On the function of placental corticotropin-releasing hormone: a role in maternal-fetal conflicts over blood glucose concentrations

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ABSTRACT

Throughout the second and third trimesters, the human placenta (and the placenta in other anthropoid primates) produces substantial quantities of corticotropin-releasing hormone (placental CRH), most of which is secreted into the maternal bloodstream. During pregnancy, CRH concentrations rise over 1000-fold. The advantages that led selection to favour placental CRH production and secretion are not yet fully understood. Placental CRH stimulates the production of maternal adrenocorticotropic hormone (ACTH) and cortisol, leading to substantial increases in maternal serum cortisol levels during the third trimester. These effects are puzzling in light of widespread theory that cortisol has harmful effects on the fetus. The maternal hypothalamic-pituitary-adrenal (HPA) axis becomes less sensitive to cortisol during pregnancy, purportedly to protect the fetus from cortisol exposure. Researchers, then, have often looked for beneficial effects of placental CRH that involve receptors outside the HPA system, such as the uterine myometrium (e.g. the placental clock hypothesis). An alternative view is proposed here: the beneficial effect of placental CRH to the fetus lies in the fact that it does stimulate the production of cortisol, which, in turn, leads to greater concentrations of glucose in the maternal bloodstream available for fetal consumption. In this view, maternal HPA insensitivity to placental CRH likely reflects counter-adaptation, as the optimal rate of cortisol production for the fetus exceeds that for the mother. Evidence pertaining to this proposal is reviewed.

Key words: corticotropin releasing hormone, placental hormones, maternal-fetal conflict, cortisol, fetal programming.

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I. INTRODUCTION

The hypothalamic-pituitary-adrenal (HPA) axis mediates the stress response of glucocorticoids (in humans, cortisol). Both physical and psychological stressors (e.g. nutritional stress, psychosocial stress) activate the production of corticotropin-releasing hormone (CRH) at the median eminence of the paraventricular nucleus (PVN) of the hypothalamus. In turn, CRH stimulates the release of adrenocorticotropic hormone (ACTH) by the pituitary gland. Circulating ACTH then leads the adrenal cortex to secrete cortisol into the bloodstream (e.g. Nelson, 2005).

The placenta produces large quantities of CRH during the second and third trimesters of pregnancy. Virtually all of the CRH produced (99%+) is sequestered in the maternal bloodstream, with little being directed to the fetus (e.g. Campbell et al., 1987). As a result, during pregnancy CRH levels in the maternal bloodstream become very high, over 1000 times those in early pregnancy (e.g. Frim et al., 1988). Maternal concentrations exceed fetal levels by more than an order of magnitude (Roe et al., 1996; Sun et al., 1999; Donoghue et al., 2000). Though not crossing the blood-brain barrier, placental CRH (structurally identical to hypothalamic CRH) can reach the pituitary gland and stimulate the production of ACTH and, in turn, cortisol. Serum levels of ACTH and cortisol during the second and third trimesters are, on average, twice those at the end of the first trimester, placental CRH likely being the major cause (e.g. Goland et al., 1992; Goland, Jozak & Conwell, 1994). CRH levels in the maternal bloodstream (virtually all of it originating as placental CRH) predict levels of cortisol, and β-endorphin (another product of HPA axis stimulation) (Chan et al., 1993; Wadhwa et al., 1997; O'Keane et al., 2011).

Why does the placenta produce CRH? And why does it secrete the vast majority into the maternal bloodstream? Remarkably, in light of the massive quantities produced, these questions have received relatively little attention from reproductive and evolutionary biologists (although see Section III; see also Florio et al., 2002; Power & Schulkin, 2006). We address these questions herein; while our analysis has implications for an understanding of placental CRH production in anthropoid primates in general (species in
which the placenta produces CRH—although recent evidence suggests that the phenomenon may occur in many other mammals; see Lovell et al., 2007), most extant data pertain to humans. Hence, most of the literature we cite refers to CRH secreted by the human placenta.

II. MATERNAL INSENSITIVITY TO CRH

(1) The phenomenon

We begin with observations that some neuroendocrinologists have recently emphasized (e.g. Brunton & Russell, 2008; Douglas, 2010): during pregnancy, HPA-mediated production of cortisol becomes relatively non-responsive (e.g. Schulte, Weisner & Alloio, 1990; Kammerer et al., 2002; de Weerth & Buitelaar, 2005). In pregnant rats, mice, and women, production of CRH, ACTH, and corticosteroids in response to stressors is dampened. These changes appear to be at least partly mediated by the neurosteroid allopregnanolone, a progesterone metabolite. Effects of allopregnanolone, in turn, appear to be at least partly mediated by upregulated opioid receptor mechanisms, which affect AVN CRH receptor responsivity (Brunton, Russell & Douglas, 2008). Progesterone production by the placenta increases substantially in the second and third trimesters of human pregnancy, and hence so do allopregnanolone levels (see Brunton & Russell, 2008; Brunton et al., 2008; Slattery & Neumann, 2008, for references).

These phenomena can be and have been demonstrated at an endocrinological level of analysis, as well as physiological and psychological response levels. During the second trimester, women report feeling calmer and less worried in response to everyday stressors, compared to non-pregnant women (e.g. Glynn et al., 2004; Pearson, Lightman & Evans, 2009). More generally, responses in cortisol production, blood pressure, heart rate, and psychological distress to laboratory stressors (e.g. procedures designed to induce pain or discomfort) are dampened in pregnant women, particularly in later stages (for a review, see de Weerth & Buitelaar, 2005; see also Entringer et al., 2010).

A functional explanation for reduced HPA-mediated cortisol production has been proposed: it reflects adaptations that serve to protect the fetus. High levels of cortisol circulating in the maternal bloodstream, this argument claims, are harmful to the fetus. In response to exposure to glucocorticoids, which partly cross the maternal-placental interface, fetuses may grow to smaller size and exhibit a hyperresponsive HPA system (see Section VII). These features are putatively debilitating to the health of the future individual. Reduced levels of circulating cortisol hence buffer the fetus from these effects. In light of HPA-mediated cortisol production in response to physical and psychological stressors, the best way for the mother to protect the fetus is for her cortisol production to become less responsive to these stressors. Hence, downregulation of the HPA axis, via selected-for effects of a neurosteroid that is at unusually high levels during pregnancy, allopregnanolone, has been favoured. This downregulation is, by definition, a putative adaptation that serves the function of protecting the fetus from harmful exposure to cortisol.

Several major reviews of literature on HPA hyporesponsiveness during pregnancy have been published in the past decade (e.g. de Weerth & Buitelaar, 2005; Brunton & Russell, 2008; Brunton et al., 2008; Slattery & Neumann, 2008; Douglas, 2010). Overwhelmingly, the primary functional explanation offered for the changes is that described above. In the representative words of Slattery & Neumann (2008), “[these] maternal adaptations. . ., with the significant attenuation of hormonal stress responses during pregnancy and lactation, are important for the healthy prenatal development of the offspring by preventing excessive levels of circulating glucocorticoids” (p. 381). [Secondarily, Slattery & Neumann (2008) suggest that HPA suppression protects mothers against mood disorders].

(2) A conundrum: why does the placenta produce CRH, which stimulates the HPA axis?

This functional explanation offers a reason why mothers might reduce their sensitivity to HPA activation. It does not explain why the placenta produces large quantities of CRH—indeed, the fact that the placenta does so poses a conundrum for this perspective. Mothers reduce activation of the HPA axis to protect the fetus against the harmful effects of cortisol; at the same time, fetuses (via the placenta) produce the hormone that stimulates the HPA axis and, thereby, raise levels of maternal cortisol. If maternal cortisol threatens the health of the fetus, the fetus engages in what, from this perspective, would appear to be potentially self-destructive behaviour.

At least a couple of responses to this problem preserve the idea that cortisol is harmful to fetuses, and mothers accordingly reduce sensitivity of the HPA axis to protect the fetus. The first is that placental CRH is produced “by accident” rather than design (e.g. Perkins & Linton, 1995). As production of placental CRH does not come cost-free and is not an obvious byproduct of another functional mechanism, it seems unlikely that it has not been directly favoured by selection and hence has had beneficial consequences for the fetus. Another, more plausible explanation, the placental clock hypothesis, has received much more theoretical and empirical attention.

