF levels are reduced during late pregnancy [9], increase during labor [383], and occipital cortex levels of GABA are reduced after laboring birth [129]. Other mammals show numerous changes in GABA signaling that may be associated with reduced postpartum anxiety. Cerebrospinal fluid levels of GABA sharply increase in lactating rats and sheep when they interact with their infants, but drop to very low levels when infants are removed [229,356]. One study in mice shows that GABA turnover is actually somewhat reduced in the first three brain sites after delivery [400]. It is not stated if dams in this study were housed with their litters until the moment of sacrifice, though, making interpretation difficult. These effects on anxiety in postpartum rats might not include all of the sites one might expect, because infusion of bicuculline into either the ventromedial hypothalamus or amygdala does not increase the duration that dams freeze in response to an acoustic startle stimulus [190]. In fact, GABA<sub>A</sub> antagonism in the ventromedial hypothalamus tends to further reduce dams’ freezing [190].

Not only is the cPAGv susceptible to the anxiolytic effects of OT, but it is also part of the network where GABA affects postpartum anxiety. As noted above, lesions encompassing the cPAGv decrease the already low levels of anxiety displayed by lactating rats [268], indicating that similar to male rats, reducing cPAGv output by completely destroying it reduces anxiety in postpartum rats. The intrinsic circuitry of the PAG is characterized by a tonically active network of inhibitory interneurons [34,361], with at least half of the neurons in the cPAGv synthesizing GABA, receiving GABAergic terminals, and/or expressing GABA<sub>A</sub> receptors [361]. The cPAGv is highly responsive to somatosensory cues from pups [269], and these cues may increase tonic inhibition of the cPAGv, thereby reducing anxiety in dams. We find that infusing bicuculline to alleviate tonic GABAergic inhibition in the cPAGv, but not dorsal to the cPAGv, reduces the percentage of time spent in the open arms of the elevated plus-maze. Different letters above bars indicates significant differences between groups (p < 0.05). [348, Miller, Peabody and Lonstein, in preparation].

6.5. Norepinephrine

Activity of the noradrenergic system is an important determinant of both human and animal anxiety. Anxiety disorders, and anxiety symptoms in depressed patients,
are often associated with increased peripheral and central measures of noradrenergic activity [172,236,252,254,354,359,373,384,479]. Strongly suggesting a functional relationship between this system and anxiety is that reuptake inhibitors affecting norepinephrine (SNRIs) are greatly effective anxiolytics [104,395,429]. How the noradrenergic system influences anxiety during the peripartum period in humans is not well studied. In pregnant women, measures of noradrenergic activity in CSF are either decreased [9] or do not differ [125,126,431] from those of non-pregnant women. Basal plasma norepinephrine is lower, and its release in response to psychosocial stress blunted, in breastfeeding women, but breastfeeding does not need to be very recent for this to occur [8,200]. This reduced basal and stimulated peripheral NE release may have more to do with the hyporesponsiveness to stress found in breastfeeding women [116], rather than central control of anxiety because positive correlations between plasma and central NE levels are not always found in humans [124,172,262,431]. Furthermore, the one study examining a relationship between plasma NE levels and postpartum anxiety shows no significant association between them [278].

Noradrenergic activity changes considerably during lactation in rats. Suckling by pups increases plasma NE [82], but because artificial stimulation of the mammary nerve does not [82], it is unclear if suckling or some other sensory cue from pups is responsible. Of course, measures of noradrenergic activity in the central nervous system are more pertinent for dams’ anxiety. In non-lactating laboratory rats, increased central adrenergic activity promotes anxiety-related behaviors and physiological responses by acting upon the cortex, amygdala, BST, hypothalamus, and brainstem [101,102,137,322,424]. It could be expected that central NE activity is lower in lactating rats to maintain a low-anxiety state, but NE levels in the CSF of lactating rats are apparently unknown. Early studies focused on the hypothalamus, to better understand how catecholamines affect suckling-induced prolactin release, but were inconsistent and reported that suckling did either not affect noradrenergic activity in the homogenized hypothalamus [301] or reduced it [311].

