

Corticotrophin releasing hormone and the timing of birth

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1. ABSTRACT

Corticotrophin-releasing hormone (CRH) is the hypothalamic peptide that controls the function of the pituitary-adrenal axis in response to stress. CRH is also expressed abundantly in the human placenta and is present in high concentrations in maternal and fetal plasma during late pregnancy. During pregnancy, CRH derived from the placenta is thought to play a crucial role in the regulation of fetal maturation and the timing of delivery, and CRH has also been implicated in the control of fetal-placental blood flow. Elevated CRH concentrations, as compared with gestational age matched controls, occur in patients in preterm labour. The exponential curve depicting the CRH increase is shifted to the left in women who will subsequently deliver preterm and to the right in women who will deliver post dates. This has led to the suggestion that CRH production is linked to a placental clock which determines the length of gestation. Clinically, maternal plasma CRH concentrations may be useful in identifying women at high risk of preterm delivery and CRH antagonists may be useful in preventing preterm labour. As significant CRH production by the placenta is restricted to primates, future research must take into account the species specificity of the mechanisms regulating parturition. A number of significant gaps remain in our knowledge of the function of this peptide in pregnancy. This review examines the current evidence regarding the role of CRH in human parturition.

2. CRH IS IDENTIFIED IN THE PLACENTA

Corticotrophin Releasing Hormone (CRH) was first identified by Wiley Vale in extracts from a lung tumour. In 1981 Vale published work describing the critical role this peptide plays in hypothalamic regulation of ACTH production from the anterior pituitary (1). The following year Shibasaki *et al* (2) made the unexpected discovery that this peptide was also present in high concentrations in the human placenta. Two years later high concentrations were found in the circulation of pregnant women (3). Interestingly, there are only very low concentrations of this hypothalamic peptide in the blood of men and non-pregnant women even in the presence of major stress stimuli. Thus, for the human, pregnancy is the only time when the peripheral circulation contains high concentrations of the peptide. The exact role of this peptide during pregnancy remains unknown but it has been linked to the timing of birth and vasodilatation.

3. CHARACTERISING CRH IN THE BLOOD OF PREGNANT WOMEN

Following the initial studies by Shibasaki and Sasaki, Robyn Goland in the USA (4) and Elizabeth Linton and Phil Lowry in the UK (5-7), made substantial progress in defining the pattern of rise during pregnancy and the relationship to pathological states of pregnancy. Goland reported concentrations rising to peak at term and that cord

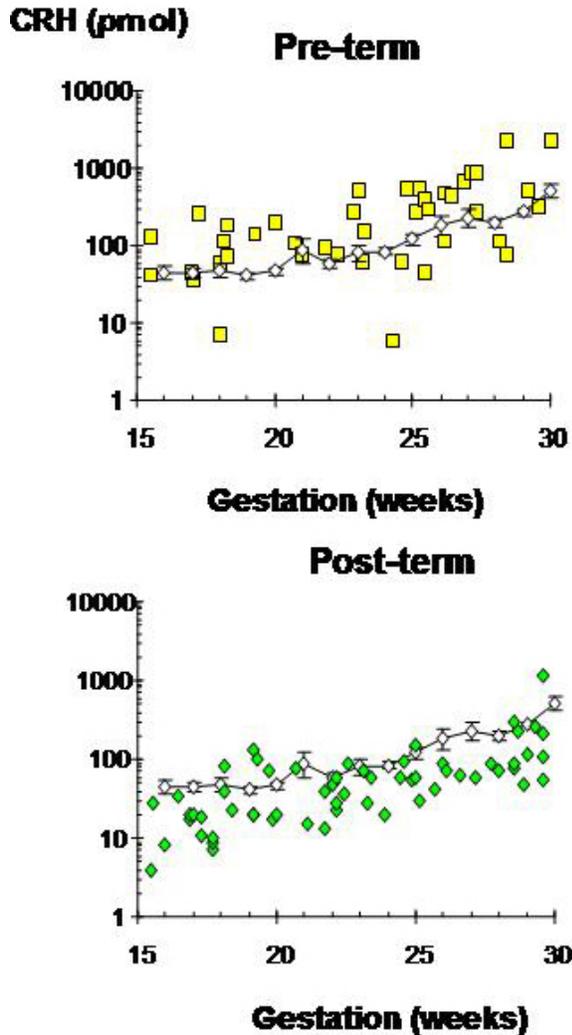


Figure 1. Maternal plasma CRH in pre-term and post-term deliveries. Reprinted with permission from McLean *et al* (15).

