

SYMPOSIUM REPORT

Attenuated hypothalamo-pituitary-adrenal axis responses to immune challenge during pregnancy: the neurosteroid–opioid connection

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In late pregnancy maternal hypothalamo-pituitary-adrenal (HPA) axis responses to emotional and physical stressors are attenuated. This is expected to minimize the detrimental programming effects of glucocorticoid exposure on the fetuses. We have utilized a model of immune challenge, systemic administration of interleukin-1 β (IL-1 β), to investigate the underlying mechanisms. Intravenous IL-1 β activates corticotropin-releasing hormone (CRH) neurones in the parvocellular division of the paraventricular nucleus (pPVN) via noradrenergic (A2 cell group) neurones in the nucleus tractus solitarius (NTS). Despite comparable activation of these brainstem neurones by IL-1 β in virgin and in late pregnant rats, pPVN CRH neurones are activated only in virgin rats. As a consequence IL-1 β fails to evoke ACTH and corticosterone secretion in late pregnant rats, in contrast to virgin rats. Suppressed responsiveness of the CRH neurones, and hence the HPA axis, following IL-1 β in late pregnancy is explained by presynaptic inhibition of noradrenaline release in the pPVN, due to increased endogenous enkephalin and μ -opioid receptor production in brainstem NTS neurones. The factor that signals to the brain the pregnancy status of the animal and stimulates opioid production in the brainstem is allopregnanolone, a neurosteroid metabolite of progesterone. The supporting evidence for these mechanisms is discussed.

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Exposure to stressful events (stressors) results in a series of orchestrated responses which act to preserve or restore homeostasis and involve complex behavioural, autonomic and endocrine adaptations (for review see Habib *et al.* 2001). The key neuroendocrine response to stress is activation of the hypothalamo-pituitary-adrenal (HPA) axis which triggers a cascade of events, the final outcome of which is increased production and secretion of glucocorticoids from the adrenal cortex. The principal actions of glucocorticoids are to promote mobilization of glucose and fat stores, stimulate gluconeogenesis, regulate immune system activity, modulate neural activity in coping circuits, and restrain the effectors of the stress response through their negative feedback actions.

Stress and the HPA axis

Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are synthesized in parvocellular neurones of the paraventricular nucleus (pPVN). When these neurones are excited (e.g. by stressors) CRH and AVP are released from axon terminals in the median eminence into the hypothalamo-hypophysial portal system to act synergistically on anterior pituitary corticotrophs, stimulating adrenocorticotrophic hormone (ACTH) secretion. ACTH in turn stimulates secretion of glucocorticoid (cortisol in humans, corticosterone in rodents) from the adrenal cortex. Stressors that activate the HPA axis are divided into two broad categories. Psychological stressors (e.g. restraint, immobilization, noise, predator odour) represent perceived threats to homeostasis and are mainly processed by forebrain limbic circuitry, whereas physical stressors (e.g. cold exposure, haemorrhage, infection) represent a real physiological threat to homeostasis and are rapidly signalled directly to the PVN via hindbrain regions, bypassing

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cognitive processing regions (for review see Herman *et al.* 2003).

Exposure to glucocorticoids during development can have detrimental programming effects on the offspring making them more susceptible to disease in adulthood, particularly to affective disorders and cardiovascular and metabolic disease (Fride & Weinstock, 1988; Barker *et al.* 1993; Lindsay *et al.* 1996; Levitt *et al.* 1996, 2000; Welberg *et al.* 2000; Barker, 2002). Defence mechanisms are in place to protect the young *in utero*: the placenta expresses the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which serves as a barrier, converting active corticosterone into inactive 11-dehydrocorticosterone (or cortisol to cortisone). This barrier is about 90% effective (Benediktsson *et al.* 1997) and while acute stress can up-regulate placental 11 β -HSD2 activity, this does not

occur after chronic stress (Welberg *et al.* 2005). Another line of defence is achieved by changes in maternal HPA axis responsiveness. During the last week of pregnancy HPA axis responses to stress are progressively reduced (Neumann *et al.* 1998) (Fig. 1) and by the end of pregnancy HPA axis responses to a range of psychological and physical stressors are markedly suppressed and in some cases completely abolished (da Costa *et al.* 1996; Neumann *et al.* 1998; Johnstone *et al.* 2000; Brunton & Russell, 2003; Brunton *et al.* 2005, 2006). The mechanisms, as currently understood, are discussed below.