More recent work reveals that norepinephrine release in the PVN is low when day 8 postpartum mothers are with their pups and increases when pups are removed [439]. However, if day 8–12 postpartum dams are separated from their pups for 4 h and reunited, NE release in the PVN increases [33]. This discrepancy may be due to separating the mothers from pups, followed by a reunion, before sampling in the latter study. It could also be due to differences in the location of the microdialysis probe within the PVN, with decreased NE release onto parvocellular PVN cells occurring to dampen HPA activity in response to stress, but increased NE release onto magnocellular PVN cells necessary for suckling-induced OT release. Fos is expressed in TH-immunoreactive cells of the A1 and A6 groups in the brainstem after dams have physical contact with pups [256], and the A1 group does provide substantial noradrenergic input to the PVN [342,418,419]. However, this Fos expression is observed after dams are separated from pups for 48 h and then reunited for 90 min [256], and may reflect an increase in NE release specifically when dams are separated from and then reunited with pups, such as that observed in the PVN by Bealer and Crowley [33]. Expression of various noradrenergic receptors in the PVN is also modified during lactation in dams continually housed with their litters [439], further reducing PVN responsiveness to noradrenergic stimulation [471].

Changes in noradrenergic activity during lactation affect the reflexive startle response made to sudden acoustic stimuli, which is modified by emotional state, and dams’ acoustic startle can be increased by peripheral administration of α-2 antagonist yohimbine, but reduced by the α-2 agonist clonidine [438]. Site-specific injections of these agents are necessary to determine if they are acting in the PVN or elsewhere in the brain to affect startle responding. If this occurs within the PVN, many neurochemicals are synthesized here that can contribute to this effect. For example, noradrenergic terminals contact OT-synthesizing cells in the PVN of both rats and monkeys [174,306], and the number of these contacts increases during lactation [306]. Most OTergic terminals in the PVN are depolarized by NE [49,218], consistent with findings that NE or noradrenergic agonists stimulate OT release in lactating rats, while noradrenergic inhibitors decrease OT release when dams are suckled [33,83; however, see 211,403]. Similar effects of NE and its antagonist are found in hypothalamic tissue in vitro [357]. It might be possible that infant contact reduces startle and other measures of anxiety through hypothalamic NE release stimulating OTergic cells. Evidence against this, though, is that NE turnover is increased in the PVN when mothers are suckled, but only in the rostral PVN [95], where OTergic cells project primarily to the posterior pituitary, rather than intracerebrally [419]. NE turnover is not increased by suckling in the caudal PVN, which has greater projections within the central nervous system [377]. Furthermore, most parvocellular neurons in the PVN are not excited by NE [98], even though some show Fos expression after unconditioned fearful stimuli [486]. It is unclear how NE release in the PVN during interactions with pups affects anxiety, and it may instead be more involved in PVN-mediated effects in the periphery, such as reduced physiological stress responsiveness when dams are not in the presence of their pups [109,258,457].

Areas of the brain where infant contact reduces NE release to alleviate anxiety during the postpartum period are probably widespread. Possible sites of action could include the amygdala, but work from the Davis laboratory indicates that the amygdala (including its noradrenergic input) is less important for unconditioned anxiety, such as that most often examined in lactating rats, than for conditioned fear [459]. The PAG may be another possibility [322], but we are currently focusing on the ventral BST as a particularly critical site (BSTv; including parts of the ventral, magnocellular, ventral principal, anterolateral,
and dorsolateral nuclei [417]). The BST is involved in the ability to “cope” with anxiogenic stimuli. Large BST lesions exacerbate the effects of stress on restraint-stress-induced stomach ulcers and cause male rats to be more behaviorally responsive to fear-associated cues [202]. In a conditioned fear inhibition paradigm, presentation of the stimulus that indicates safety and the absence of electric shock increases Fos expression in only a few neural sites—including the BSTv [74]. It is also activated during anxiogenic situations in primates [221]. The BSTv also has one of the densest noradrenergic innervations of the rat brain [137,478], arising primarily from the A1 and A2 brainstem groups [362,368,376,478]. Innate fearful stimuli such as TMT, a component of fox odor, increase NE release in the BSTv [137]. An increase also occurs in response to conditioned fearful stimuli [340]. Reducing noradrenergic activity in the BSTv in males by infusing clonidine (which acts as a presynaptic autoreceptor to reduce NE release), or by lesioning noradrenergic fibers, reduces freezing during exposure to these stimuli [137,340]. The effects of simply lesioning the BSTv on unconditioned anxiety in rats requires further investigation, as lesions are typically very large and include both the dorsal and ventral BST, and produce inconsistent effects [440,453].