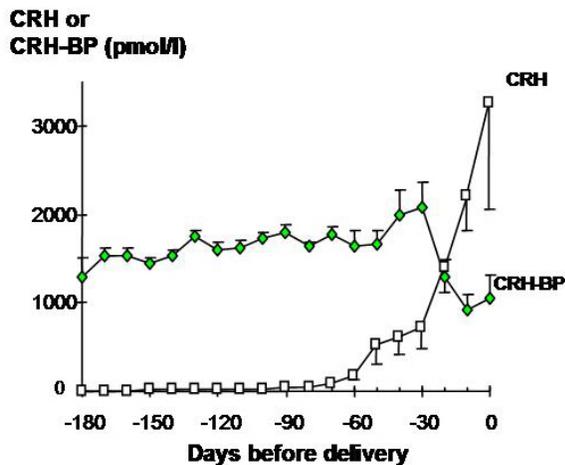


Figure 2. Maternal plasma CRH and CRH-BP before spontaneous term labour. Reprinted with permission from McLean *et al* (15).

blood CRH was elevated, and correlated with maternal CRH, strongly supporting a placental origin for circulating CRH during pregnancy. Both Goland's group and the Linton/Lowry team reported that women in preterm labour had elevated concentrations of maternal plasma CRH relative to gestational age-matched controls (Figure 1). Elevated levels were also reported in subjects with pre-eclampsia.

4. THE EFFECT OF PLACENTAL CRH ON THE MATERNAL HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

An early question concerned the impact of placentally derived CRH on the functioning of the maternal hypothalamic-pituitary adrenal axis. It was known that cortisol excretion increased as pregnancy advanced and that pro-opiomelanocortin derived peptides such as ACTH also increased marginally in maternal plasma with advancing gestation. Several studies on cohorts of pregnant women were examined to determine if a correlation existed between maternal plasma CRH and pro-opiomelanocortin molecules or cortisol. Studies were made difficult by the variability in ACTH levels and the variability in cortisol associated with diurnal and stress related patterns of secretion. While the association is not strong, a weak relationship was observed in some of the larger studies (8).

It seems likely that the slight increase in ACTH observed during pregnancy is related to placental production of CRH but workers puzzled over the relatively modest nature of this increase. Two explanations have been advanced. Firstly, blunting of the ACTH response to CRH was observed in late pregnancy and this continued into the immediate postnatal period. Studies on the perfused pituitary indicated that down regulation of CRH receptors occurred following chronic exposure to CRH (9). This pattern of a relatively modest ACTH response to chronically elevated CRH levels was also observed in the rare patients who developed Cushing's Syndrome due to ectopic production of CRH. It seems likely that CRH receptor down regulation largely protects the mother's pituitary-adrenal axis from over-stimulation during pregnancy. However, a second important factor may be the binding protein for CRH (CRH-BP) that has been studied extensively, initially by Phil Lowry's group in the UK (10), and more recently by Audrey Seasholtz's group in the USA (11, 12). The tight binding between CRH and CRH-BP largely prevents the peptide from exerting biological actions until the capacity of the binding protein has been saturated late in pregnancy (10). Additional work has demonstrated that when saturation of the binding protein occurs the binding protein dimerises and the clearance of the CRH-binding protein complex increases reducing the CRH binding capacity of the plasma and increasing the biological activity of residual CRH (Figure 2).

5. CRH AND PLACENTAL VASCULAR REGULATION

At an early stage in the investigation of the physiology of CRH it was noticed that human subjects

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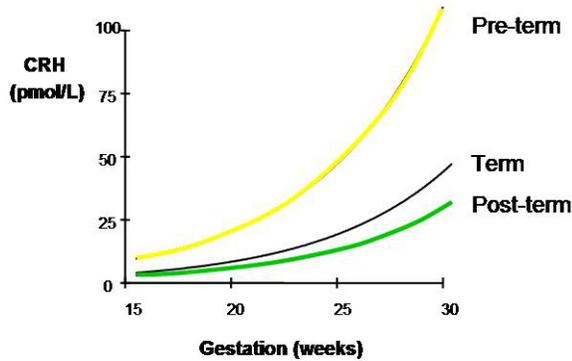


Figure 3. Maternal plasma CRH versus Gestation. Reprinted with permission from McLean *et al* (15).

frequently experienced a flushing sensation and sometimes hypotension that suggested a vascular action. This combined with the studies that reported an association between maternal CRH and pre-eclampsia provoked further investigation of the role of CRH in the regulation of placental blood flow. Studies by Clifton *et al.*, firstly determined that CRH receptors were present in the placenta and then that CRH was a powerful vasodilator in this vascular bed (13, 14). CRH appears to cause vasodilation via a nitric oxide mediated pathway that leads to mast cell degranulation. More recent work suggests that these effects may occur predominantly via the type 2 CRH receptor which is also recognised by the urocortins, which are peptides that belong to the CRH peptide family.

