

SYMPOSIUM REPORT

No stress please! Mechanisms of stress hypo-responsiveness of the maternal brain

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The time around birth is accompanied by behavioural and physiological adaptations of the maternal brain, which ensure reproductive functions, maternal care and the survival of the offspring. In addition, profound neuroendocrine and neurobiological adaptations have been described with respect to behavioural and neuroendocrine stress responsiveness in rodents and human mothers. Thus, the hormonal response of the hypothalamo-pituitary-adrenal (HPA) axis and the response of the sympathetic nervous system to emotional and physical stressors are severely attenuated. Moreover, anxiety-related behaviour and emotional responsiveness to stressful stimuli are reduced with the result of general calmness. These complex adaptations of the maternal brain are likely to be a consequence of an increased activity of brain systems with inhibitory effects on the HPA axis (such as the oxytocin and prolactin systems) and of a reduced activity of excitatory pathways (noradrenaline (norepinephrine), corticotrophin-releasing factor and opioids). Experimental manipulation of these systems using complementary approaches indeed demonstrates their importance in these maternal brain adaptations. Maternal stress adaptations are not only important for the healthy prenatal development of the offspring by preventing excessive glucocorticoid responses and in the promotion of postnatal maternal behaviour, but are also vital for the well-being of the mother and her mental health.

(Received 1 October 2007; accepted after revision 29 October 2007; first published online 1 November 2007)

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Introduction

Across all mammalian species, both physiological and behavioural changes occur throughout pregnancy in order to prepare the mother for the birth. These changes include the onset of maternal behaviours (i.e. maternal aggression, milk production and let-down and nursing of offspring) (Rosenblatt *et al.* 1994; Neumann *et al.* 2001) to ensure the development and survival of the offspring. Moreover, profound alterations have been shown in pregnancy and lactation with respect to maternal stress-coping style with severely attenuated activity of the hypothalamo-pituitary-adrenal (HPA) axis (Stern *et al.* 1973; Neumann *et al.* 1998*b*; Russell *et al.* 1999; Lightman *et al.* 2001; Kammerer *et al.* 2002; de Weerth & Buitelaar, 2005). Such changes seem to be essential for

the healthy development of the offspring; for example, to prevent excessive circulating stress hormone levels. Moreover, there is a growing body of evidence to suggest that these altered stress responses are also important for maternal mental health.

In the following review, we focus on the physiological, behavioural and molecular adaptations underlying the stress hypo-responsiveness, with particular emphasis on the brain oxytocin (OXT) and prolactin (PRL) systems.

Animal research

The end of pregnancy and the onset of lactation is accompanied by the activation of neurobiological systems that are directly related to reproductive functions (i.e. maternal behaviour and nurturing of the newborn). Specifically, the neuropeptide OXT is increasingly synthesized in hypothalamic supraoptic nucleus/paraventricular nucleus (SON/PVN) neurons and secreted into the blood to promote labour during parturition and to release milk (e.g. in response to

This report was presented at *The Journal of Physiology* Symposium on Brain adaptations for a successful pregnancy, IBRO World Congress of Neuroscience, Melbourne, Australia, 16 July 2007. It was commissioned by the Editorial Board and reflects the views of the authors.