Recent data from our lab implicate the BSTv in how infant contact affects anxiety in lactating rats. As discussed above, separating a mother rat from her pups increases her anxiety-related behavior to levels found in diestrous virgins [265,325]. We examined Fos expression in the brains of separated and non-separated dams who were placed in the elevated plus-maze, or simply left in their home cages. We find that, although the plus-maze behavior differed between the groups, only a small number of neural sites showed differences in Fos expression between separated and non-separated dams. The greatest difference between them was in the BSTv, with greater Fos expression in less anxious dams that had their pups before exposure to the plus-maze [398]. Control dams housed with their pups but not placed in the plus-maze had low levels of Fos in the BSTv, indicating that the display of maternal behavior before testing did not generate this increase in Fos protein [332,333], and that it was instead in response to being exposed to the plus-maze.

It may be somewhat surprising that dams with pups before testing, and therefore lower anxiety, had increased Fos in the BSTv. NE in the BSTv inhibits glutamate release and cellular activity [78,122,155], so removing this inhibition could increase neural activity and Fos expression in the dams’ BSTv. Recent contact with pups may, therefore, decrease NE release in the BSTv when dams are exposed to an anxiogenic situation. Increased glutamate release and BSTv activity could readily inhibit anxiety, as most BSTv neurons are GABAergic [317,404,415]. Activation of inhibitory projections from the BSTv to many areas of the brain, including the PVN, amygdala, preoptic area, cPAGv, and supramammillary nucleus [19], could modulate their activity to suppress anxiety responses in lactating rats. Indeed, inhibiting GABA synthesis within the BST, which would impair the function of these projection neurons, may increase anxiety [387]. GABAergic projections to the PVN could be particularly important for disinhibiting OT and PRL projecting locally and to distant sites affecting anxiety-related behaviors [Fig. 5]. Conversely, when dams are separated from pups, NE release in the BSTv might increase, reducing its GABAergic output and increasing anxiety. We have preliminary data suggesting that BSTv infusion of clonidine (1 ng or 100 μg), an α2 receptor antagonist that can act on presynaptic autoreceptors to reduce norepinephrine release, does reduce anxiety in dams that were separated from their pups before testing [Fig. 6; Smith and Lonstein, unpublished data].

All of this remains to be reconciled with the increase in Fos, not decrease or lack of expression, in A1 noradrenergic cells after dams interact with pups following a 48-h separation [256]. This implies that NE is released from the A1 group when dams interact with pups, but only 37% of these noradrenergic cells express Fos [256], and it is unknown if these particular cells project to the BSTv, or are even activated during mother–infant interactions not following such a long separation. Our hypothesis also will need to accommodate the dampening of light-enhanced startle found after dorsal or ventral BST infusion of the AMPA receptor antagonist NBQX, which would decrease glutamatergic neurotransmission in the BSTv [458]. Alternatively, NE release in the vBST might increase while dams interact with pups, but that BSTv neurons providing excitatory input to areas promoting anxiety are inhibited by local GABAergic

![Diagram](image_url)

**Fig. 5.** In a relatively small component of the larger network reducing mothers’ anxiety, we propose that physical interaction with pups maintains low norepinephrine release from the brainstem A1 and A2 groups into the BSTv. This inhibits GABAergic projections from the BSTv to numerous areas of the brain including the PVN, numerous subregions of the amygdala, and cPAGv. Potentially excitatory projections from the PVN and amygdala to the cPAGv are also inhibited. Intracerebral release of OT and PRL within and from the PVN may also result from vBST disinhibition, although excitatory inputs are probably also involved. Direct noradrenergic inputs from the brainstem to the PVN, amygdala and cPAGv exist, but are not indicated.
neurons within the vBST [see 119,171]. In any case, the BSTv has connections with both the mesolimbic and emotional systems in the brain [154,171,459], and may be a site of interface between networks controlling the rewarding properties of infants and other emotion-laden stimuli in the environment. Pereira and colleagues [351] have found that mothers’ anxiety can be overridden by the presence of highly rewarding pups, an effect associated with high maternal dopamine neurotransmission, and possibly modulated by the vBST. If this is universal, aberrant vBST activity could reduce mesolimbic dopamine function in human women, diminishing their perception of infants as rewarding, hence leading to reduced infant contact and higher anxiety.

