Corticotropin-releasing hormone, stress and human reproduction: an update

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Abstract

The stress system has suppressive effects on female and male reproductive function. Corticotropin-releasing hormone (CRH), the principal regulator of stress, has been identified in the female and male reproductive system. Reproductive CRH participates in various reproductive functions that have an inflammatory component, where it serves as an autocrine and paracrine modulator. These include ovarian and endometrial CRH, which may participate in the regulation of steroidogenesis and the inflammatory processes of the ovary (ovulation and luteolysis) and the endometrium (decidualization and blastocyst implantation) and placental CRH, which is secreted mostly during the latter half of pregnancy and is responsible for the onset of labor. It has been suggested that there is a “CRH placental clock” which determines the length of gestation and the timing of parturition and delivery. The potential use of CRH-antagonists is presently under intense investigation. CRH-R1 antagonists have been used in animal studies to elucidate the role of CRH in blastocyst implantation and invasion, early fetal immunotolerance and premature labor. The present review article focuses on the potential roles of CRH on the physiology and pathophysiology of reproduction and highlights its participation in crucial steps of pregnancy, such as implantation, fetal immune tolerance, parturition and fetal programming of the hypothalamic–pituitary–adrenal (HPA) axis.

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1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis along with the arousal and autonomic nervous systems constitute the stress system. The stress system is activated in a coordinated fashion during stress, influencing central and peripheral functions that are important for adaptation and survival (Chrousos and Gold, 1992). Stress has suppressive effects on the female and male reproductive systems.

The main central regulators of the HPA axis are corticotrophin-releasing hormone (CRH) and arginine-vasopressin (AVP), both produced by parvicellular neurons of the paraventricular nucleus of the hypothalamus into the hypophysial portal system (Chrousos and Gold, 1992). CRH and AVP synergistically stimulate pituitary adrenocorticotropic hormone (ACTH) secretion and subsequently, glucocorticoid secretion by the adrenal cortex. CRH and its receptors are also found in many extra-hypothalamic sites of the central nervous system, playing a major coordina-
tive role for the stress response (Chrousos et al., 1998). Three CRH receptor genes have been identified so far—CRH-R1, CRH-R2, and CRH-R3 (Hillhouse and Grammatopoulos, 2006; Kalantaridou et al., 2007). In mammals, only the CRH-R1 and CRH-R2 receptors have been identified (Hillhouse and Grammatopoulos, 2006), whereas the CRH-R3 has only been identified in the catfish (Zoumakis et al., 2009). Furthermore, the biological effects of CRH are modulated by CRH-binding protein (CRH-BP), which controls CRH bioavailability (Smith, 2007).

CRH and its receptors have also been identified in the female and male reproductive system. Thus “reproductive” CRH is a form of “tissue” CRH, i.e., CRH found in peripheral tissues. Reproductive CRH participates in various reproductive functions with an inflammatory component, where it serves as an autocrine and paracrine modulator. These include ovarian and endometrial CRH, which may participate in the regulation of steroidogenesis and the inflammatory processes of the ovary (ovulation and luteolysis) and the endometrium (decidualization and blastocyst implantation) and placental CRH, which is secreted mostly during the latter half of pregnancy and is responsible for the onset of labor.

The present review article focuses on the potential roles of CRH on the physiology and pathophysiology of reproduction and highlights its participation in crucial steps of pregnancy, such as implantation, fetal immune tolerance in early pregnancy, parturition and fetal programming of the HPA axis.

2. Effect of stress on female and male reproduction

An increased glucocorticoid activity is the hallmark of stress. As the end product of the HPA axis, glucocorticoids have a wide range of effects in multiple systems involved in growth, maintenance and reproduction.

The HPA axis, when activated by stress, exerts an inhibitory effect on the female reproductive system (Fig. 1). CRH and CRH-induced proopiomelanocortin peptides, such as β-endorphin, inhibit hypothalamic GnRH secretion (Chen et al., 1992). In addition, glucocorticoids suppress the female gonadal axis function at the hypothalamic, pituitary and uterine level (Sakakura et al., 1975; Rabin et al., 1990). Indeed, glucocorticoid administration significantly reduces the peak luteinizing hormone response to intravenous GnRH, suggesting an inhibitory effect of glucocorticoids on the pituitary gonadotroph (Sakakura et al., 1975). Furthermore, glucocorticoids inhibit estradiol-stimulated uterine growth (Rabin et al., 1990). These effects of the HPA axis are responsible for the “hypothalamic” amenorrhea of stress, which is observed in anxiety and depression, malnutrition, eating disorders and chronic excessive exercise, and the hypogonadism of the Cushing syndrome (Chrousos et al., 1998).