suckling). Another neuropeptide, PRL is not only up-regulated in lactotrophs to ensure lactogenesis, but also in the hypothalamus and is similarly involved in the regulation of maternal behaviour. In addition, during lactation a chronic elevation in plasma corticosterone has been described under basal conditions (see Table 1) (Stern *et al.* 1973; Walker *et al.* 1995; Windle *et al.* 1997b) accompanied by alterations of the diurnal pattern of activity (for review see Lightman *et al.* 2001). Increased vasopressin expression in parvocellular PVN neurons (Walker *et al.* 2001), accompanied by an enhanced sensitivity of the PVN to vasopressin (Toufexis *et al.* 1999b), may contribute to the altered basal activity of the HPA axis during lactation. Of importance, despite the elevated basal activity of the HPA axis, it has been shown in various mammalian species that the responsiveness of the HPA axis to a broad variety of psychological and physiological stressors is severely attenuated from mid-pregnancy through to the end of lactation (Stern *et al.* 1973; Walker *et al.* 1995; Windle *et al.* 1997b; Neumann *et al.* 1998b; Shanks *et al.* 1999; Johnstone *et al.* 2000; Lightman *et al.* 2001; Neumann, 2001; Brunton & Russell, 2003). In agreement, the expression of corticotrophin-releasing factor (CRF) within the PVN is reduced both in pregnancy, which might be related to elevated glucocorticoid levels and negative feedback effects (Douglas & Russell, 1994; Johnstone *et al.* 2000; da Costa *et al.* 2001), and during lactation (Lightman *et al.* 2001; Walker *et al.* 2001). Moreover, the pituitary sensitivity to CRF is reduced due to reduced CRF receptor binding at pituitary corticotrophs (Neumann *et al.* 1998a). The lactation-associated reduction in CRF expression has also been described in the central nucleus of the amygdala, a region important not only for HPA axis regulation, but also for emotionality (Davis & Whalen, 2001). A potential mechanism underlying the attenuated CRF system is via the immediate-early gene *nur77* (Nerve Growth Factor-induced B (NGFI-B)), which controls *CRF* gene expression and is up-regulated after emotional stress (Kirschbaum *et al.* 1999), but to a lesser extent in the hypothalamus of pregnant mice (Douglas *et al.* 2003). As the brain CRF system is the main stimulator of the HPA axis, lowered activity of the system may contribute to the attenuated corticotrophin (ACTH) and corticosterone responses observed during pregnancy and lactation. Thus, reduced (re)activity of the brain CRF system may also be related to behavioural changes of the dam including reduced anxiety (Hard & Hansen, 1985; Windle *et al.* 1997b; Toufexis *et al.* 1998; Neumann, 2003), but also enhanced maternal behaviour (Pedersen *et al.* 1991) and maternal aggression when protecting the offspring (Gammie *et al.* 2004).

There is also a loss of excitatory inputs of the HPA axis in pregnancy, including a reduced noradrenergic excitatory tone within the hypothalamic PVN (Toufexis *et al.* 1998; Douglas *et al.* 2005), which contributes to its

attenuated responsiveness during lactation. Further, there is a lower expression of noradrenergic α_{1A} -adrenoceptors in the parvo- and magnocellular PVN of pregnant rats (Douglas *et al.* 2005). These alterations could contribute to the loss of hypothalamic noradrenergic excitation and the low level of *CRF* gene expression within the hypothalamus found under resting conditions. Another excitatory input to the HPA axis that is attenuated in pregnancy is that of endogenous opioids (Douglas *et al.* 1998; Kammerer *et al.* 2002; Kofman, 2002). The effects of endogenous opioids are reversed during parturition, when opioids appear to inhibit, rather than stimulate, HPA axis activity (Wigger *et al.* 1999). Further, endogenous opioid actions on OXT neurons within the hypothalamic PVN differ between virgin and pregnant rats (see Fig. 1) (Douglas *et al.* 1995; Wigger & Neumann, 2002). As brain OXT is an important regulator of the activity of the HPA axis (Windle *et al.* 1997a; Neumann *et al.* 2000a; Neumann, 2003), the inhibitory effects of endogenous opioids on intra-PVN release of OXT in virgins and the excitatory effects of endogenous opioids in pregnant rats are of interest in the context of mechanisms regulating stress adaptations peripartum (Wigger & Neumann, 2002).

Involvement of brain OXT and PRL in decreased stress responsiveness

Both OXT and PRL have important reproductive functions including promotion of labour and milk ejection and lactogenesis, respectively, when released from the neurohypophysis (OXT) or adenohypophysis (PRL) into the blood. Furthermore, as potential neuro-modulators/neurotransmitters, they are synthesized and released within the brain, and significant effects on maternal behaviour (among others) have been established (Pedersen & Prange, 1979; Neumann & Landgraf, 1989; Neumann *et al.* 1993b, 1994a,b; Bridges *et al.* 2001; Torner *et al.* 2002).

OXT. Despite a general activation of the OXT system around birth in direct relation to reproductive functions (Pedersen & Prange, 1979; Insel, 1986; van Leengoed *et al.* 1987; Neumann & Landgraf, 1989; Landgraf *et al.* 1991; Neumann *et al.* 1993a, b; Insel *et al.* 1997), responses of the OXT system to stimuli not directly related to parturition or lactation were found to be lower both in pregnancy and lactation (Lightman & Young, 1989; Walker *et al.* 1995; Neumann *et al.* 1995, 1998a, 2001; Douglas *et al.* 1998). OXT neurons generally respond to emotional, physical or pharmacological stressors with elevated neurohypophysial release into the blood (Neumann *et al.* 1993a, 1995, 1998a; Douglas *et al.* 1998; Wotjak *et al.* 1998; Neumann, 2002; Landgraf & Neumann, 2004) and release within the hypothalamus (Wigger & Neumann, 2002; Bosch *et al.* 2004), and the amygdala (Bosch *et al.* 2004,

2005) in male and female rats (Nishioka *et al.* 1998; Wotjak *et al.* 1998; Neumann, 2002; Landgraf & Neumann, 2004; Ebner *et al.* 2005). Recently, we have extended previous findings (Windle *et al.* 1997a) and demonstrated that endogenous brain OXT regulates the activity of the HPA axis both in virgin female and male rats. Thus, central infusion of a selective OXT receptor antagonist dis-inhibited the release of ACTH and corticosterone under basal and stress-induced conditions (Neumann *et al.* 2000b,c). Effects of OXT were found to depend on the brain region (PVN, amygdala or medio-lateral septum) and experimental conditions (basal *versus* stress) studied (Neumann *et al.* 2000a; Neumann, 2001). How can these effects of brain OXT on HPA axis responses be related to the peripartum period? Chronic infusion of OXT into the brains of virgin rats attenuated neuronal and neuroendocrine responses to stress (Windle *et al.* 2004) making an involvement of endogenous OXT on HPA axis responses during the peripartum period probable. However, our own experimental evidence indicates that blockade of brain OXT receptor actions in pregnant or lactating rats does not result in a dis-inhibition of the HPA axis in response to various stressors (novel environment, swimming or maternal defence) as found in virgins (Neumann *et al.* 2000b,c). Similarly, during parturition, when the brain OXT system is highly activated (Neumann *et al.* 1993b),

the non-responsiveness of the HPA axis to repeated air puff applied in the home cage in rats or to novel environment in mice (Douglas *et al.* 2003) is not due to a significant inhibition by OXT at this time. Therefore, it is likely that other additional inhibitory factors, among them endogenous opioids and PRL, act in concert with OXT to attenuate HPA axis hormonal responses in the peripartum period (see Fig. 1).

PRL. There is an increase in plasma PRL levels seen at the end of pregnancy (Grattan, 2001), as well as an up-regulation of PRL and PRL receptor expression within the hypothalamus in the peripartum period (Pi & Grattan, 1999). Furthermore, our studies have revealed an increased neuronal PRL synthesis within the hypothalamus in late pregnancy and lactation (Torner *et al.* 2004). The relevance of this centrally synthesized PRL is provided by the fact that PRL is locally released from neurons within selected hypothalamic regions, including the PVN, in lactating rats in response to suckling (Torner *et al.* 2004). The detailed function of such centrally released PRL in the context of suckling remains to be elucidated. However, in the context of altered stress responsiveness peripartum, it is of interest to note that acute or chronic intracerebroventricular (i.c.v.) administration of PRL to virgin female rats results in attenuated stress-induced

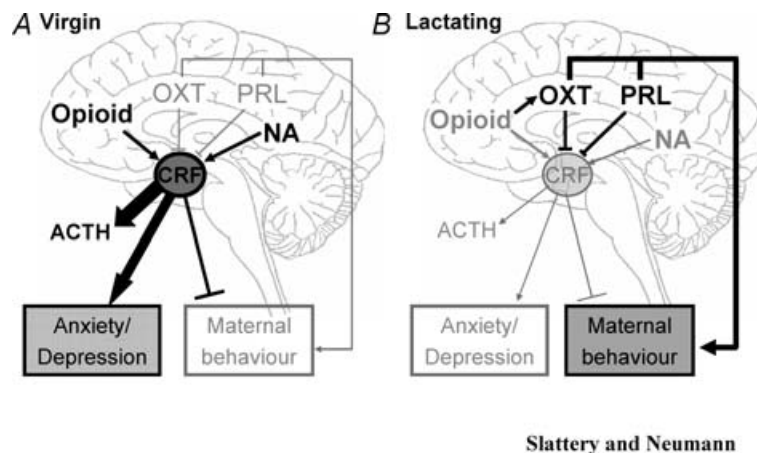


Figure 1. Schematic representation of some of the neuroendocrine alterations that occur between virgin and lactating dams