7. Conclusions

Every year, millions of postpartum women and their infants around the world are affected by the onset or worsening of maternal anxiety disorders, and yet, there is virtually no information in either humans or animals about the endocrine, neuroendocrine, and neurotransmitter factors leading to high anxiety during this particular reproductive state. At least it is known that postpartum anxiety can be naturally reduced by infant contact. Studies in humans have been somewhat unclear, but physical contact with infants—even without breastfeeding—seems to be an important contributor to positive mood and reduced anxiety in mothers. This is a somewhat troubling conclusion, as infant care in the United States and similar societies involves a system of infant “caching”, which diminishes physical contact between mothers and infants, and differs dramatically from the pattern of very frequent mother-infant contact that existed over the course of human evolution [273]. The reduced contact that bottlefeeding mothers make with their infants, even in non-feeding contexts [79,243,248], further compounds the problem. This seems particularly relevant for low-income mothers of some minority groups, who are at higher risk for postpartum emotional dysregulation [24,213], but the least likely to breastfeed their infants [242,257,375]. It is also a concern for mothers who give birth prematurely or have perinatal complications, because they are also more prone to elevated anxiety [61,135,231,249,350,469,485], but less likely to breastfeed [72]. Even independent of such factors, women with the highest trait anxiety, who might benefit the most from the anxiolytic effects of continual infant contact, are the least likely to initiate and persist in breastfeeding [84,156,344].

The relatively few studies in humans have not revealed much empirical data about the neurochemistry of how infant contact regulates maternal anxiety. Research on laboratory animals reveals that numerous hormones, neuropeptides, and neurotransmitters acting upon multiple brain sites are responsible. Neurochemicals not yet investigated in detail in the context of postpartum anxiety or discussed here—including serotonin, thyroid hormones, vasopressin, galanin, endorphins, substance P, CCK, and neurotrophic factors—also have unique patterns of activity during the peripartum period, and may eventually be revealed to affect mothers’ anxiety. It is striking that some of the systems discussed here seem to act redundantly. Pharmacological manipulation of OT, PRL, GABA, or NE can each affect anxiety in mother rats to a similar degree. This may be expected, as some neural sites regulating anxiety—including the BST, amygdala, and PAG—have receptors for all of these neurochemicals [26,51,481,484]. The relevant neurochemical factors probably do not only function in parallel and with redundancies, but also sequentially and interactively. For example, the anxiolytic effects of OT may partly be mediated through its ability to modulate release of excitatory amino acids [121] and GABA [64]. Similarly, neurosteroids affect GABA<sub>A</sub> receptor subunit expression and activity of hypothalamic OT cells [203]. Another example is that intracerebral OT release in response to stressful or anxiogenic stimuli depends on the inherent responsiveness of the mothers’ HPA axis [46]. Considering how detrimental maternal anxiety and other mood disorders are to infant development, the maternal brain would be best served by a wide array of redundant and interactive systems, to better ensure a positive maternal emotional state.

The sheer number of neurochemical changes occurring across pregnancy, parturition, and lactation may explain why this topic is understudied and why it is difficult to generate an overarching biological model for either the onset or infant-mediated alleviation of postpartum anxiety. Even small advances in understanding individual components of this enormous sensory, endocrine, neuroendocrine, neuropeptide, and neurotransmitter network could still lead to valuable interventions. Educating millions of at-risk mothers about the association between infant contact and reduced anxiety could help optimize maternal mood, and subsequently, mother-infant interaction. Enhancing
mother–infant contact, and concomitant release of endogenous anxiolytic neurochemicals, has already been suggested to reduce anxiety in new mothers [68,390]. In addition, non-traditional anxiolytics, such as neuropeptides, may be more amenable than traditional anxiolytics for treating anxiety in postpartum women, particularly those who are breastfeeding. When administered intranally, OT rapidly reaches the brain and affects socially and emotionally relevant neural processing in humans [113,199,233,239]. OT levels are already high in breastmilk [250,423], and if small increases in breastmilk OT result from maternal administration of OT as an anxiolytic, this may not be of great concern [but see 75,245,246]. A combination of unique behavioral and pharmacological interventions might someday help prevent the detrimental effects of high postpartum anxiety on parental well-being and child development. Studying genetic differences between anxious and non-anxious postpartum humans will also prove to be incredibly helpful in understanding differences in their affective states [414].