III. THE PLACENTAL CLOCK HYPOTHESIS

(1) Overview

A second response is to claim that placental CRH serves an adaptive function, but one that has nothing to do with stimulating the maternal HPA axis. Fetuses may benefit from the production and secretion of CRH, but not because it stimulates maternal production of ACTH and, subsequently, cortisol. Receptors for CRH exist in maternal tissue other
than the pituitary gland. Perhaps CRH offers fetal benefits through stimulation of a subset of these receptors. From this perspective, placental CRH has a cost (a maladaptive byproduct), in that it also stimulates production of cortisol, which may harm the fetus. Clearly, for placental CRH production to have been favoured by selection, benefits derived from placental CRH to the fetus must exceed costs of this byproduct (and other costs, e.g. production costs). But if the maternal HPA axis has become relatively insensitive to CRH, the costs may not be excessive.

The most prominent functional hypothesis for placental CRH in the literature argues that CRH serves as a “placental clock,” a mechanism that times the duration of gestation, ultimately triggering labour and parturition (e.g. McLean et al., 1995; Sandman et al., 2006; Smith & Nicholson, 2007). In humans, placental CRH levels in maternal blood rise exponentially during the third trimester. Most placental CRH is bound by CRH-binding protein (CRH-BP) (Linton et al., 1990), rendering it biologically inactive. Late in pregnancy however, production of placental CRH outpaces that of CRH-BP. Placental CRH may affect, directly or indirectly, the uterine myometrium, leading to labour contractions (e.g. McLean & Smith, 2001). CRH also plays roles in implantation during the first trimester through effects on the maternal endometrium, although that CRH is not of placental origin; e.g. Choy, Leung & Lau (2004); see also Makrigiannakis et al. (2004).

(2) Evidence for the placental clock hypothesis

Two kinds of evidence bolster the placental clock hypothesis. First, placental CRH levels rise more dramatically during gestation ending in preterm birth (e.g. McLean et al., 1995; Wadhwa et al., 2004; Sandman et al., 2006). Indeed, placental CRH levels as early as a gestational week 20 are reliably associated with preterm birth, leading some investigators to propose that the events responsible for preterm birth precede actual timing of the births by weeks or months. Implicit in some discussions is the idea that, as preterm birth is harmful to the fetus, dysfunction or poor regulation of the placental clock is responsible for preterm birth. (High levels of cortisol very early during the pregnancy may be partly responsible; Sandman et al., 2006). By contrast, and also consistent with the placental clock hypothesis, postterm births are associated with low levels of placental CRH (e.g. Wadhwa et al., 2004). As noted by Inder et al. (2001) however, covariation between CRH levels and timing of parturition is not perfect.

Second, CRH receptors are found in uterine tissue, fetal pituitary and human fetal adrenal gland. Though not entirely understood, placental CRH is thought to have varied actions in uterine tissue (reviewed in Ishimoto & Jaffe, 2011) from modulating the secretion of bioactive molecules to the prevention of and initiation of myometrial contractions. Early during pregnancy, uterine CRH plays a role in implantation (e.g. Makrigiannakis et al., 2004). Placental CRH can hence play roles in processes that do not involve effects on maternal cortisol levels. The mere fact that uterine receptors exist suggests a function for these effects.

(3) Empirical and conceptual challenges to the placental clock hypothesis

If placental CRH production does function as a clock, this function leaves important features of placental CRH production unexplained. Hence, though CRH may play a role in the timing of parturition, it may well function in other roles too (perhaps ones that, evolutionarily, predate its role as a clock; see Section IV).

The precise physiological mechanisms through which placental CRH brings about labour are not presently understood; in the words of one review article’s title, they remain “a scientific enigma” (Grammatopoulos, 2008). Stimulation of uterine CRH receptors during pregnancy appears to suppress contractions of the myometrium (e.g. Zhang et al., 2008; Tyson, Smith & Read, 2009)—an effect precisely the opposite to that expected if uterine stimulation by CRH initiates labour directly.

In light of this, a second, indirect route through which placental CRH times labour has been proposed. A small portion of placental CRH does go to the fetus, and this portion could play a role in a placental clock. It stimulates the fetal adrenal gland to produce the androgen dehydroepiandrosterone sulfate (DHEAS), which in turn leads to placental production of oestrogen (e.g. Sirianni et al., 2005). As with CRH, placental oestrogen levels ramp up during the last trimester. Placental oestrogen production may be key to the production of oxytocin, which directly causes the uterine contractions of labour (e.g. Chibbar et al., 1995).

This conjecture faces its own challenges. In particular, if the functional effects of placental CRH derive from fetal stimulation, why does the placenta secrete most CRH into the maternal bloodstream? Once again, a modification can be proposed: a positive feedback between placental CRH and maternal cortisol production leads placental CRH levels to increase through the last two trimesters. That is, maternal cortisol appears itself to stimulate production of placental CRH, which then increases cortisol levels, and so on. The timescouse of this build-up is perhaps key to the “clock-like” property of placental CRH (e.g. Hobel et al., 1999).

Another challenge, however, arises: this modification no longer explains how placental CRH has beneficial effects not reliant on the maternal HPA axis. An appeal of the placental clock hypothesis is that it can simultaneously explain why the placenta produces large quantities of CRH, and yet retain the idea that maternal HPA insensitivity to CRH protects the fetus: the benefits derive from stimulation of receptors not residing in the mother’s pituitary. Yet this modification proposes that the process through which placental CRH achieves its adaptive effects is stimulation of the maternal pituitary. In this particular view, then, the design of the placental clock would appear to be seriously flawed; more proficient timing mechanisms would seem to have been possible.

Furthermore, it is not clear how placental CRH as a timing mechanism requires high levels near the start of the second trimester, as opposed to later in pregnancy, particularly as putative maladaptive byproducts of placental CRH via

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Placental CRH secreted into the maternal bloodstream by the placenta. Two other, structurally similar hormones abundantly produced in the maternal-fetal conflicts. The production of maternal cortisol, which reflects broader metabolic effects. Cortisol may have evolved to have additional functions in specific species, including in humans, such as those mediated by effects on the nervous system; e.g., increasing insulin insensitivity and, thereby, reduced peripheral utilization of glucose. At a fundamental level, then, cortisol production by the mother during pregnancy has effects similar to those of hGH-V and hPL: it increases the amount of blood sugar available for uptake by the placenta and, hence, fetus. [Cortisol may have evolved to have additional functions in specific species, including in humans, such as those mediated by effects on the nervous system; e.g., Sapolsky et al. (2000). Cortisol receptors in the amygdala, biological effects of cortisol.

(2) Arguments for a similar function for CRH

(a) The metabolic effects of cortisol

Cortisol is widely known as a stress hormone, as it is normally produced in response to both physiological and psychosocial stressors (e.g., starvation, unpredictability of aversive stimuli; e.g., Sapolsky, Romero & Munck, 2000). Glucocorticoids, including cortisol, derive their name from their effects on glucose metabolism. Cortisol’s primary function is arguably to increase blood sugar levels through hepatic glycogenolysis. Cortisol also maintains high levels of blood sugar indirectly increasing insulin insensitivity and, thereby, reduced peripheral utilization of glucose. At a fundamental level, then, cortisol production by the mother during pregnancy has effects similar to those of hGH-V and hPL: it increases the amount of blood sugar available for uptake by the placenta and, hence, fetus. [Cortisol may have evolved to have additional functions in specific species, including in humans, such as those mediated by effects on the nervous system; e.g., Sapolsky et al. (2000). Cortisol receptors in the amygdala,

Placental lactogen (hPL). Human growth hormone (hGH) does not increase growth directly per se; its effects on growth are mediated by insulin-like growth factor-I (IGF-I), produced in the liver. hGH directly affects metabolic activities specifically through utilization of lipids. hGH increases the rate at which lipolysis occurs—breakdown of triglycerides into fatty acids, which, through additional reactions, can be taken up by cells to be used for energy. Hence, hGH levels rise during starvation, a time at which energy stored in lipids is adaptively accessed. During the last half of pregnancy, women’s pituitary glands almost completely cease production of hGH and, hence, virtually all hGH in the maternal bloodstream is produced by the placenta (hGH-V). hGH-V levels in late pregnancy track levels of IGF-I in the bloodstream. Hence, hGH-V functions in much the same way that hGH does. hGH-V not only stimulates production of IGF-I; it also enhances availability of energy for the fetus through lipolysis of maternal fats. That is, hGH-V increases the concentration of energy sources in the maternal bloodstream, accessible to the fetus via the placental-maternal interface (see Haig, 2008).

hPL ligands bind to receptors of another related hormone, human prolactin (hPRL), itself related to hGH. hPRL is essential to the production of milk during lactation. Haig (1993) proposed that the placenta secretes hPL into the maternal bloodstream to produce effects similar to putative effects of hPRL and hGH: to increase levels of glucose in the maternal bloodstream. As hP's effect on IGF-I production is much less potent than that of hGH, hPL may have evolved to have targeted effects on the breakdown of triglycerides and insulin insensitivity (Haig, 2008; see also Handwerger & Freemark, 2000).

In sum, the placenta likely evolved to produce and secrete hGH-V and hPL into the maternal bloodstream because they increase the availability of energy to the fetus in its preferred form, glucose.
hippocampus, and prefrontal cortex are all important in the stress response. But the primary function of cortisol is likely to pertain to metabolic effects.]

(b) Vasocostrictive effects of cortisol

Cortisol has another effect on mothers that potentially benefits the fetus. It promotes vasocostriction by increasing vascular sensitivity to epinephrine and norepinephrine (e.g. Sapolsky et al., 2000), which increases peripheral blood pressure. In turn, enhanced peripheral blood pressure shunts blood to core organs, including the uterus. This effect of cortisol too may aid glucose uptake by placental tissues or availability of oxygen to the fetus (for further discussion of fetal attempts to affect vasocostriction, see Haig, 2007). Gestational diabetes, which may be linked to cortisol levels, (Ryan & Enns, 1988; Ahmed & Shalayel, 1999; cf. Grigorakis et al., 2000) is also a risk factor for hypertension and preecclampsia (Schneider et al., 2012).

(c) The metabolic effects of cortisol in functional perspective

These effects readily suggest a function for placental production of CRH. The fetus, via its placenta, produces CRH for reasons akin to why it produces hGH-V and hPL: to regulate the concentrations of glucose, a source of energy the fetuses prefer, in the maternal bloodstream. As shown by Smith et al. (2001), even peripheral administration of CRH increases fat oxidation. Whereas hGH-V and hPL have direct effects, the effects of placental CRH are mediated through maternal production of cortisol.

(d) Effects of cortisol on glucose uptake

If placental CRH production functions to enhance glucose uptake by the fetus via effects on maternal cortisol, then, in addition to increasing glucose concentrations (e.g. Sapolsky et al., 2000), cortisol should not adversely affect the proportion of glucose available to placental uptake. Norris et al. (2011) recently addressed this issue in rats by tracing marked glucose infused into pregnant females. In control females, glucose uptake by the placenta was greater than uptake by any maternal organ aside from the brain. Administration of the synthetic glucocorticoid dexamethasone for three days previously had no effect on relative uptake. Thus, if absolute blood levels of glucose are increased by cortisol, then, so too should be absolute amounts absorbed by the fetus.

Administration of insulin, by contrast, led to increased uptake by maternal muscles, which accordingly left less available for uptake by the placenta. Glucocorticoid administration in this study was of very short duration. The cumulative effects of cortisol over time include insulin resistance and vasocostriction, effects that could lead to proportionately greater uptake of glucose by the placenta. Women's basal metabolic rate, perhaps not surprisingly, increases during pregnancy, but high levels of cortisol during pregnancy strongly predict smaller increases in women's own basal metabolic rate (Damjanovoc et al., 2009). The less glucose utilized by women's bodies, the more blood glucose can be absorbed by the fetus.

(e) Effects of fetal metabolic demands on placental CRH production

If placental CRH production evolved for its effects on blood sugar levels via cortisol, then the placenta should increase its production of placental CRH when fetal metabolic demands increase. Cortisol is normally released following periods of fasting or starvation to mobilize energy stores and make them available for utilization. The placenta should similarly produce placental CRH to stimulate cortisol production following periods of maternal fasting, if placental CRH functions to increase the availability of maternal glucose. In fact, controlled experimental research shows that placental CRH levels do increase following a period of maternal fasting (Herrmann et al., 2001). This effect is not readily explained by other putative functions of placental CRH (see also Power et al., 2010). For related effects of maternal hypoglycemia on placental hGH-V secretion, see Bjorklund et al. (1998), Fuglsang et al. (2008) and Romero-Prado, Barrera-Saldana & Castrillo-Diez (2010); for mixed evidence of reduced secretion of hGH-V as a function of increased maternal blood glucose levels, see Patel et al. (1995) and McIntyre et al. (2002).

In twin gestations, where fetal nutritional demands are greater than singleton gestations, placental CRH levels are also significantly higher (Warren et al., 1990).

(f) Additional ways the fetus regulates glucose availability

Through placental actions, the fetus may regulate maternal metabolism in a variety of ways, including but not limited to secretion of hGH-V, hPL, and CRH (see e.g. Lowry, 2008). The human placenta, for instance, produces substantial amounts of leptin as well. Most placental leptin is secreted into the maternal compartment, and placental leptin accounts for the majority of the increase of leptin circulating in mothers during pregnancy (Linnemann et al., 2000). Leptin during pregnancy may function to mobilize fat stores to increase availability of absorption of fatty acids or glucose by the fetoplacental unit (Hauguel-del Mouzon, Lepercq & Catalano, 2006). Circulating leptin levels are robust predictors of measures of insulin resistance in mothers, even controlling for maternal pre-pregnancy body mass index (BMI) and a variety of other hormones and physiological parameters (e.g. triglyceride levels) (McIntyre et al., 2010). As increased glucose levels do not affect leptin production in pregnant female baboons (Santolaya-Forgas, Mehta & Castracane, 2006), this association may be due to effects of placental leptin on insulin resistance, mediated through alterations in maternal metabolism (although see also the following remarks on inflammation).

The placenta also produces and stimulates monocyte production of pro-inflammatory cytokines, including tumour necrosis factor α (TNF-α), interleukin (IL)-1β, IL-6, and IL-8 (e.g. Germain et al., 2007; Southcombe et al., 2011). Inflammatory signaling interferes with insulin action (perhaps reflecting adaptive immunomodulation of
Placental CRH

metabolic processes; see Hotamisligil, 2006). In experimental work, TNF-α in particular has been shown to induce insulin resistance (e.g. Krogh-Madsen et al., 2006). By rendering pregnancy a mild inflammatory state, then, the placenta may maintain heightened maternal blood glucose levels. Leptin increases production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in the placenta (Lappas, Permezel & Rice, 2005). Hence, the association between leptin and insulin resistance may be partly mediated by inflammatory signaling.

Research generally demonstrates that circulating CRH stimulates monocyte production of pro-inflammatory cytokines (e.g. Masterakos, Karoutsou & Mizamtsidi, 2006), though inflammatory effects may depend on the receptor type [CRH-R1 (pro-inflammatory) versus CRH-R2 (anti-inflammatory)] and thereby the tissue (Zhu, Wang & Li, 2011). One way that placental CRH may function to increase maternal blood glucose levels, then, is via inflammatory signaling. At the same time, however, cortisol has well-known anti-inflammatory effects; it fosters insulin resistance despite these effects and through other pathways, not via pro-inflammatory cytokines (see Andrews & Walker, 1999). The pro-inflammatory effects of CRH may partly counteract direct effects of cortisol on inflammation.

Detailed review of the broader ways placental actions regulate maternal metabolism is beyond the reach of this review. But clearly, the current proposal should be both understood and, as it becomes better clarified empirically, evaluated within this more extensive network.

(3) Challenges to be addressed by this framework

The claim that a primary function of placental CRH production is to alter maternal metabolism via effects on the maternal HPA system must address several theoretical and empirical challenges.

(a) Why does the placenta produce CRH rather than cortisol?

The current perspective suggests that CRH is produced to increase concentrations of cortisol in the maternal bloodstream, thereby increasing the availability of glucose to the fetus. So why does the placenta not secrete cortisol instead? One possible reason is that cortisol can, in fact, harm the fetus and, even though the placenta has evolved mechanisms of protecting the fetus from harm due to maternal cortisol (see Section VII), placental production of cortisol would be energetically costly or risky to the fetus. Second, placental production of cortisol might interfere with placental production of progesterone, as pregnenolone is a precursor of both hormones. Third, CRH has pro-inflammatory effects that may counteract (adaptively, from the perspective of the fetus) the anti-inflammatory effects of cortisol. These arguments require further evaluation.

(b) Placental CRH production and conditions that increase it

If placental production of CRH functions to regulate the concentration of glucose available in the maternal bloodstream we would expect placental production of CRH to increase under conditions of low glucose availability. One study demonstrates that maternal fasting leads to increased CRH levels, consistent with this expectation (Herrmann et al., 2001)—but, remarkably, no other published study has examined this prediction and further research is clearly needed (see Section V for a discussion of links between fetal insufficiency and placental CRH, which could reflect similar forms of placental CRH regulation).

One might expect that, under conditions of high glucose levels, such as gestational diabetes, placental CRH production should be diminished. A complicating factor, however, is that high placental CRH levels may contribute to insulin insensitivity and hyperglycemia. Again, further research is needed into associations of gestational diabetes with CRH; one study yielded no link (Wolfe et al., 1988).

(c) Research finds a modest covariation between maternal CRH levels and ACTH

The placenta manipulates cortisol levels, in theory, via the effect of placental CRH on the release of ACTH from the maternal pituitary gland, which then stimulates the maternal adrenal glands to produce cortisol. Research has generally found covariation between CRH and cortisol levels (e.g. Goland et al., 1992, 1994; Chan et al., 1993; Magiakou et al., 1996; Wadhwa et al., 1997; Glynnt al., 2007; cf. Sandman et al., 2006). Investigations of associations between CRH and ACTH levels have produced mixed results. Wadhwa et al. (1997) and Goland et al. (1993) reported significant positive correlations; O’Keane et al. (2011) and Magiakou et al. (1996) found no robust association. Cortisol may affect placental CRH rather than vice versa (e.g. O’Keane et al., 2011).

In fact, placental CRH may affect cortisol production independent of increases in ACTH. CRH receptors exist in the adrenal cortex. CRH stimulation upregulates the impact of ACTH on cortisol production (Tsatsanas et al., 2007). Even in the absence of a direct effect on the maternal HPA system, then, placental CRH secretion can increase cortisol levels, which perhaps explains the fact that CRH covaries more reliably with maternal cortisol than with ACTH.

Independent evidence, however, indicates an effect of CRH on the maternal HPA system. Maternal CRH levels have been found to predict blood levels of β-endorphin (Wadhwa et al., 1997), another hormone secreted by the pituitary gland. Furthermore, ACTH and cortisol levels increase dramatically during the third trimester of human gestation, rendering human pregnancy a condition of hypercortisolism, and placental CRH appears to be the primary driver of these increased levels (e.g. Goland et al., 1992, 1994).

All in all, research firmly suggests that placental CRH does lead to increased maternal cortisol levels via both direct effects on ACTH secretion and by modulation of ACTH effects. There are also effects of cortisol itself on placental CRH secretion (see Sandman et al., 2006).
(d) The effects of CRH are multiple and complex

CRH receptors are found in many organs outside of the HPA axis: the uterus, liver, pancreas, skin, and brain regions outside of the HPA system (e.g. Hillhouse & Grammatopoulos, 2006). The current perspective locates a function of placental CRH in its effects on the HPA system and, ultimately, on maternal cortisol production. From this view, the variety of other effects of placental CRH represent either (1) non-functional byproducts of placental CRH (though, presumably, functional, beneficial effects of CRH secreted by individuals themselves, leading receptor sites to be shaped by selection), or (2) other functional effects of placental CRH. In light of the multitude of potential effects of CRH secreted by the placenta, one can reasonably ask why effects on cortisol production should be treated as the primary function of placental CRH.

Alternative views locate a primary function of placental CRH elsewhere. For instance, the placental clock hypothesis proposes a central role for placental CRH stimulation of receptors in the uterus and fetus.

In defence of the view that effects on cortisol are core functional ones, the effects of CRH on cortisol production, and the effect of cortisol on maternal metabolism, are neither obscure nor inconsequential. If not beneficial to the fetus, these effects are likely to be harmful to it; it would be surprising if they were so minor as to have no meaningful impact, positive or negative, on the fetus. Indeed, a weakness of the placental clock hypothesis is that arguments for it have not, to date, dealt with the effects of placental CRH on maternal metabolism.

Urocortin-1, -2, and -3 are peptides that share homology with CRH. Whereas CRH preferentially has high affinity for CRH-R1 receptors, and low affinity for CRH-R2 receptors, urocortin-1 has near-equal affinity for both receptor types, and urocortin-2 and -3 have higher affinity for CRH-R2 (and very little for CRH binding protein; see Section V.3d). Urocortin-2 and -3 are present in human placental tissue (Pepels et al., 2009) and are strongly expressed under certain conditions (e.g. hypoxia; Imperatore et al., 2010). In contrast to CRH, however, none of the urocortin peptides are markedly elevated in maternal plasma during pregnancy, and they do not show the increase at the end of gestation characteristic of CRH (Pepels et al., 2010). The placenta, then, does not appear to secrete urocortins into the maternal compartment to an appreciable degree. This pattern is consistent with the proposal that CRH is secreted partly for the function of stimulating the maternal HPA axis: release of ACTH in the pituitary occurs via CRH-R1 receptors, to which CRH has high affinity and urocortin-2 and -3 have low affinity. It is also, however, consistent with other functions of placental CRH secretion. As noted above, pro-inflammatory cytokine production may be mediated via binding to CRH-R1 receptors. And CRH may affect production of cortisol through CRH-R1 receptors in the adrenal gland as well (Tsatsanis et al., 2007; see Section IV.3e). [By contrast, CRH-R2 receptors are prominent in the liver; e.g. Simopoulos et al. (2009)]. Placental urocortin-2 and -3 may play roles as paracrine agents in the local synthesis of oestradiol (Pepels et al., 2010).

Even if placental CRH functions to manipulate maternal metabolism, alternative functions may have shaped other effects of placental CRH. One possible scenario, for instance, is that placental CRH secretion first evolved to affect maternal metabolism with mechanisms underpinning a role for placental CRH in a placental clock arising subsequently. Other functions then may have evolved as well. Little is known about placental CRH production in mammals other than primates (see Lovell et al., 2007, and Section IV.3e). Phylogenetic reconstruction of the evolution of placental CRH and its specific effects may ultimately address which function(s) are (in terms of evolutionary origin; Gould & Vrba, 1982) primary and which are secondary.

(e) Comparative data on placental CRH

As already noted, patterns of placental CRH production vary across monkeys and apes. In humans and anthropoid apes, weight gain and hence the metabolic demands of the fetus increase dramatically (~threefold) during the last trimester. Placental CRH levels also increase exponentially at this time. By contrast, in baboons (Van Calsteren et al., 2009), rates of fetal weight gain tend to be fairly constant from the mid-second through the third trimester. As noted above, in this species production of placental CRH peaks during the second trimester, then decreases and levels off during the third trimester. Similarly, in marmosets, owl monkeys, and squirrel monkeys, placental CRH production is maximal mid-gestation (Power et al., 2006, 2010), Power et al. (2006; their fig. 1), for instance, maximal placental CRH production estimated to be about day 67 in marmosets.

In several New World monkey species, fetuses grow and differentiate very little during the first trimester. Marmosets, for instance, complete organogenesis from day 50 through day 80 of a 144 day gestation, and experience near-constant growth from mid-gestation onwards [Jaquish et al. (1995) and Chambers & Hearn (1983); see also Schuler et al. (2010), on owl monkeys, in which growth rates are slightly greater from day 40–90 than day 90–133 (term)]. In light of greater maintenance costs as fetuses grow larger, overall energy demands are greatest during late gestation.