Virgins are characterized by having higher levels of opioid and noradrenergic (NA) inputs to the PVN than in lactating animals but lower expression of oxytocin (OXT) and prolactin (PRL). Whereas opioids have no apparent influence on OXT in virgin animals, they have been shown to increase OXT in the PVN during lactation. Furthermore, the effect of endogenous opioids on CRF release is attenuated during lactation. The combined effect of these alterations is an enhanced corticotrophin-releasing factor (CRF) release in response to stress in virgins, which leads to the release of corticotrophin (ACTH) and increased anxiety- and depression-related behaviour in comparison to lactating animals. By contrast, the low OXT and PRL levels, as well as elevated the CRF level, leads to lower levels of maternal behaviour in virgins compared with lactating animals. Thus disruption of these factors may contribute to postpartum depression, which is associated with increased anxiety and depression, as well as reduced maternal care. Black and thick arrows represent the predominant pathways in virgins and lactating animals while the grey and thin arrows show the systems that are at low levels (i.e. OXT and PRL in virgins) or attenuated (i.e. opioid and NA in lactation). Blocked lines represent factors which are inhibitory; factors with thick and black lines again represent the predominant systems in virgins or lactating animals compared with one another.

Table 1. Examples of neuroendocrine and behavioural alterations observed in pregnancy and lactation

Behavioural alterations	References
HPA axis alterations	
Chronic basal hypercortisolism and altered diurnal pattern	(Stern <i>et al.</i> 1973; Walker <i>et al.</i> 1995; Windle <i>et al.</i> 1997b; Lightman <i>et al.</i> 2001)
Decreased responsiveness of HPA axis (ACTH, corticosterone) to psychological and physiological stressors	(Stern <i>et al.</i> 1973; Windle <i>et al.</i> 1997b; Neumann <i>et al.</i> 1998a; Shanks <i>et al.</i> 1999; Lightman <i>et al.</i> 2001; Neumann <i>et al.</i> 2001; Walker <i>et al.</i> 2001; Brunton & Russell, 2003)
Decreased stressor perception and stress-induced expression of <i>c-fos</i> in limbic brain regions	(da Costa <i>et al.</i> 1996)
Alterations in excitatory pathways	
Decreased noradrenergic excitatory tone in the PVN	(Toufexis <i>et al.</i> 1998; Douglas, 2005)
Reduced excitatory opioid tone on CRF neurons	(Douglas <i>et al.</i> 1998)
Attenuated pituitary sensitivity to CRF	(Neumann <i>et al.</i> 1998a; Toufexis <i>et al.</i> 1999a)
Decreased sympathetic responsiveness to stressors	(Douglas <i>et al.</i> 2005)
Alterations in inhibitory pathways	
Elevated OXT system activity	(Insel, 1990; Douglas & Russell, 1994)
Increased prolactin synthesis and binding	(Pi & Grattan, 1999; Torner <i>et al.</i> 2002)
Decreased CRF mRNA expression in the PVN	(Johnstone <i>et al.</i> 2000; Lightman <i>et al.</i> 2001; Walker <i>et al.</i> 2001)
Alterations in behaviour	
Increased maternal behaviour including aggressive behaviour	(Rosenblatt <i>et al.</i> 1994; Neumann <i>et al.</i> 2001)
Increased calmness, reduced anxiety and reduced emotional responsiveness to stressors	(Carter <i>et al.</i> 2001; Heinrichs <i>et al.</i> 2001; Glynn <i>et al.</i> 2004)

secretion of ACTH and corticosterone accompanied by an elevated basal plasma level of ACTH (Torner *et al.* 2001; Donner *et al.* 2007). Furthermore, chronic PRL administration has also been demonstrated to attenuate neuronal (hypothalamic *fos* mRNA and CRF mRNA) responses to restraint stress (Donner *et al.* 2007). Thus, the lactation-like neuroendocrine state induced by i.c.v. application of PRL indicates a strong involvement of high PRL expression within the maternal brain in altered stress-coping style and stress attenuation. In support of this, use of antisense oligodeoxynucleotides directed against the long form of PRL receptors in the brain resulted in a significant dis-inhibition of stress-induced ACTH secretion in lactating rats, demonstrating that brain PRL is a central factor inhibiting the HPA axis response in lactation (Torner *et al.* 2001).

Alteration of behavioural stress responses peripartum: involvement of OXT and PRL

The reduced emotional responsiveness observed during lactation can be explained, at least in part, by an enhanced activity of the brain OXT and PRL systems as both have anxiolytic properties, especially peripartum (Neumann *et al.* 2000b; Torner *et al.* 2002). The anxiolytic effect of OXT could be localized within the central amygdala via local infusion (Bale *et al.* 2001) as also shown by reverse microdialysis studies (Neumann, 2001); however, further regions, including the PVN, may be involved.

Further, OXT released within the PVN and the central amygdala is correlated with the level of maternal aggressive behaviour displayed by the lactating dam, and such locally released OXT promotes maternal aggression (Bosch *et al.* 2005). It is interesting that in virgin female and male rats and male mice (Ring *et al.* 2006), administration of synthetic OXT directly into the hypothalamic PVN (i.c.v. in male mice) results in reduced anxiety levels, both on the elevated plus-maze and the light–dark box, an effect which we could block with an inhibitor of the extra cellular regulated kinase (ERK) signalling cascade (Neumann *et al.* 2007). Furthermore, a chronic elevation of brain OXT concentrations in virgin rats was directly related to an attenuation of the emotional response to an acute noise stress (Windle *et al.* 1997a, 2004). Therefore, in addition to their main roles in promoting maternal behaviour (Pedersen & Prange, 1979; Insel, 1990; Neumann *et al.* 1994a,b; Torner *et al.* 2004), the emerging evidence clearly demonstrates that the high levels of brain OXT and PRL (Insel, 1990; Douglas & Russell, 1994; Mann & Bridges, 2002; Torner *et al.* 2004) also play a crucial role in the dampened emotional responsiveness observed in the peripartum period.

Human research. In humans, progressively increasing levels of placental CRF and gradually decreasing levels of CRF-binding protein (Magiakou *et al.* 1996a,b) may contribute to the elevated basal activity of the HPA axis at the end of pregnancy. Additionally, attenuation of the

responsiveness of the HPA axis, and other relevant systems, to physiological or psychological stressors has been found both in pregnant and lactating women (Nisell *et al.* 1985; Schulte *et al.* 1990; Altemus *et al.* 1995; Kammerer *et al.* 2002; for review see de Weerth & Buitelaar, 2005). For example, the pituitary responses to an i.v. bolus of CRF were found to be attenuated in lactating women (Magiakou *et al.* 1996a). Further, and in line with animal studies, in late human pregnancy and lactation, increased calmness, a more positive mood state and a reduced emotional response to stressful life events have been described (Carter *et al.* 2001; Heinrichs *et al.* 2001; Glynn *et al.* 2004). These changes are likely to be due to a reduced activity of the brain CRF system, among others. Of importance, suckling-related factors, possibly including the activation of the brain OXT and PRL systems, were recently shown to contribute to the reduced HPA axis response to stress and to the positive mood state (Heinrichs *et al.* 2001). Thus, the experimental evidence accumulated to date in humans is largely in agreement with the findings from animal research. Thus, brain CRF, OXT and PRL are likely to play a significant role in altered emotionality in humans in the peripartum period. Therefore, disruption of these systems may be a risk factor for the development of postpartum mood disorders.

Significance of the adaptations of the maternal stress responsiveness peripartum

The maternal adaptations described above, with the significant attenuation of hormonal stress responses in pregnancy and lactation, are important for the healthy prenatal development of the offspring by preventing excessive levels of circulating glucocorticoids (Altemus *et al.* 1995; McCormick *et al.* 1995; Vallee *et al.* 1997; Weinstock, 2001). For example, it has recently been demonstrated that lactating dams whose mothers were exposed to stressful stimuli during pregnancy do not display the normal adaptations observed in pregnancy (Bosch *et al.* 2007). In more detail, these dams had elevated CRF and vasopressin mRNA expression within the PVN suggesting a dysregulation of the stress circuitries, which in turn leads to the elevated HPA axis reactivity found in these rats (Bosch *et al.* 2007).