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6.1. CRH as a biological clock

Following the initial work of Goland and Lowry, several groups have examined the relationship between maternal plasma CRH and the timing of birth. The first large prospective study was conducted by McLean *et al* (15). This study in approximately 500 unselected pregnancies identified that CRH rose exponentially to peak at the time of birth and that subjects who delivered preterm had a more rapid rate of rise that was detectable from early in the second trimester, in contrast women who delivered post-dates had a slower rate of rise that was again demonstrable from early in pregnancy (Figure 3). These data lead to the hypothesis that the length of human pregnancy was determined early in pregnancy by a type of biological clock that was linked in some way to the placental production of CRH. Similar data have now been reported by many different groups (16-19).

6.2. Ethnic influences on CRH

One early study failed to identify a statistically significant relationship between maternal plasma CRH and the timing of birth (20). Interestingly, the cohort for the negative study contained a racially mixed sample. More recent work has revealed that African Americans have, in general, lower levels of maternal plasma CRH than other racial groups, but African American women delivering preterm still demonstrate a high maternal plasma CRH for their racial group (21, 22). It is likely that important racial

differences exist in the CRH gene which has a very high number of described polymorphisms.

6.3. Other means of elevating CRH

While the relationship between maternal plasma CRH and the timing of birth has proved robust in many studies, in individual subjects maternal plasma CRH has a high specificity but a relatively low sensitivity, meaning women may deliver prematurely without having an elevated plasma CRH. Preterm birth may be a consequence of multiple different pathologies from infection to multiple gestations and premature rupture of the membranes and retroplacental haemorrhage, in addition to elevated placental production of CRH. Many of these different pathologies are probably not linked to CRH production, reducing the predictive power of an individual maternal plasma CRH measurement. However, in many situations that produce fetal stress, such as small for gestational age (23, 24), reduced umbilical artery blood flow (25) and reduced scalp vein pH, CRH production is elevated. Additionally in women who undergo preterm elective caesarian section due to obstetric concern for fetal well-being, CRH concentrations rise more rapidly in maternal plasma (26). This suggests that fetal-placental signalling can influence placental CRH production and potentially the timing of birth.

7. ANIMAL MODELS FOR PLACENTAL CRH PRODUCTION

Discovery of substantial placental CRH production and the linkage to significant pathologies such as preterm birth and pre-eclampsia has provoked interest in identifying appropriate animal models. Early studies by Robinson *et al* (27), established that CRH was only expressed in the placentas of primates. Within the order of primates, lemurs do not express placental CRH but all other members examined have demonstrated substantial CRH expression (28). Expression of CRH-BP in maternal plasma is more variable, with apes appearing to possess the protein, but new and old monkeys demonstrating variability in this characteristic in an unpredictable fashion (29). This variability in CRH-BP expression is likely related to the structure of the promoter. The CRH-BP promoter contains a liver expression cassette and a signal peptide. If the protein is expressed in the liver it is promptly secreted into the maternal circulation and, although the issue has not been carefully explored, it seems probable that mutations that affect the liver expression cassette determine if a given species possesses a circulating CRH-BP.

While all primates except the lemurs express CRH in placental tissue the pattern of production across pregnancy varies considerably. In baboons and marmosets maternal plasma CRH peaks in mid-gestation, while humans, chimpanzees and gorillas exhibit an exponential rise peaking at the time of delivery (30). The situation in rhesus monkeys is less clear as sampling has not been conducted across the full length of gestation. Interestingly, maternal plasma CRH binding protein concentrations in the gorilla fall in the last few weeks of pregnancy as observed