Immune signalling and the HPA axis

A bi-directional relationship exists between the immune system and the HPA axis. Following immune system activation (e.g. by infection), macrophages increase the production of cytokines (e.g. interleukins). As well as regulating immunity and inflammation, cytokines also inform the brain that an immune response is occurring and stimulate HPA axis activity (Rivier, 1993). Glucocorticoids have immunosuppressive actions and their release following HPA axis activation by immune challenge modulates the immune response.

Systemic administration of interleukin-1 β (IL-1 β) is a potent activator of the HPA axis (Besedovsky *et al.* 1991; Harbuz *et al.* 1992). IL-1 β given peripherally activates neurones in the nucleus tractus solitarii (NTS; A2 cell group) and ventrolateral medulla (VLM; A1 cell group) (Ericsson *et al.* 1994) which represent rich sources of afferent catecholaminergic innervation to the PVN (Sawchenko & Swanson, 1981), resulting in increased noradrenaline release in the PVN (Brunton *et al.* 2005) (Fig. 2). These inputs play an important role in mediating HPA axis responses to IL-1 β , hence surgical or pharmacological lesions of these noradrenergic projections abolish HPA axis responses to IL-1 β , and adrenoceptor antagonists suppress IL-1 β -induced ACTH secretion and pPVN neurone activation (Weidenfeld *et al.* 1989; Ericsson *et al.* 1994; Parsadaniantz *et al.* 1995; Li *et al.* 1996; Buller *et al.* 2001).

IL-1 β does not act directly on brainstem catecholamine neurones to exert its effects: few of these neurones express IL-1 receptors, and given systemically IL-1 β is unlikely to cross the blood–brain barrier (Rivest *et al.* 2000). Instead, IL-1 β relies on prostaglandins to mediate its effects. IL-1 β binds to IL-1 receptors located on the endothelium of brain blood vessels (Ericsson *et al.* 1995) to stimulate cyclo-oxygenase (COX) (Cao *et al.* 1996; Lacroix & Rivest, 1998) and hence local production of prostaglandin (Komaki *et al.* 1992), which activates NTS neurones via EP4 receptors (Zhang & Rivest, 1999; Rivest *et al.* 2000) (Fig. 2). Hence, COX inhibitors and antisera against various prostaglandins block IL-1 β -induced HPA

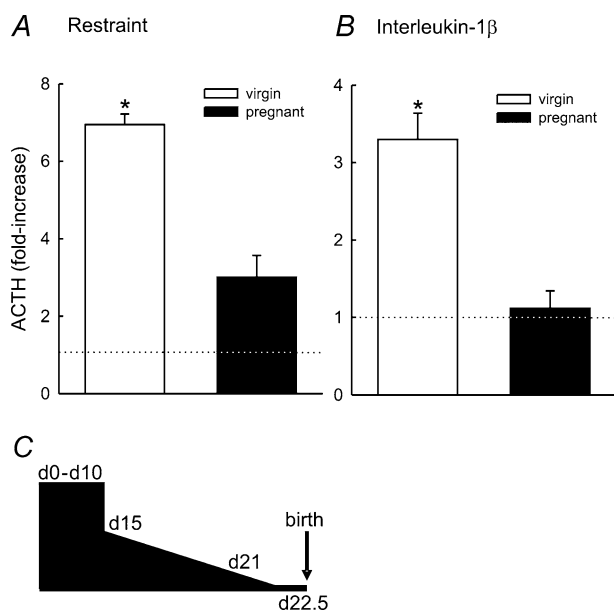


Figure 1. Responsiveness of the HPA axis in late pregnancy

The mean increase in ACTH secretion (expressed relative to basal (dotted line) plasma concentrations). *A*, 15 min after the onset of a 30 min period of restraint (a psychological stressor) in conscious virgin ($n = 4$) and day 21 pregnant ($n = 5$) rats. *B*, 15 min after administration of interleukin-1 β (a physical stressor; 500 ng kg $^{-1}$ i.v.) in conscious virgin ($n = 8$) and day 21 pregnant ($n = 7$) rats. Values are group means \pm s.e.m. * $P < 0.001$ Student's *t* test. Blood was collected from rats via a chronic jugular vein cannula implanted 5 days prior to the experiment under inhalation of halothane anaesthesia (2–3% in 600 ml min $^{-1}$ each of oxygen and nitrous oxide) in accordance with the UK Home Office Animals (Scientific Procedures) Act 1986 and local (University of Edinburgh) ethics guidelines. Data in *B* from Brunton *et al.* (2005). *C*, schematic diagram representing the timescale of the change in HPA axis responsiveness during pregnancy. In early pregnancy (days 0–10) ACTH secretory responses to stressors (elevated plus maze, forced swimming, restraint) are indistinguishable from those observed in virgin rats. Between days 11 and 15 the mechanisms that restrain the HPA axis in late pregnancy emerge resulting in a progressive reduction in HPA axis responsiveness until term when ACTH responses are minimal.

activity *in vivo* and CRH release from hypothalamic explants (Watanobe *et al.* 1995; Niimi *et al.* 1996; Ericsson *et al.* 1997; Buller *et al.* 1998). Peripherally administered IL-1 β also activates neurones in the central nucleus of the amygdala (CeA) (Xu *et al.* 1999), an action mediated via the parabrachial nucleus, which receives inputs from activated NTS and VLM neurones following systemic IL-1 β (Buller *et al.* 2004). Neurones in the CeA relay information via the bed nucleus of the stria terminalis (BNST) to the pPVN and lesions of this pathway result in attenuated HPA axis responses to IL-1 β (Xu *et al.* 1999; Crane *et al.* 2003).

Mechanisms of suppressed HPA axis responses to IL-1 β in late pregnancy

We have employed a model of immune challenge (intravenous administration of IL-1 β) to tease out the mechanisms underlying attenuated HPA axis responses to inflammatory stress in late pregnant rats. Systemic IL-1 β administration fails to evoke ACTH (Fig. 1B) and corticosterone secretion in late pregnancy (Brunton *et al.*

2005). This is a result of reduced CRH drive by the pPVN, as up-regulation of CRH mRNA expression is not stimulated by IL-1 β in late pregnant rats, in contrast to non-pregnant rats (Brunton *et al.* 2005). Furthermore, IL-1 β increases pro-opiomelanocortin (POMC) mRNA expression in the anterior pituitary in virgin rats (Brunton *et al.* 2005), indicating corticotroph exposure to CRH; however, this was not observed in late pregnant rats, consistent with studies where centrally administered IL-1 β was shown to deplete CRH content in the median eminence in virgin, but not pregnant rats (Nakamura *et al.* 1998). The pPVN CRH neurones are prevented from responding to IL-1 β in late pregnancy as a consequence of reduced drive from the brainstem noradrenergic neurones. COX-2, the inducible form of this enzyme, is involved in prostaglandin generation and subsequent activation of brainstem noradrenergic neurones following systemic IL-1 β . We have found a significant increase in COX-2 mRNA expression in the NTS after IL-1 β in virgin rats, but not late pregnant rats (P. J. Brunton & J. A. Russell, unpublished observations), consistent with

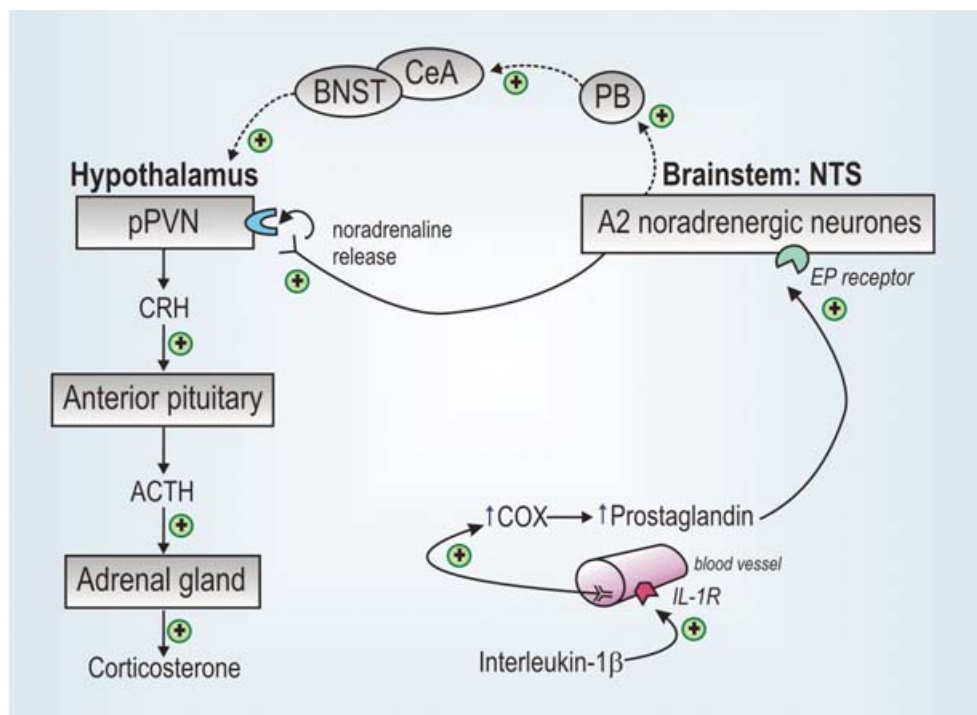


Figure 2. How circulating IL-1 β signals to the HPA axis

Circulating interleukin-1 β (IL-1 β) binds to IL-1 receptors (IL-1R) on the endothelium of brain blood vessels, stimulating (+) cyclo-oxygenase (COX) and local production of prostaglandins. Prostaglandins activate A2 noradrenergic neurones (via EP receptors) in the nucleus tractus solitarius (NTS) which project directly to the parvocellular division of the paraventricular nucleus (pPVN). Noradrenaline released from the nerve terminals in the pPVN acts via α -adrenoreceptors to activate CRH neurones. CRH released at the median eminence enters the hypothalamo-hypophysial portal system and acts on CRH type 1 receptors on anterior pituitary corticotropes to trigger ACTH secretion, which in turn stimulates corticosterone secretion from the cortex of the adrenal glands. Other neural circuitry involving the parabrachial nucleus (PB), central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST) is also involved in signalling to the CRH neurones following systemic IL-1 β .

other studies comparing COX-2 induction by endotoxin in the hypothalamus in mid- and late-pregnancy (Mouihate *et al.* 2002). Despite these differences in COX-2 induction, brainstem neurones in the A2 cell region of the NTS are similarly activated (they express Fos protein) in virgin and late pregnant rats following IL-1 β (Brunton *et al.* 2005), suggesting that in pregnancy COX-1 (the constitutive form) effectively generates prostaglandins that activate the NTS. In addition to the NTS, the number of neurones in the CeA activated by systemic IL-1 β is comparable in virgin and late pregnant rats, indicating that the NTS projection via the parabrachial nucleus to the CeA is functioning in late pregnancy (P. J. Brunton & J. A. Russell, unpublished observations). Hence, suppressed HPA axis responsiveness to IL-1 β in late pregnancy is not the result of a global suppression of the ascending NTS noradrenergic projections, but may arise from selective inhibition of noradrenergic transmission at the level of the PVN, in particular at terminals that innervate the CRH neurones.

Systemic IL-1 β evokes noradrenaline release in the PVN of virgin rats; however, this response is absent in late pregnant rats even though the cell bodies in the A2 region of the NTS are similarly excited (Brunton *et al.* 2005). This is explained by endogenous opioid inhibition of noradrenaline release in the PVN. In males and non-pregnant females opioids have excitatory actions on HPA axis activity (Buckingham & Cooper, 1986; Buller

et al. 2005); however, in late pregnancy opioids have a net inhibitory effect, such that systemic naloxone (an opioid receptor antagonist) reinstates HPA axis responses to IL-1 β (Brunton *et al.* 2005). In our model opioids are evidently acting at the level of the noradrenergic nerve terminals in the PVN to inhibit noradrenaline release evoked by IL-1 β since naloxone retro-dialysed into the PVN restores a noradrenaline response in late pregnant rats (Brunton *et al.* 2005). Expression of mRNAs for proenkephalin-A and μ -opioid receptor is increased in the NTS at the end of pregnancy (Brunton *et al.* 2005). It is not known whether the NTS neurones expressing these opioid genes are the same set of neurones that also produce noradrenaline, project to the PVN and are activated by systemic IL-1 β . If this is the case it provides a mechanism by which up-regulated enkephalin could act on the up-regulated opioid receptor at the A2 nerve terminals in the PVN to auto-inhibit release of noradrenaline (and other co-peptides) in late pregnancy (Fig. 3). Whether endogenous opioids also have postsynaptic actions on the CRH cell bodies is as yet unknown.

What pregnancy-related factor triggers these adaptations in HPA axis responsiveness?

Circulating concentrations of oestrogen and progesterone are greatly increased in late pregnancy implicating these sex steroids as candidate mediators in signalling to the brain to

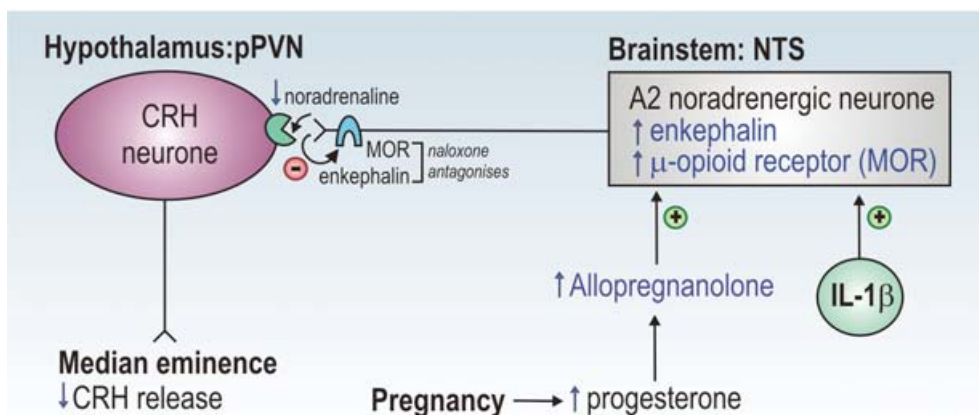


Figure 3. Proposed mechanism of suppressed HPA axis responses in late pregnancy

Central and circulating levels of allopregnanolone are increased (\uparrow) in pregnancy. Allopregnanolone increases the expression of mRNA for proenkephalin-A (and perhaps for μ -opioid receptor) in the A2 cell region of the nucleus tractus solitarius (NTS). NTS noradrenergic A2 neurones innervate CRH neurones in the parvocellular division of the paraventricular nucleus (pPVN) and are activated ($+$) following systemic administration of interleukin-1 β (IL-1 β ; see Fig. 2). However, in late pregnancy, increased opioid (enkephalin) inhibition prevents IL-1 β from stimulating noradrenaline release in the PVN. Enkephalin acts presynaptically on μ -opioid receptors (MOR) to inhibit noradrenaline release from nerve terminals in the PVN. The opioid receptor antagonist, naloxone, restores HPA axis responses to IL-1 β when administered systemically, and when infused directly into the PVN reinstates noradrenaline release evoked by IL-1 β . Induction of this inhibitory ($-$) opioid mechanism by allopregnanolone in late pregnancy prevents activation of the CRH neurones and consequently HPA axis responses to IL-1 β are suppressed (\downarrow).

induce adaptations in HPA axis responsiveness. We have previously found that prolonged exposure of virgin rats to pregnancy levels of oestrogen and progesterone induces inhibitory opioid tone over stimulated oxytocin secretion, as is found in late pregnancy, but does not alter HPA axis responses to stress (Douglas *et al.* 2000).

Progesterone is metabolized by the enzyme 5α -reductase to dihydroprogesterone, which is converted to allopregnanolone by 3α -hydroxysteroid dehydrogenase. Circulating and central levels of allopregnanolone increase during pregnancy, peaking around 2 days prior to parturition (Concas *et al.* 1998). Allopregnanolone is a neuroactive steroid and it acts allosterically on GABA_A receptors to prolong the opening time of the activated GABA_A receptor chloride channel, hence enhancing inhibitory GABA neurotransmission (Brussaard *et al.* 1999). Furthermore, allopregnanolone attenuates stress-induced HPA axis activity in male rats (Patchev *et al.* 1996).

We have investigated a role for allopregnanolone in the suppressed HPA axis responses to IL-1 β in late pregnancy by blocking its production with finasteride, a 5α -reductase inhibitor (P. J. Brunton & A. J. Russell, unpublished observations). Finasteride had little effect on the HPA axis response to IL-1 β in non-pregnant rats; however, in late pregnant rats, blocking allopregnanolone production substantially restored an ACTH response. This effect of finasteride in pregnant rats was reversed by simultaneous allopregnanolone treatment, and allopregnanolone treatment suppressed IL-1 β -induced ACTH secretion in virgin rats. However, the same effect was not achieved with either progesterone or dihydroprogesterone treatment, suggesting that the activity of one or both of the progesterone-converting enzymes is up-regulated centrally in pregnancy.

In late pregnant rats pre-treated with finasteride and then naloxone we observed ACTH responses to IL-1 β similar to those measured when either drug was administered alone. The inference that allopregnanolone might induce opioid inhibition of HPA axis responses to IL-1 β was confirmed by finding that allopregnanolone treatment induced inhibitory opioid tone over HPA axis responses to IL-1 β in virgin rats, and furthermore that allopregnanolone induced proenkephalin-A mRNA expression in the NTS of virgin rats, as found at the end of pregnancy (Brunton *et al.* 2005). The mechanism of this neurosteroid-opioid connection needs further investigation.

Conclusions

In late pregnancy HPA axis responses to IL-1 β are essentially absent. This is a consequence of a lack of excitatory noradrenergic drive to the CRH neurones in the PVN. Up-regulated opioid peptide and receptor expression, originating from NTS neurons, act

presynaptically on noradrenergic terminals in the PVN to inhibit noradrenaline release in response to IL-1 β in late pregnancy. In pregnancy, increased concentrations of central allopregnanolone induce the changes in opioid expression. Whether the collective effects of allopregnanolone and opioids reported here represent a global mechanism acting to restrain HPA axis responses to other types of stress remains to be elucidated.

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