Lastly, the effects of elevated anxiety and other mood disorders on father–infant interactions has rarely been addressed [67,288]. Rodent models in which both parents are parental, such as prairie voles or dwarf hamsters [77,462,480], could help reveal how hormones, parenting, and infant contact affect anxiety in both sexes. There could be surprising similarities in the neurochemistry of human mothers and fathers [410], and how their anxiety is regulated.

Acknowledgments

I thank Stephanie Miller and Carl Smith for critically reading and commenting upon previous versions of this article, and two anonymous reviewers for their valuable suggestions for how to improve this review. Portions of the published and unpublished work cited here were supported by an intramural grant for new faculty from Michigan State University to J.S. Lonstein.

References


[70] E.M. Byrne, R.S. Bridges, Reproductive experience reduces the sedative, but not anxiolytic effects of diazepam, Psychoneuroendocrinology 31 (2006) 988–996.


E.S. Mezzacappa, E.S. Katkin, Breast-feeding is associated with reduced perceived stress and negative mood in mothers, Health Psychol. 21 (2002) 187–193.


I.D. Neumann, H.A. Johnstone, M. Hatzinger, G. Liebsch, M.
I.D. Neumann, Brain mechanisms underlying emotional alterations
I.D. Neumann, Alterations in behavioral and neuroendocrine stress
S.I. Neophytou, S. Aspley, S. Butler, S. Beckett, C.A. Marsden,
C.B. Nemeroff, The role of GABA in the pathophysiology and
C.B. Nemeroff, The role of GABA in the pathophysiology and
S.I. Neophytou, S. Aspley, S. Butler, S. Beckett, C.A. Marsden,
C.B. Nemeroff, The role of GABA in the pathophysiology and
C.B. Nemeroff, The role of GABA in the pathophysiology and
M.B. Nayak, J.S. Milner, Neuropsychological functioning: compar-
sion of mothers at high- and low-risk for child physical abuse, Child
J.M. Najman, J. Morrison, G. Williams, M. Andersen, J.D.
Keeping, The mental health of women 6 months after they give
birth to an unwanted baby: a longitudinal study, Soc. Sci. Med. 32
B.S. Nashold, W.P. Wilson, D.G. Slaughter, Sensations evoked by
M.B. Nayak, J.S. Milner, Neuropsychological functioning: compar-
sion of mothers at high- and low-risk for child physical abuse, Child
C.B. Nemeroff, The role of GABA in the pathophysiology and
133–146.
S.I. Neophytou, S. Aspley, S. Butler, S. Beckett, C.A. Marsden,
Effects of lesioning noradrenergic neurones in the locus coeruleus
on conditioned and unconditioned aversive behaviour in the rat,
1321.
I. Neumann, M. Ludwig, M. Engelmann, Q.J. Pittman, R. Land
graf, Simultaneous microdialysis in blood and brain: oxytocin and
vasopressin release in response to central and peripheral osmotic
stimulation and suckling in the rat, Neuroendocrinology 58 (1993)
637–645.
I.D. Neumann, Alterations in behavioral and neuroendocrine stress
coping strategies in pregnant, parturient and lactating rats, Prog.
Brain Res. 133 (2001) 143–152.
I.D. Neumann, Brain mechanisms underlying emotional alterations
in the peripartum period in rats, Depress. Anxiety 17 (2003) 111–
121.
I.D. Neumann, H.A. Johnstone, M. Hatzinger, G. Liebsch, M.
Shipston, J.A. Russell, R. Landgraf, A.J. Douglas, Attenuated
neuroendocrine responses to emotional and physical stressors in
pregnant rats involve adenhypophysial changes, J. Physiol. 508
I.D. Neumann, S.A. Kromer, O.J. Bosch, Effects of psycho-
social stress during pregnancy on neuroendocrine and behav-
ioural parameters in lactation depend on the genetically deter-
mimed stress vulnerability, Psychoneuroendocrinology 30 (2005)
791–806.
I.D. Neumann, L. Torner, A. Wigger, Brain oxytocin: differential
inhibition of neuroendocrine stress responses and anxiety-related
behaviour in virgin, pregnant, and lactating rats, Neuroscience 95
I.D. Neumann, A. Wigger, G. Liebsch, F. Holsboer, R. Landgraf,
Increased basal activity of the hypothalamo–pituitary–adrenal axis
during pregnancy in rats bred for high anxiety-related behaviour,
E. Nissen, P. Gustavsson, A.M. Widstrom, K. Uvnas-Moberg,
Oxytocin, prolactin, milk production and their relationship with
personality traits in women after vaginal delivery or Cesarean sec-
P.N. Nott, M. Franklin, C. Armitage, M.G. Gelder, Hormonal
changes and mood in the puerperium, Br. J. Psychiatry 128 (1976)
379–383.
M. Numan, M.J. Numan, Expression of Fos-like immunoreactivity
in the preoptic area of maternally behaving virgin and postpartum
M. Numan, M.J. Numan, Important of pup-related sensory inputs
and maternal performance for the expression of Fos-like immuno-
reactivity in the preoptic area and ventral bed nucleus of the stria
L.M. O'Brien, E.G. Heycock, M. Hanna, P.W. Jones, J. L. Cox,
Postnatal depression and rationalizing growth: a community study,
T.G. O’Connor, J. Heron, J. Golding, M. Beveridge, V. Glover,
Maternal antenatal anxiety and children’s behavioural/emotional
nerve peptides on midbrain periaqueductal gray neuronal activity
M.W. O’Hara, J.A. Schlechte, D.A. Lewis, M.W. Varner, Con-
trolled prospective study of postpartum mood disorders: psycho-
logical, environmental, and hormonal variables, J. Abnorm.
Psychol. 100 (1991) 63–73.
M.W. O’Hara, J.A. Schlechte, D.A. Lewis, E.J. Wright, Prospective
study of postpartum blues. Biological and psychosocial factors, Arch.
D.B. Olatzabal, A. Ferreira, Maternal behavior in rats with kainic
acid-induced lesions of the hypothalamic paraventricular nucleus,
T. Onaka, K. Yagi, Role of noradrenergic projections to the bed
nucleus of the stria terminals in neuroendocrine and behavioral
B. Oztas, M. Kaya, S. Camurcu, Influence of pregnancy on blood–
brain barrier integrity during seizures in rats, Pharmacol. Res. 28
K. Pacak, M. Palkovits, R. Kvetnansky, J.J. Kopin, D.S. Goldstein,
Stress-induced norepinephrine release in the paraventricular nucleus
of rats with brainstem lesions: a microdialysis study, Neuro-
J. Pandaranandaka, S. Poupart, S. Kaldanakanond-Thongsong,
Anxiolytic property of estrogen related to the changes of the
monoamine levels in various brain regions of ovarietomized rats,
T.A. Papineczak, C.T. Turner, An analysis of personal and social
factors influencing initiation and duration of breastfeeding in a large
S. Parmigiani, P. Palanza, J. Rogers, P.F. Ferrari, Selection,
evolution of behavior and animal models in behavioral neuroscience,
B.L. Parry, D.L. Sorensen, C.J. Meliska, N. Basavaraj, G.G.
Zirpoli, A. Gamst, R. Hauger, Hormonal basis of mood and
L. Paut-Pagano, R. Roky, J.L. Valatx, K. Kitahama, M. Jouvet,
Evolution of behavior and animal models in behavioral neuroscience,
T.G. Peake, M.T. Buckman, L.E. Davis, J. Standeford, Pituitary and
placentally derived hormones in cerebrospinal fluid during normal
D. Pelchat, J. Bisson, N. Ricard, M. Perreault, J.M. Bouchard,
Longitudinal effects of an early family intervention programme on
the adaptation of parental of children with a disability, Int. J. Nurs.
M. Pereira, N. Uriarte, D. Agrati, M.J. Zuluaga, A. Ferreira,
Motivational aspects of maternal anxioyis in lactating rats,