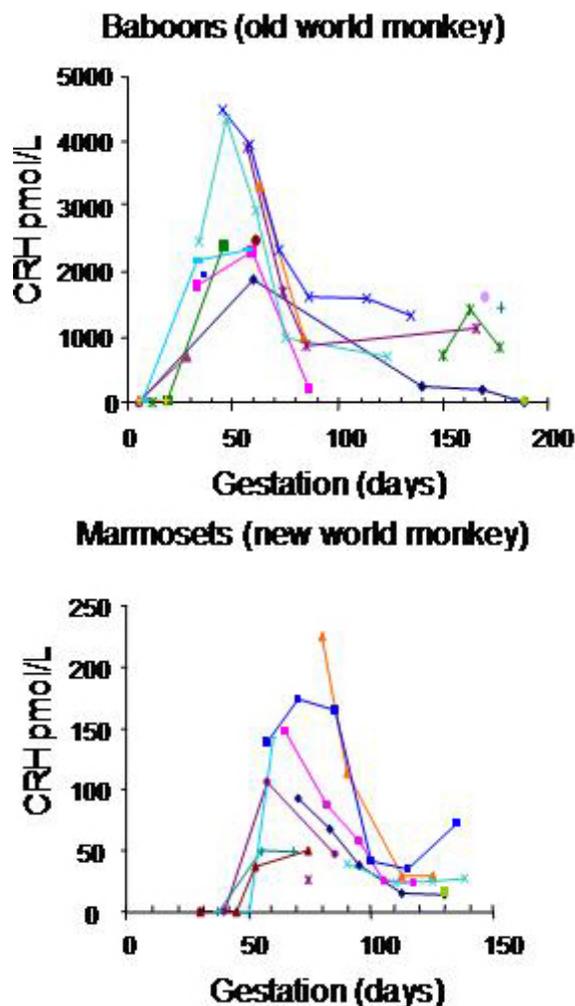


Figure 4. CRH in Pregnant New and Old World Monkeys. Baboons data republished with permission from Bowman *et al* (29); Marmoset data republished with permission from Power *et al* (47).

in the human (Figure 4). The topic of primate CRH has recently been thoroughly reviewed (31).

8. FACTORS THAT DETERMINE THE PRODUCTION OF CRH IN THE PLACENTA

While the factors that permit CRH gene expression in primate placentas but not in those of other mammals is unclear there has been considerable investigation of CRH gene and protein regulation in human placental tissue. Felice Petraglia and co-workers in Italy examined the regulation of placental peptide secretion using primary placental cultures (32). Stimulation was observed with a wide range of neuropeptides and neurotransmitters. Studies by Joe Majzoub and co-workers in the USA extended these studies using northern analysis for the CRH gene mRNA. In these studies a prominent finding was a stimulation of CRH protein and gene expression by glucocorticoids (33). This finding was unexpected because in the hypothalamus glucocorticoids suppress CRH production.

The stimulation of CRH gene expression by glucocorticoids permitted a new understanding of the exponential rise in CRH which had been observed during pregnancy. If CRH stimulated glucocorticoid production and glucocorticoids stimulated CRH production, a positive feed forward system could be generated that would lead to an exponential rate of increase in CRH as observed in human pregnancy. The mechanism of glucocorticoid regulation of CRH gene expression has been investigated and found to operate, through a non-classical mechanism, at the cyclic AMP response element (CRE) in the CRH promoter (34, 35). Similarly, other regulators such as estrogen and progesterone have been shown to also modulate the expression of CRH in the placenta through the CRE (36, 37).

9. CRH AND THE MYOMETRIUM

While the production of CRH within the placenta has been examined, and circulating concentrations defined, a major question remains concerning the physiological target of placentally produced CRH. CRH receptors have been identified in the human myometrium (38-42). Myometrial CRH receptors are biochemically heterogeneous and alternative splicing gives rise to multiple forms of the products of the two CRH receptor genes: CRHR1 and CRHR2. The variations in receptors may well have important physiological consequences as the different receptors link differently to second messenger signalling pathways which then promotes either contractile or relaxatory mechanisms within the myometrial cell. Dimitris Grammatopoulos and Ed Hillhouse in the UK have been major contributors to this literature (43). A specific hypothesis is that heterologous or homologous down regulation of the CRH receptor cyclic AMP signalling pathway occurs at term leading to reduced relaxatory activity and consequently an increase in contractility (44). This is an interesting but as yet unconfirmed possible role for maternal CRH.

10. CRH AND THE FETAL ADRENAL

During fetal life the adrenal gland is relatively large compared to that of the adult human. The large size of the fetal adrenal gland is due to a zone, the fetal zone that produces the steroid DHEA-S that is a critical precursor for placental estrogen production. The fetal zone atrophies and disappears shortly after birth. A collaborative project between US and Australian workers identified the presence of CRH receptors in the human fetal adrenal gland and determined that CRH could directly stimulate DHEA-S production in cells cultured from the fetal zone of the human fetal adrenal (45). This work has recently been confirmed by a second group (46). CRH in the fetal circulation may therefore have a critical role in placental steroidogenesis.

11. PERSPECTIVES

Corticotrophin releasing hormone is produced in large amounts by the human placenta. Placental CRH is secreted into the maternal circulation predominantly where

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a potential target is the myometrium of the uterus. Placental CRH is also released into the fetal circulation where a likely target is the fetal adrenal which expresses CRH receptors and, *in vitro*, responds to CRH by increasing synthesis of DHEA-S a critical precursor for placental estrogen production. The rise of CRH in maternal plasma follows an exponential curve and the rate of rise is related to the timing of birth with rapid increases associated with preterm birth and slow rises with post dates delivery. CRH also has potent vasodilator effects in the placental circulation. CRH is a likely determinant of the timing of human birth but the exact pathways that mediate this effect remain unclear.

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Key Words: Corticotrophin-Releasing Hormone, Placenta, Gestation, Pregnancy, Preterm labour, Corticotrophin-Releasing Factor, Review

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