Stress exerts inhibitory effects on the male reproductive system as well (Fig. 1). Glucocorticoids inhibit testosterone production by Leydig cells (Orr et al., 1994). In addition, experimental evidence suggests that chronic stress may further decrease LH secretion (Norman, 1993; Orr et al., 1994; Almeida et al., 1998). These changes result in diminished libido and fertility (Phillips et al., 1989). In humans, the severe psychological stress brought on by the death of a relative or spouse lowers sperm count (Fenster et al., 1997). Although this effect may occur due to the stress-induced testosterone decrease, direct effects of stress on the seminiferous epithelium have also been reported (Yazawa et al., 1999). The extent of glucocorticoid activity in the testis is modulated by metabolism catalyzed by 11β-hydroxysteroid dehydrogenase (Hu et al., 2008). This enzyme is bidirectional, with both oxidase and reductase activities, and in the rat testis is exclusively localized in Leydig cells where it is abundantly expressed and may catalyze the oxidative inactivation of glucocorticoids.

Increased glucocorticoid levels are responsible for the hypogonadism of men with Cushing syndrome (Smals et al., 1977; Chrousos et al., 1998). Interestingly, preliminary evidence suggests that testosterone levels in adult males may be lower after stress in individuals that had been exposed to maternal or early postnatal stress compared to individ-
uals that were not stressed prenatally (Barbazanges et al., 1996).

3. CRH in the reproductive system

3.1. CRH in the female reproductive system

3.1.1. Ovarian CRH

Ovarian CRH is primarily localized in thecal cells surrounding the ovarian follicles, in luteinized cells of the stroma and also in the cytoplasm of the ovum (Mastorakos et al., 1993). In vitro experiments indicated that CRH exerts an inhibitory effect on ovarian steroidogenesis in a dose-dependent, interleukin (IL)-1-mediated manner (Calogero et al., 1996; Ghizzoni et al., 1997), suggesting that increased ovarian CRH concentrations might be related to premature ovarian failure observed in women exposed to high psychosocial stress (Bromberger et al., 1997).

There is no detectable CRH in oocytes of primordial follicles in human ovaries, whereas there is abundant expression of the CRH and CRH-R1 genes in mature follicles, implying that CRH may play autocrine and paracrine roles in follicular maturation (Asakura et al., 1997). Polycystic ovaries present diminished amounts of CRH immunoreactivity, suggesting that decreased ovarian CRH might be related to the anovulation of polycystic ovarian syndrome (Mastorakos et al., 1993). Finally, the concentration of CRH is higher in the premenopausal than the postmenopausal ovaries, indicating that ovarian CRH may be related to normal ovarian function during the reproductive life span (Zoumakis et al., 2001).

3.1.2. Intrauterine CRH

Intrauterine CRH appears to have a fundamental role in the mechanisms responsible for embryo implantation and maintenance of human pregnancy. Human and rat uterus express the CRH gene (Makrigiannakis et al., 1995a; Mastorakos et al., 1996). Epithelial cells are the main source of endometrial CRH, while stromal cells do not express it, unless differentiation to decidual cells occurs (Ferrari et al., 1995; Makrigiannakis et al., 1995a; Mastorakos et al., 1996; Di Blasio et al., 1997). In addition, CRH-R1 receptors are present in both epithelial and stromal cells of the human endometrium (Di Blasio et al., 1997) and in human myometrium (Hillhouse et al., 1993), suggesting a local effect of uterine CRH.

In humans, initiation of endometrial stroma decidualization occurs spontaneously in the luteal phase of the menstrual cycle. The endometrial glands are full of CRH during both the follicular and the luteal phases of the cycle (Makrigiannakis et al., 1995a; Mastorakos et al., 1996). However, the concentration of CRH is significantly higher in the luteal phase. CRH induces the decidualization of endometrial stroma (Ferrari et al., 1995). Progestins stimulate the expression of endometrial CRH in a cAMP-dependent manner (Makrigiannakis et al., 1999). In addition to progesterone, several locally produced pro-inflammatory immune factors, such as prostaglandins and interleukins, also exert a decidualizing effect. CRH inhibits the production of prostaglandin E2 by human endometrial stromal cells (Zoumakis et al., 2000). