Corticotropin-releasing hormone signals adversity in both the placenta and the brain: regulation by glucocorticoids and allostatic overload

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Abstract
Glucocorticoids regulate corticotropin-releasing hormone (CRH) gene expression in the placenta and the brain. In both the placenta and two extrahypothalamic sites in the brain (the amygdala and the bed nucleus of the stria terminalis), glucocorticoids elevate CRH gene expression. One functional role of the elevation of CRH by glucocorticoids may be to signal adversity. When CRH is over-expressed in the placenta, it may indicate that the pregnancy is in danger, and preterm labor may result. When CRH is over-expressed in the brains of animals, they may become more fearful. Both situations possibly reflect allostatic mechanisms and vulnerability to allostatic overload, a condition in which biological tissue may be compromised.

Introduction
Preterm delivery accounts for up to 11% of all births and is a leading factor in neonatal morbidity; consequences of preterm birth include low birth weight and decreased respiratory function (Center for Disease Control 1997). Several physiological systems linked to the placenta may play a role in preterm labor (see e.g. Goland et al. 1992, MacGregor et al. 1995, Pepe & Albrecht 1995).

A large number of hormones are produced in the placenta. The list includes but is not limited to: corticotropin-releasing hormone (CRH), urocortin, adrenocorticotropin (ACTH), angiotensin, atrial natriuretic factor, prolactin, oxytocin, cytokines, gonadotropin releasing hormone, opioids, somatostatin, prostaglandin and parathyroid hormone (see e.g. Taniguchi et al. 1991, Ahmed et al. 1992, Lefebvre et al. 1992, Bramley et al. 1994, Lim & Gude 1995, Petraglia et al. 1990a, 1996). These placental peptides are homologous in structure to those in the fetal and in the mature brain (Challis et al. 1995).

The hypothesis in this review is that CRH is elevated during adverse events in pregnancy, that it may be a predictor of preterm labor when there are conditions of adversity (see e.g. Wolfe et al. 1988b, Goland et al. 1993), and that it is altered in the brain when we experience fear and anxiety (Gold et al. 1984, Nemeroff et al. 1984, Nemeroff 1992), or a sense of potential harm (Kalin et al. 1989, Koob 1993, Schulkin et al. 1994). In the case of adverse events in pregnancy, CRH may be over-expressed in the placenta; in the case of fear and anxiety, CRH may be over-expressed in the brain.

Expression of corticotropin-releasing hormone in the placenta
The activation of the fetal hypothalamic–pituitary–adrenal axis promotes the maturation of the fetus and parturition (Challis et al. 1995). CRH is a peptide hormone which was originally discovered in the paraventricular nucleus of the hypothalamus and which is fundamental to the regulation of pituitary secretion of ACTH (Vale et al. 1981). CRH was subsequently isolated in the placenta, and found to be identical to CRH in the hypothalamus (Shibasaki et al. 1982), and in extrahypothalamic sites in the brain (Swanson et al. 1983). In placental tissue, CRH is largely localized in syncytiotrophoblast and intermediate trophoblast cell bodies (see e.g. Firn et al. 1988; F Petraglia & P Sawchenko, unpublished data) (Fig. 1).
CRH in humans is not detectable in plasma except during pregnancy (Sasaki et al. 1984, Cambell et al. 1987, Goland et al. 1988, Wolfe et al. 1988). In the second and third trimesters of normal pregnancy, CRH is elevated in maternal plasma that is derived from the placenta (Fig. 2). At the same time, both fetal and maternal ACTH and cortisol levels are elevated (Challis et al. 1995, Goland et al. 1995). Following parturition, CRH levels in the plasma rapidly decrease to nadir levels (Laatikainen et al. 1987). In other words, CRH gene expression in placental trophoblast cells rises towards the end of pregnancy in several species, including humans (Firn et al. 1988, Riley et al. 1991), gorillas (Robinson et al. 1989), and rhesus monkeys (Wu et al. 1995), although there appear to be species in which this is not the case (e.g. baboons; Goland et al. 1992, Smith et al. 1993).

Regulation of CRH by glucocorticoids

Classically, glucocorticoids are known to restrain CRH production by negative feedback (Munck et al. 1984) but, importantly, in one early study it was reported that dexamethasone treatment did not suppress levels of CRH in the plasma of pregnant women (Tropper et al. 1987). It was then demonstrated that glucocorticoids do not inhibit the production of CRH in the placenta as expected; rather, they increase CRH gene expression in the placenta (Robinson et al. 1988, Jones et al. 1989). Glucocorticoids increase CRH gene expression in primary cultures of human placental trophoblasts. These effects are dose related, and may be greater in response to dexamethasone than for cortisol, suggesting that these effects are dependent upon type II glucocorticoid receptor sites (Jones et al. 1989, Challis et al. 1995). Moreover, a recent study demonstrated that pregnant women treated with betamethasone after 30 weeks gestation had increased CRH levels in both plasma and placental tissue (Marinoni et al. 1998) (Fig. 3). An additional study also revealed that pregnant patients at 24 weeks also have increased levels of plasma CRH following betamethasone treatment (Korebrits et al. 1998). Thus, in marked contrast to glucocorticoids' well known inhibition of CRH via type II glucocorticoid receptor sites at the level of the paraventricular nucleus of the hypothalamus, and the negative restraint of the hypothalamic–pituitary–adrenal axis (Munck et al. 1984, Sawchenko 1987, Swanson & Simmons 1989), glucocorticoids increase CRH gene expression in the placenta.

Placental CRH expression under duress

The most consistent fact about CRH detected in plasma in pregnant women is its link to both potential maternal–fetal distress, or greater metabolic and physiological demands, in women who go on to experience preterm labor (Wolfe...
CRH and parturition

Oxytocin and prostaglandin, linked to parturition, enhance CRH gene expression in placental tissue (Petraglia et al. 1989). Bacterial microbial induced cytokine production may facilitate parturition via changes in CRH; there is a well established link between cytokine production, the release of CRH (Chrousos 1996) and a reduction in reproductive fitness (Ferin 1995).

Decreases in progesterone levels lead to the upregulation of CRH in the placenta, perhaps by enhanced binding of glucocorticoids (Karalis et al. 1996). In addition, decreases in CRH binding protein are linked to the upregulation of CRH (Behan et al. 1996). Finally, a recent study found that a CRH type I receptor antagonist can delay parturition in sheep (Chan et al. 1998).

Clearly, there is more than one mechanism to facilitate an event as important as birth—after all, the end-point of evolution is successful reproduction. For example, estrogen is known to increase oxytocin gene expression in the placenta, which facilitates the onset of labor. An important point is that the steroid is sustaining or increasing the peptide, which then contributes to the onset of parturition.

In general, steroids act to regulate peptides (see e.g. Pfaff 1980, Petraglia et al. 1990b, Herbert 1993, Schulkin 1998). In the placenta, glucocorticoids increase CRH expression. What seems clear about CRH is its overexpression by the placenta under adverse pregnancy conditions, which might reflect allostatic regulation and allostatic overload.

Allostasis and allostatic overload

The concept of allostasis is tied to systems in which there is no clear physiological set point. That is, the set point is fluid and changing (Sterling & Eyer 1988). Allostasis refers to the ability to achieve stability through change. Whereas homeostatic systems such as blood oxygen, blood pH, and body temperature must be maintained within a narrow range, allostatic systems are more labile, allowing them to adjust to external and internal circumstances (McEwen & Stellar 1993). Both homeostatic (Bernard 1865; Cannon 1932, Richter 1943) and allostatic regulation help maintain the internal milieu (Sterling & Eyer 1988, Schulkin et al. 1994, 1998, McEwen 1998). It is the latter concept that we hypothesize has relevance to understanding the endocrine mechanisms that may underlie preterm labor induced by maternal–fetal distress.

Allostatic responses, within limits, may prove adaptive and protective. Hormones such as CRH or cortisol can be destructive when they are activated for long periods of time, or when the body is unable to stop producing them (Sapolsky 1992, McEwen 1998). Glucocorticoids, such as cortisol, restrain hormone production by inhibiting CRH gene expression in the paraventricular nucleus of the hypothalamus (see e.g. Munck et al. 1984, Sawchenko 1987). In this context, the event is protective. If high cortisol levels continue to persist, it may be destructive (e.g. bone demineralization, immune defense degradation). Biological tissue is compromised when pushed beyond its limits. The CRH that is hypersecreted in pregnant women following situations of bacterial infectious diseases, pre-eclampsia or hypertension, multiple gestations, and psychosocial stress may be conditions of allostatic overload. Under conditions of allostatic overload, parturition may be adaptive to both mother and fetus, by both reducing stress on the pregnant woman and removing the fetus from an over-stressed environment.

Expression of CRH in the brain

Corticotropin-releasing hormone and binding protein are widely distributed in the central nervous system (see e.g. Swanson et al. 1983, Sawchenko 1993, Behan et al. 1996, Gray & Birnmann 1996). In addition to the paraventricular nucleus and lateral region of the hypothalamus, CRH is found in the frontal cortex and regions of the thalamus, as well as brainstem regions near the locus coeruleus.
At least two CRH receptors sites are found in the brain (Potter et al. 1994, Lovenberg et al. 1995). Two regions in which CRH is particularly conspicuous are in the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis (Ju et al. 1989, Moga et al. 1989, Makino et al. 1994b). Both regions are known to influence the regulation of the hypothalamic–pituitary–adrenal axis (Herman & Cullian 1997). The lateral bed nucleus of the stria terminalis is particularly important in regulating CRH gene expression in the paraventricular nucleus of the hypothalamus under a number of conditions (Herman & Cullian 1997). The bed nucleus of the stria terminalis (e.g. extended amygdala) is ideally situated to regulate the paraventricular nucleus, because of the massive anatomical connectivity between these two regions (Alheid et al. 1996).

Regulation of CRH by glucocorticoids

Importantly, CRH gene expression is differentially regulated in the brain by glucocorticoid hormones (Swanson & Simmons 1989, Imaki et al. 1991, Tanimura & Watts 1998). In the parvocellular region of the paraventricular nucleus, glucocorticoid activation decreases CRH gene expression, while in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, CRH gene expression is enhanced by glucocorticoids (Swanson & Simmons 1989, Makino et al. 1994a,b, Watts & Sanchez-Watts 1995, Watts 1996) (Fig. 5). These effects on the upregulation of CRH gene expression may be mediated by both type I and type II glucocorticoid receptor sites (Watts & Sanchez-Watts 1995, Tanimura & Watts 1998).

Corticotropin-releasing hormone regulation by negative feedback is not axiomatic even at the level of the paraventricular nucleus (Swanson & Simmons 1989, Tanimura & Watts 1998). Interestingly, under various conditions, glucocorticoids in the paraventricular nucleus of the hypothalamus stop inhibiting CRH gene expression (Pich et al. 1993a, Kalin et al. 1994, Albeck et al. 1997, Tanimura & Watts 1998). These findings at the level of the paraventricular nucleus suggest a breakdown of normal regulatory function and, together with the elevated levels of CRH gene expression in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, may reflect allostatic overload (Schulkin et al. 1998). Consistent with this, CRH is elevated in the cerebrospinal fluid, together with elevated systemic levels of cortisol, in people who are chronically fearful/anxious and depressed (Nemeroff et al. 1984, Gold et al. 1988, Kling et al. 1993, Nemeroff 1992). This condition is also one in which there is a vulnerability to bone loss (Michelson et al. 1996), or hippocampal deterioration (Sheline et al. 1996), which are perhaps also examples of allostatic overload (McEwen 1998).

Behavioral effects of elevated CRH

Elevated levels of CRH (Koob & Bloom 1985) in specific regions of the brain that include the central nucleus of the

Figure 5 Corticotropin-releasing hormone gene expression in the lateral bed nucleus of the stria terminalis in (B) rats treated with corticosterone and (A) those that were untreated (from Makino et al. 1994b).
amygdala and the lateral bed nucleus of the stria terminalis increase the likelihood that an event will be perceived as dangerous (see e.g. Koob 1993, Kalin et al. 1994, Lee & Davis 1997). These two neural sites underlie the behavioral response to fear and anxiety (LeDoux 1987, 1996, Rosen & Schulkin 1998).

Transgenic mice with overexpression of CRH in the brain demonstrate exaggerated fear responses (Stenzel-Poore et al. 1994). Fear responses are attenuated by central pharmacological blockade of CRH expression (Swerdlow et al. 1989, Koob 1993), but not peripheral blockade of CRH expression (Pich et al. 1993b). In particular, antagonists of CRH directed at the central nucleus of the amygdala reduce a number of fear-induced behavioral responses (Swerdlow et al. 1989, Koob 1993). Infusion of CRH directly into the lateral or third ventricle (e.g. Koob 1993) or the bed nucleus of the stria terminalis (extended amygdala) facilitates fear responses (Lee & Davis 1997).

Interestingly, it has been suggested that pharmacological blockade of type I CRH receptor sites reduces fear–related behavioral responses (Deak et al. 1999) and, perhaps together with decreased levels of central CRH binding protein, facilitates the binding of CRH and the expression of fear. It should also be remembered that the type I CRH receptor antagonist has been reported to delay parturition (Chan et al. 1998).

Animal studies suggest that excessive prenatal stress and fear can have long term impact on the offspring (Weinstein 1996). One study, for example, has shown that aversive stress results in elevated cortisol levels in both the mother and the fetus(es). When sacrificed as young adults, the offspring demonstrate increased levels of CRH (49%) in the central nucleus of the amygdala compared with control rats. Prenatal stress experiences can increase fear responses when these animals are provoked as adults (Cratty et al. 1995). Consistent with this picture are the experiments demonstrating that CRH injections during pregnancy in rats increase the vocalization of the offspring when tested in isolation chambers during ontogeny (Williams et al. 1995).

Glucocorticoid and CRH elevation decrease reproductive fitness and decrease sexual behavior (e.g. Nappi & Rivier 1995). When glucocorticoids are elevated under duress, testosterone or estrogen is reduced in most species that have been studied (Sapolsky 1992). The state of combating disease or experiencing fear (or psychological stress) are metabolically expensive events, and thereby reduce the hormones of reproduction and the likelihood of successful reproduction (Wasser 1996). Interestingly, in experiments in which there is elevated estrogen there is decreased CRH expression in the brain (Patchev & Almeida 1996).

Importantly, rather than restraining behavioral effects, glucocorticoids, via central activation of CRH, enhance these effects (Schulkin et al. 1998). For example, glucocorticoids facilitate CRH-induced fear responses (Lee et al. 1994). Rats treated with glucocorticoids systemically have increased fear-related startle responses to central CRH infusions.

When given centrally high doses of CRH also facilitate the vulnerability to seizures (Weiss et al. 1986). This event is linked to the activation of the amygdala (Weiss et al. 1986, Helfer et al. 1996). While it was hypothesized that glucocorticoids should restrain CRH-related seizures, we found that glucocorticoids facilitated the onset of CRH-induced seizures (Rosen et al. 1994) (Fig. 6). Moreover, we also found that, rather than restraining cocaine-induced seizures, which are linked to CRH expression in the amygdala, glucocorticoids actually increase them (Kling et al. 1993).

Conclusion

The underlying hypothesis is that CRH is a signal of danger in both the placenta and the brain. In one context, the impact of elevated glucocorticoids on CRH gene expression may render women more vulnerable to preterm labor. In the other context, glucocorticoids facilitate the perception of danger. Glucocorticoids act to magnify and sustain the CRH signal.

Glucocorticoid regulation of CRH gene expression in the placenta and in the amygdala and bed nucleus of the stria terminalis look remarkably similar. While glucocorticoids restrain CRH gene expression in the paraventricular region of the paraventricular nucleus of the hypothalamus, they magnify the effects of CRH in these other areas. This induction of CRH gene expression under certain conditions may contribute to regulatory or allostatic overload.

It should be noted that we do not know whether the mechanisms that underlie the placental increase of CRH by glucocorticoids are the same for both the brain and the placenta. Nor do we know whether the induction of CRH gene expression in the placenta originates with the mother, the fetus, or even the placenta itself. What is clear, however, is that, contrary to the belief that glucocorticoids
always react to restrain the expression of CRH, glucocorticoids facilitate CRH expression in the placenta and in regions of the brain that underlie the experience of adversity, and it is this CRH expression that may be significant in preterm labor (e.g. allostatic overload) at the level of the placenta, and in the brain to sustain the experience of adversity.

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