Therefore, we hypothesize that the attenuation of the stress responsiveness around birth is also vital for the well-being of the mother and her mental health. Thus, in humans, the postpartum period is a time of increased vulnerability to mood disorders (O'Hara & Swain, 1996; Llewellyn *et al.* 1997; Pedersen, 1999; Mastorakos & Ilias, 2000), which can last up to a year and significantly affect the development of the newborn and the family unit. Prior history of depressive disorders, lack of social support and stressful life events, particularly during pregnancy, increase the risk of perinatal mood disorders (O'Hara

& Swain, 1996; Pedersen, 1999). However, to date, the underlying mechanisms of postpartum mood disorders are largely unknown, but it is likely that disruption of the mechanisms leading to reduced stress-hyporesponsiveness during lactation plays a significant role.

In general, it is well accepted that CRF is a relevant neuropeptide involved in the pathogenesis of psychopathologies, including depression- and anxiety-related disorders, as a hyperactive state of the HPA axis has been found in patients with major depression (Nemeroff, 1996; Mitchell, 1998; Arborelius *et al.* 1999; Wong & Licinio, 2001; Bakshi *et al.* 2002; Heinrichs & Koob, 2004). Accordingly, the reduced activity of the brain CRF system may represent a protective mechanism of the maternal brain to cope with the dramatic alteration in various hormonal systems, in particular gonadal steroids, around birth. Because gonadal steroids are important regulators of the HPA axis and the CRF system (Kirschbaum *et al.* 1999; Young *et al.* 2001), the large shifts in hormone levels that occur peripartum may particularly contribute to the relapse of major depression in women with a history of psychopathologies. Thus, general suppression of the activity of the HPA axis during lactation was hypothesized to prevent the development of depression in vulnerable women (Carter *et al.* 2001). In support of our hypothesis of dampened CRF activity being important for the well-being of the mother, elevated CSF concentrations of CRF were found in rhesus macaque females that abused their infants. These females also rated higher in their level of anxiety and aggression (Maestripieri *et al.* 2005). According to another hypothesis, the central suppression of hypothalamic CRF causes the increased vulnerability to affective disorders postpartum (Magiakou *et al.* 1996a; Mastorakos & Ilias, 2000) as a more pronounced attenuation of the ACTH response to a CRF bolus was found in women with postpartum blues compared with euthymic women.

Other factors possibly involved in these mood disorders include brain vasopressin and OXT, which exert opposite effects on anxiety-like behaviour and contribute to the regulation of HPA axis responses (Landgraf *et al.* 1995; Purba *et al.* 1996; for review see (Landgraf & Neumann, 2004). Also, relationships between PRL and mood state, including depression and anxiety, have been found with high circulating PRL levels in breastfeeding women associated with hypo-anxiety (Asher *et al.* 1995) and lower levels with the occurrence of depression (Abou-Saleh *et al.* 1998). Furthermore, according to the monoamine hypothesis, depression results from under-activity of noradrenaline and serotonin systems, and accepted treatment is generally with their respective reuptake inhibitors (Ressler & Nemeroff, 1999; Wong & Licinio, 2001). However, whether these factors are also dysregulated in postpartum mood disorders is presently unknown.

Conclusions

The findings from animal and human studies in late pregnancy and lactation, reveal profound physiological adaptations of neuroendocrine and behavioural stress responses occurring at various brain levels. The adaptations ensure the healthy development of the offspring by preventing excess prenatal glucocorticoid exposure and appropriate maternal care in the postpartum period. These adaptations include activation of brain OXT and PRL systems, which act to attenuate the HPA axis activity and emotional responsiveness in the peripartum period, coupled with a dampening of opioid and noradrenergic systems, which are the main excitatory inputs of the HPA axis. If these important adaptations are prevented, for example by chronic life stress especially during pregnancy, hormonal or other physiological events around birth may alter the activity of the brain CRE, OXT, vasopressin and PRL systems thus increasing the risk for mood disturbances and post-partum depression.

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