Why, then, does placental CRH production peak mid-gestation? One possibility is suggested by data on common marmosets Callithrix jacchus presented by Tardif et al. (2004). Pregnant marmoset females were put on modestly energy-restricted diets either mid-gestation (commencing ~day 67—at peak placental CRH production) or late-gestation (~day 99). Every fetus of mothers that were energy-restricted mid-gestation was lost preterm. By contrast, every fetus of mothers energy-restricted late-gestation was born live, at more than half normal term. In marmosets, lack of energy availability appears to be particularly devastating to fetuses mid-term. Although overall energy demands are greater during late gestation, the marginal benefit of increased access to energy may be greatest, in this species, mid-gestation. Perhaps, for that reason, selection has shaped
placental CRH production to be maximal at that time. Subsequent research showed that cortisol levels of energy-restricted females experiencing loss were low relative to females that delivered at full-term (Tardif et al., 2005).

Whether a similar explanation can account for patterns of placental CRH production in other New World monkeys or baboons may be investigated in future research. It is also possible that the function of placental CRH production differs across apes and monkeys (e.g. Power et al., 2006).

(f) The effects of cortisol on the fetus

The hypothesis that placental CRH functions to stimulate maternal production of cortisol conflicts with the assumption that maternal cortisol threatens the fetus. A defence of this hypothesis must address these purported threats. As this topic merits extended discussion, we consider it in detail in Section VII.

V. PLACENTAL CRH IN CONTEXT: MATERNAL-FETAL CONFLICTS OF INTEREST AND ANTAGONISTIC COEVOLUTION OF MOTHERS AND FETUSES?

(1) Maternal-fetal conflicts of interest over maternal metabolism

Haig (1993) famously applied parent-offspring conflict theory (Trivers, 1974) to an understanding of maternal-fetal interactions. Haig’s (1993) analysis builds on the idea that the optimal rate of transfer of nutrients (e.g. glucose) across the feto-maternal barrier differs between mothers and fetuses. That is, the rates of flow that best facilitate the fitness of offspring are not identical to the rates of flow that best facilitate the fitness of mothers.

Mothers can exert control over the settings that affect the rate of transfer (e.g. concentrations of glucose in the bloodstream, rate of blood flow to the placenta). But through the placenta, fetuses have access to the maternal bloodstream and hence can, in theory, manipulate those same settings via chemicals secreted into the bloodstream. As Haig (2008) notes, under highly favourable conditions, when glucose and lipids are in plentiful supply, the optimal settings affecting glucose flow for mothers and fetuses may be a matter of “no more than a petty squabble” (p. S39). By contrast, when the mother’s levels of current and anticipated resources are poor, “maternal and fetal interests can diverge markedly” (p. S39). For the fetus, too low a rate of growth and sustenance could threaten life itself, whereas a mother can replace a lost fetus with another. As ancestral humans may often have experienced conditions of physiological stress, both mothers and fetuses may have evolved to be prepared for conflict over maternal settings affecting nutrient flow. As Haig (2008) further notes, even small differences in optima can lead to the evolution of simple yet extensive attempts by each party to nudge the maternal settings in its own favour, for instance, by increasing or decreasing glucose availability for fetal consumption.

(2) Placental production of hGH-V in the context of maternal-fetal conflicts

As noted above, human mothers cease production of hGH during most of pregnancy, such that virtually all circulating hGH in the maternal bloodstream is of placental origin. Haig (2008) explains this fact: the placenta takes over the production of GH because optimal levels in the bloodstream differ for mothers and fetuses. For any non-zero level that the mother would produce to achieve an optimum, the placenta could produce more, moving production away from the maternal optimum. Hence, selection drives mothers to cease production of hGH. To date, no alternative theory can adequately explain cessation of maternal hGH production. [Although theory strongly argues that hPRL is similarly produced by fetuses against the interests of mothers, current evidence for this idea is less compelling. hPRL exerts its effects via hPRL and hGH receptors; there are no receptors unique to hPRL. Yet unlike hGH, mothers continue to produce hPRL. Haig (2008) conjectures why, within a maternal-fetal conflict framework.]

(3) Placental production of CRH in the context of maternal-fetal conflicts

(a) Placental versus maternal production of CRH

As pregnancy progresses, mothers reduce CRH-mediated production of cortisol in response to stressors, whereas the placenta produces massive quantities of CRH. Haig’s (2008) theory offers an explanation: conflict over levels of cortisol concentrations in the maternal bloodstream drive mothers to reduce production of CRH while fetuses counteract with a substantial increase.

(b) Maternal pituitary insensitivity to CRH as potential counterresponse

Maternal-fetal conflict theory furthermore offers an explanation as to why the maternal HPA system becomes less sensitive to stressors. In this view, maternal reductions in HPA-mediated production of cortisol in response to stress did not evolve to protect the fetus from the harmful effects of cortisol. Rather, they evolved to counteract fetal attempts to manipulate cortisol levels, and thereby blood glucose levels.

This explanation predicts that the phylogenetic distribution of maternal HPA suppression should mirror that of placental CRH production. HPA suppression in rats has been well documented (e.g. Brunton et al., 2008). It used to be thought that the rat placenta did not produce CRH (e.g. Robinson et al., 1989; see also Bowman et al., 2001) although recent evidence shows that it does (Lovell et al., 2007). Placental production of CRH has similarly been found in sheep during late pregnancy, although levels are much lower than observed in primates (e.g. Jones, Gu & Parer, 1989; Keller-Wood et al., 1991). Keller-Wood (1998) found no evidence...
of maternal suppression of HPA responsiveness to CRH in sheep, consistent with the idea that maternal HPA suppression co-evolves with placental CRH production, although Young & Rose (2002) found evidence of HPA suppression during late pregnancy. At present, little is known about the phylogenetic distribution of maternal HPA suppression and its relationship with placental CRH production.

(c) GH-binding proteins

Human mothers nearly cease production of hGH during the latter months of pregnancy. Beginning in the first trimester, they also produce large amounts of GH-binding protein (GH-BP) (e.g. Blumenfeld et al., 1992; Barnard, Fung-Yee & McIntyre, 1997; McIntyre et al., 2000). By binding to hGH, GH-BP renders hGH unable to bind to hGH receptors, and thereby unable to stimulate production of IGF-I and promote lipolysis of triglycerides. Hence, production of GH-BP offers a mechanism for mothers to counteract and neutralize placental production of hGH-V. While GH-BP may also function to create a pool of bound hGH that is available for use at a later time (e.g. Baumann, 2001), it is not clear how this would explain the increase in maternal production of GH-BP during pregnancy; if mothers were benefited by the presence of hGH then they would not cease production themselves. Hence, on theoretical grounds it seems likely that mothers produce GH-BP to inhibit, not facilitate, the actions of hGH-V. As levels of GH-BP late in pregnancy covary negatively with blood glucose levels, as well as with fetal head circumference and crown-heel length, empirical data too imply that production of GH-BP is due to its inhibitory effects on hGH-V (McIntyre et al., 2000).

(d) CRH-binding proteins

Quantities of CRH-binding protein (CRH-BP) are found in the maternal bloodstream during mid-term pregnancy (e.g. Linton et al., 1990, 1993; Perkins et al., 1995). Most placental CRH in the maternal bloodstream is bound by CRH-BP (e.g. Bowman et al., 2001). While there is no convincing evidence to demonstrate that pregnancy levels of CRH-BP exceed those in the non-pregnant state (Linton et al., 1993), CRH production itself suppresses levels of detectable CRH-BP, as the binding protein gets bound and cleared (Woods et al., 1994). Hence, equivalent levels during pregnancy and in the non-pregnant state, despite massive secretion of placental CRH, may actually reflect large increases in CRH-BP production. CRH-BP renders CRH biologically inactive (although CRH-BP may also facilitate certain actions of CRH; see Westphal & Seasholtz, 2006). CRH-BP is produced in both the maternal liver and the placenta. Currently, it is not known whether most circulating CRH-BP during pregnancy is of maternal or placental origin. The conflict hypothesis predicts that most CRH-BP in the maternal bloodstream is maternally produced. Thomsen (1998) argued that CRH-BP in the brain could explain why very high maternal CRH levels do not translate into similarly high ACTH levels (see also Linton et al., 1993). It is possible that placental CRH-BP could be largely directed towards protecting the fetus from effects of CRH, rather than entry into the maternal bloodstream (Petraglia et al., 1993). In the absence of evidence for the source of CRH-BP in the maternal bloodstream it is not possible to determine whether high levels of CRH-BP reflect a maternal adaptation to counteract placental production of CRH.

During the last month of pregnancy, both CRH-BP levels (Linton et al., 1993; Perkins et al., 1995) and GH-BP levels fall, (e.g. Blumenfeld et al., 1992). One possible reason is that, as parturition approaches, maternal-fetal conflicts over fetal access to glucose decline, leading to a reduction in maternal efforts to buffer the effects of CRH. An alternative explanation, however, is that the dramatic increase in CRH levels during the last month directly cause a reduction in CRH-BP levels by binding and clearance (Woods et al., 1994). Some research has shown that maternal HPA sensitivity returns during the latter phase of the third trimester (Teixeira et al., 2009; cf. Slattery & Neumann, 2000), possibly due to changes in the ratio of CRH to CRH-BP at that time.

Notable CRH-BP levels during pregnancy are found in most, but not all, other primate species with placental CRH production (e.g. Bowman et al., 2001; Power et al., 2010). In rats, high CRH-BP levels during pregnancy have not been detected (see Lovell et al., 2007). Unlike in humans, much CRH produced by the rat placenta remains in a preliminary form, meaning that levels of active placental CRH in the maternal bloodstream are lower than in humans. Possibly, the high levels of placental CRH in the maternal bloodstream observed in humans and apes evolved through antagonistic coevolution with maternal production of CRH-BP. Again, more comparative research is needed.

(e) Maternal HPA responsivity

In light of the substantial energetic demands of pregnancy, it makes sense that mothers may benefit from tapping into stored energy via the action of cortisol. The maternal-fetal conflict perspective merely requires that the optimal level of cortisol in the maternal bloodstream from the mother’s point of view is, on average, less than what is optimal from the point of view of the fetus. In certain circumstances, mothers may benefit from a higher level of cortisol production than that stimulated by the fetus. The fact that mothers cannot completely shut off the HPA response is, perhaps, why the fetus can manipulate these responses indirectly through production of placental CRH.

(4) An alternative view: mothers enable fetal regulation of glucose availability

An alternative view to that considered above is that some degree of fetal control is in both parties’ interests. Fetuses have access to information about their current state and requirements that is not available to mothers. Perhaps, then, it makes sense that fetuses partially regulate (and mothers permit fetuses to regulate) maternal blood levels of glucose.
Haig (1993, 2008) argues that consistent push-pull dynamics are signatures of maternal-fetal conflict. Hence, for instance, fetuses secrete hGH-V; mothers, by contrast, produce GH-BP (see Section V). Fetuses secrete peripheral vasoconstrictors; mothers produce vasodilators (Haig, 1993). Mothers appear to have reduced HPA sensitivity to CRH, and potentially produce and secrete large quantities of CRH-BP into their bloodstream. As noted above, these features may reflect push-pull dynamics indicative of conflict. Still, the fact that we have not yet identified the source of CRH-BP during pregnancy (maternal versus placent al) limits our ability to conclude in favour of the conflict hypothesis. Identification of the primary source of CRH-BP during the second and third trimesters could serve as a critical test of the conflict hypothesis.

A nuanced blend is possible. Even in the absence of conflict, maternal interests perhaps may be fostered by relinquishment of some regulation of maternal metabolism to fetuses, as discussed above. But particularly under conditions of energetic constraint, fetal regulation may conflict with maternal interests, activating maternal counter-measures. Hence, the extent to which fetal regulation acts against maternal interests may be condition-dependent. Below, we discuss ways in which levels of placental CRH production vary with conditions.

VI. VARIABLE PRODUCTION OF PLACENTAL CRH ACROSS INDIVIDUALS

(1) Placental CRH, fetal growth restriction, and placental resistance

Fetal growth restriction (IUGR) is reliably associated with unusually high levels of maternal placental CRH, even as early as the second trimester (e.g. Goland et al., 1993; Wadhwa et al., 2004; Power & Schulkin, 2006). Preeclampsia, characterized by poor placental implantation and hence poor fetal access to maternal nutrients as well as hypoxia, is also associated with high levels of placental CRH, even weeks before the onset of symptoms (e.g. Laatikainen et al., 1991; Goland et al., 1995; Florio et al., 2004). A measure of restriction of blood flow to the placenta, placental resistance, covaries positively with CRH levels (Harville et al., 2008).

In these conditions it has been suggested that high levels of placental CRH are harmful, and hence a component of the pathophysiology causing growth restriction (e.g. Petraglia, Imperatore & Challis, 2010). However, there is no definitive evidence to confirm this. An alternative interpretation readily is that in the face of restricted rates of glucose absorption, the placenta increases CRH production to attempt to extract additional glucose from mothers (for related views, see Schulkin, 1999; Florio et al., 2002). In this view, placental CRH does not cause the pathophysiology of growth restriction; rather, growth restriction reflects a condition under which the placenta has been selected to secrete greater amounts of placental CRH.

(2) The placental clock hypothesis revisited

As discussed above (Section III.2), high levels of placental CRH in the second trimester are associated with preterm birth, a link consistent with the CRH placental clock hypothesis. The current perspective offers an alternative interpretation. As a fetus grows, it demands an increasing rate of nutrient delivery, both to support growth and to support maintenance of its increasing mass. At some point in its growth, the metabolic demands of the fetus will exceed the rate at which glucose is transported across the maternal-placental interface. At this critical juncture, the fetus begins consuming its own fat reserves to meet energy demands (i.e. it begins to starve). It is then better to be born and to extract maternal nutrients via lactation rather than continue to run at a calor ic deficit (Ellison, 2001, 2003). According to this “metabolic cross-over” hypothesis, at this point the fetus will initiate labour. Fetal cortisol production appears to set off a cascade of events, not yet understood fully, that lead to parturition (e.g. Ellison, 2008).

From this perspective, an infant born preterm is simply one that reached the metabolic cross-over relatively early in gestation. Precipitating conditions include restricted bloodflow to the placenta, low levels of glucose in the maternal bloodstream (e.g. when the mother does not mobilize sufficient energy stores available to the fetus), and an inefficient fetal metabolism. Under these conditions, fetuses may secrete increased levels of placental CRH to attempt to enhance concentrations of glucose in the maternal bloodstream. By contrast, a postterm fetus is one whose ability to meet its metabolic demands in utero persists past its due date, conditions under which fetuses need not produce the same high levels of placental CRH.

The association between placental CRH levels and preterm birth, then, need not be due to direct or even indirect effects of placental CRH on labour, and one need not assume that the primary evolved function of CRH is to time parturition. That said, the view that high levels of placental CRH during the second trimester function to manipulate maternal metabolic processes is not incompatible with placental CRH having been co-opted in certain species, including humans, to participate in the cascade of events leading to labour (see e.g. Power & Schulkin, 2006).

(3) Placental CRH and conditions that lead to restricted fetal growth

Placental CRH levels should be associated with restricted growth and preterm birth and also with the conditions that lead to restricted growth. Research indicates that, at least in certain respects, this appears to be the case. High cortisol levels early in the second trimester predict high levels of CRH during the second and third trimesters, which in turn predict preterm birth (Sandman et al., 2006; Glynn et al., 2007; but see also lack of replication by Harville et al., 2009). Elevated cortisol levels early during pregnancy may reflect physiological or psychological stressors indicative of conditions relatively unfavourable for current reproduction and, hence, poor flow of nutrients to fetuses.
Other predictors of high placental CRH levels may include perceived inadequacy of income (Latendresse & Ruiz, 2010), perceived stress (Hobel et al., 1999; Mancuso et al., 2004; but see also Harville et al., 2009), and young age (Hobel et al., 1999; but see Harville et al., 2009). The first may be associated with poor nutritional status. The second may as well, although it is also possible that increases in placental CRH production overcome maternal suppression of the HPA axis, leading to perceived stress. Finally, maternal-fetal conflicts may be greater in youth, when a mother has reproductive opportunities ahead of her, compared to the end of a mother’s reproductive career. A fuller exploration of such predictors is needed.

(4) Variation in placental production of hGH-V in relation to placental CRH

Fetal production of hGH-V varies too, but the conditions that lead to increased production differ from those provoking increased production of placental CRH. In late pregnancy or at birth, a fetus that is growth-restricted tends to have a placenta that produces less hGH-V, not more, than normal fetuses (e.g. Mirlesse et al., 1993; McIntyre et al., 2000; Schiesel et al., 2007; Setia et al., 2007; Setia & Sridha, 2009). hGH-V levels late in pregnancy hence positively covary with birth weight (Chellakooty et al., 2004). By contrast, during the early second trimester, hGH-V levels in the bloodstream of mothers with preeclampsia carrying IUGR fetuses (Papadopoulou et al., 2006; cf. Sikafis et al., 2011) or Down’s syndrome fetuses (Papadopoulou et al., 2008; Sikafis et al., 2009) are high. hGH gene expression in the placenta is enhanced with IUGR during the second trimester (Sheikh, Satoshar & Bhatiya, 2001). High hGH-V levels may persist in mothers with preeclampsia whose fetuses grow to normal weight through the third trimester (Mittal et al., 2008).

These patterns suggest that the placenta of fetuses challenged with meeting nutritional needs first responds (early in the second trimester) by increasing hGH-V secretion into the maternal bloodstream. If this tactic succeeds, as is in the case of fetuses of preeclamptic mothers whose fetuses grow to normal weight, the placenta continues to produce high levels of hGH-V to term. If it fails, as in the case of IUGR fetuses, the placenta may shift its efforts and instead produce large quantities of placental CRH, thereby stimulating maternal production of cortisol. Ultimately, both hGH-V and cortisol should increase maternal blood glucose levels. Cortisol may affect metabolism through a broader array of pathways (e.g. through breakdown of proteins and glycolysis as well as fats), and has additional effects, both potentially beneficial to fetuses (e.g. vasoconstriction, reduction of inflammation) and detrimental to them (e.g. immunosuppression; see also Section VII). The primary additional effect of hGH is that it stimulates fetal growth through maternal production of IGF-1. During the third trimester, a growth-restricted fetus may not benefit from growth (which increases its energy demands) as much as from caloric intake to maintain neural and organ development. Consistent with this view, preeclampsia is also associated with increased placental stimulation of the production of pro-inflammatory cytokines (e.g. Germain et al., 2007), which may target insulin resistance and hence glucose availability for, not anabolic processes. Future research should address why the placenta of a stressed fetus shifts from producing hGH-V to placental CRH.

VII. DO FETUSES HARM THEMSELVES BY INCREASING MATERNAL CORTISOL LEVELS VERSUS PLACENTAL CRH?

(1) Effects on somatic growth and birth weight

(a) Evidence for effects of cortisol on fetal somatic growth

The hypothesis that the maternal HPA system suppresses production of cortisol during pregnancy to protect the fetus is based on a widely held assumption—that maternal cortisol harms the fetus (see e.g. Brunton & Russell, 2008). The hypothesis that placental CRH functions to stimulate maternal production of cortisol conflicts with this assumption.

Both correlational and experimental evidence has been used to support the claim that cortisol harms the fetus. Cortisol levels in pregnant women negatively predict infant birth weights (e.g. Austin & Leader, 2000; Diego et al., 2009; Bolten et al., 2011). One recent study measured morning cortisol levels in pregnant women during the second and third trimesters. Cortisol levels at both time points negatively covaried with birth weight, even after controlling for gestational age and pre-pregnancy BMI (Bolten et al., 2011).

Of course, correlational studies cannot establish causality. It is possible that poor access to nutrients (or other factors affecting growth, e.g. oxygen) causes increases in maternal cortisol levels, rather than vice versa. The placenta of a fetus that has poor access to nutrients may increase production of placental CRH, in turn stimulating higher levels of maternal cortisol. Consistent with this scenario, Bolten et al. (2011) found that mothers with high cortisol levels reported no greater levels of perceived stress or stressful life events than mothers with low cortisol levels (see also Sarker et al., 2008; Harville et al., 2009; Davis et al., 2011; cf. Diego et al., 2006). Placental CRH, not maternal stress, may be the primary driver of increased cortisol levels.

Experimental research includes studies on both non-human animals and humans. Injection of pregnant ewes with synthetic corticosteroids (betamethasone, dexamethasone) negatively affects the birth weight of lambs (e.g. Jobe et al., 1998, 2003). It is thought that reductions in birth weight are due to the catabolic effects of cortisol and its inhibitory effects on bone growth. Studies on humans do not achieve the same level of experimental control, but evidence strongly suggests that administration of betamethasone to pregnant women leads to lighter full-term infants (e.g. Banks et al., 1999; French et al., 1999; Bloom et al., 2001; Thorp et al., 2002). Even a single course of betamethasone appears to reduce birth weight (Davis et al., 2009). This procedure is used to improve lung maturation in fetuses expected to be...
preterm; cortisol has benefits to fetuses as well as potential costs, e.g. Muglia et al. (1995).

(b) **The 11βHSD2 placental barrier to cortisol**

The relevance of these studies for appreciating the effects of naturally circulating cortisol, however, is uncertain. The placenta produces an enzyme, 11 beta-hydroxysteroid dehydrogenase-2 (11βHSD2), which converts cortisol to an inactive metabolite, cortisone (e.g. Albiston et al., 1995). Placental 11βHSD2 production purportedly functions to protect the fetus from detrimental effects of cortisol (e.g. reduced growth). The synthetic forms of cortisol administered in these studies may not be effectively converted by 11βHSD2 into inactive metabolites (e.g. Jobe et al., 2003; but see Murphy et al., 2006) or may interfere with 11βHSD2 function (Vackova et al., 2009). Hence, these forms may pass unimpeded into the fetus. In fact, amniotic fluid levels of betamethasone following maternal administration reach, after three days, maternal serum levels (Anderson et al., 1977) although cortisol was detected at ∼2% of maternal levels following cortisol administration (e.g. Glover et al., 2009). If maternal betamethasone readily reaches the fetus, but little cortisol does, then effects of circulating betamethasone need not generalize to cortisol. And, indeed, Jobe et al. (2003) found that, whereas maternal administration of betamethasone reduced the birth weight of ewes, administration of an equal amount of cortisol had no effect. Though the placental barrier inhibits transfer of maternal cortisol into the fetus, it does so imperfectly. Gitau et al. (1998, 2001) measured cortisol levels in the plasma of women and their fetuses. Fetal levels were only about 7–9% that of women, consistent with 11βHSD2 being a placental barrier. At the same time, however, maternal levels positively covaried with fetal levels (see also Murphy et al., 1974). Studies examining associations between maternal blood levels of cortisol and levels in amniotic fluid (which arguably have almost exclusively fetal origins) yield modest but reliable correlations as well (e.g. Sarker et al., 2007, 2008; Glover et al., 2009). Two studies found a moderating influence of maternal stress—little association for relatively unstressed women, but an increased association for stressed women (Sarker et al., 2008; Glover et al., 2009)—leading to speculation that maternal stress or a correlated feature affects the capability of the 11βHSD2 barrier. In fact, a number of factors (e.g. infection, inflammation, protein restriction, hypoxia), reduce 11βHSD2 activity (Seckl & Holmes, 2007; see also Edwards et al., 1996; Ni et al., 2009).

That said, the implications of a correlation between maternal and fetal cortisol levels should not be overstated. Even if due to unmetabolized maternal cortisol crossing the placenta into the fetus (and other causal scenarios are possible, particularly as fetal and maternal HPA responses are independent; Gitau et al., 2001), it need not mean that seriously harmful levels reach the fetus when the 11βHSD2 barrier is functioning normally. Regression equations (Gitau et al., 1998, 2001) imply that a 500 nmol l⁻¹ increase in cortisol concentration in maternal serum (1.5 standard deviation change) results in just a 30 nmol l⁻¹ increase in fetal serum concentration—5% of the increase in maternal levels. Atypical compromises in the 11βHSD2 barrier might lead to seriously detrimental levels.

(c) **Stressful events during pregnancy and birth weights**

Another set of findings is perhaps pertinent. A number of studies have examined the outcomes of pregnancies during which a widely stressful event occurred (e.g. the 9/11 World Trade Center attack, Hurricane Katrina, other natural disasters, the death of a loved one). Harville, Xiong & Buekers (2010) recently reviewed this work, and concluded that women pregnant during these events gave birth to slightly smaller infants (although results are not consistent; see also Class et al., 2011). One conjectured mechanism is that stress increases cortisol levels, which then reduces fetal growth (e.g. Smits et al., 2006). But as Harville et al. (2009, 2010) note, other causal routes are possible. For instance, stressed women may have smoked or used substances more; their diet may have been affected; stress can affect other systems, such as immune function and vasculature (Dunkel Schetter & Glynn, 2011). In some studies (e.g. Smits et al., 2006; Khashan et al., 2008) specific confounds (e.g. smoking) have been controlled. But in the absence of direct measurements of cortisol levels, it is difficult to attribute any effects to it. In light of near-zero correlation between perceived stress and cortisol levels during late pregnancy (e.g. Harville et al., 2009), some researchers doubt that cortisol mediates the effects of perceived stress on fetal outcomes (e.g. Davis et al., 2011a).

(2) **Effects on fetal programming**

(a) **The putative effect of cortisol on settings of the fetal HPA axis**

In addition to growth, cortisol purportedly affects other offspring outcomes. Most notably, fetal levels of cortisol may affect the “settings” of the HPA axis in the offspring. Babies born at low birth weight are at risk for a variety of cardiovascular diseases in later life, including hypertension, diabetes, and heart disease (reviewed by Barker, 2004). One hypothesized mediator is heightened levels of prenatal cortisol in the fetus, increasing the responsivity of the HPA axis and, due to vasoconstrictive and metabolic effects of cortisol accumulated over time, in turn giving rise to hypertension and insulin resistance (e.g. Seckl, 2001; Seckl & Holmes, 2007). As already noted, small fetuses produce high levels of placent al CRH, which stimulates production of maternal cortisol, and offspring birth weight covaries negatively with maternal cortisol levels.

The association between low birth weight and HPA axis responsivity has been empirically supported (although not in every study; e.g. Clark et al., 1996; Dahlgren et al., 1998; Phillips et al., 1996, 2000; Levitt et al., 2000; Kajantie et al., 2002; Ward et al., 2004). Until recently, no study had examined directly the association between maternal cortisol levels and HPA reactivity of newborns. Davis et al. (2011a) found that maternal cortisol levels measured on
four occasions during the last half of pregnancy covaried positively with newborn cortisol responses to a heel-stick. A second study demonstrated that a single administration of betamethasone prenatally similarly affected newborn HPA reactivity to a heel-stick (Davis, Waffarn & Sandman, 2011).

(b) Fetal programming: pathological outcomes or adaptively contingent responses?

Heightened HPA responsivity and downstream effects have received multiple interpretations (see Ellison, 2010). Some describe them as pathological outcomes of a “dysregulated” HPA axis (e.g. Weinstock, 2005). Others propose that they reflect contingently adaptive development (e.g. Gluckman & Hanson, 2006, 2010). Fetuses experiencing poor nutrition in utero may expect a post-birth world of food scarcity. The developmental trajectory of these fetuses may yield phenotypic features suitable for that world: by enhancing insulin resistance, cortisol reduces metabolic rate and growth, and instead favours sequestering of fat, features that might serve well an individual facing food shortages (even if maladaptive in a modern world in which cheap fat is readily available).

Some theorists have questioned the evolutionary plausibility of this particular argument for adaptive plasticity (Jones, 2005; Rickard & Lummaa, 2007)—in particular, its assumption that the in utero experience of a fetus predicts conditions during its future life. Fetal growth restriction can have multiple causes, some independent of the nutritional status of the mother. And food shortages (e.g. due to drought) in hominid history may have often been short-lived. Rather than preparing the individual for a lifetime of food shortage, then, developmental trajectories of low-birth-weight babies may be best construed as short-term strategies. Organisms develop under constraints of energy consumption. A fetus with access to fewer calories has, de facto, less energy to dedicate to growth and development. Its optimal allocation of energy may also differ from that of a better fed fetus. Consistent with this idea, Barker et al. (2002) proposed that a food-limited fetus trades off development of organs of the gut to protect brain development. Furthermore, although a fetus with limited access to energy may not be able to predict similar circumstances throughout its life, it may well expect such circumstances in the short term; hence, it may be better to limit skeletal growth. It may also be best off with a reactive HPA system (Rickard & Lummaa, 2007). The HPA system was likely designed by selection to respond to energetic stress by metabolizing stores of energy, and an individual likely to experience energetic stress often may benefit from a relatively quick “trigger” of this response.

In theory, it is plausible that in utero fetal cortisol levels mediate adaptive development contingent upon access to nutrients. Nutritionally stressed mothers may experience greater levels of cortisol (whether due to placental CRH or their own response). Recurrently through evolutionary time, then, maternal cortisol concentrations may well have been a reliable cue to conditions precipitating nutritional stress. If a small percentage of unmetabolized maternal cortisol crosses the placental barrier into the fetus, selection may have favoured contingent development (e.g. of the HPA axis) dependent on this cue.

In this view, maternal cortisol levels covary with relatively poor fetal outcomes. But maladaptation is not due to the presence of cortisol itself. Rather, conditions associated with maternal cortisol levels constrain the level of functioning the fetus can achieve. Developmental responses to cortisol have been selected to make the best outcome achievable under those poor circumstances: Cortisol-dependent developmental trajectories in utero may be contingent responses to mitigate partially the possible costs associated with energetic stresses (e.g. Jones, 2005; Rickard & Lummaa, 2007).

Once again, the hypothesis that women’s HPA axis becomes insensitive to CRH for the function of protecting the fetus from cortisol assumes that, in the absence of these inhibitory effects on the HPA axis, cortisol would cause pathology and maladaptation in fetuses. And once again, evidence for this assumption is far from compelling.

VIII. CONCLUSIONS

(1) This review addresses the evolution of a very specific feature: why does the placenta in humans and, perhaps, other anthropoid primates, produce and secrete massive amounts of CRH? Our conceptualization of a variety of disparate, and yet interconnected literatures has allowed us to advance novel interpretations.

(2) Our interpretation of the growing literature on the CRH placental clock hypothesis suggests that it reflects placental CRH secretion contingent on a low flow of nutrients to the fetus, which leads to an early metabolic cross-over and hence initiation of birth.

(3) Our perspective contrasts with the widespread view that maternal cortisol is generally detrimental to the fetus; covariation between cortisol levels and infant outcomes may be largely due to the fact that placentas of fetuses poorly supplied with nutrients adaptively secrete high levels of placental CRH, and/or to contingent fetal and infant tactics for dealing with conditions of low flow of nutrients.

(4) In this view, the blunting of maternal HPA responsivity, rather than primarily functioning to protect the fetus, may well function in the interests of the mother.

(5) Placental CRH production is placed in a broader conceptualization of maternal-fetal conflicts of interest, consistent with a coherent framework for understanding the costly placental production of hormones (Haig, 2008).

(6) Production of placental CRH is also considered in the context of fundamental transactions between mothers and fetuses. Fetal growth and development demand tremendous amounts of energetic resources. Provisioning of those resources trades off against energy that mothers can allocate to other fitness-enhancing activities. Cortisol and, by extension, CRH play fundamental roles in modulating utilization and allocation of resources.

(7) Previous conceptualizations of the function of placental CRH production have virtually ignored the effects of the
HPA axis on metabolism and energetics. Yet some of the primary beneficial effects of placental CRH to fetuses pertain to these energetic effects. Our most fundamental claim is precisely this point.

(8) While a central thrust of this paper has been to propose a novel functional framework for understanding placental CRH production and to review and re-interpret about the veracity of the hypothesis. Another purpose of placental CRH production and to review and re-interpret propose a novel functional framework for understanding to these energetic effects. Our most fundamental claim is primary beneficial effects of placental CRH to fetuses pertain to fetal growth.

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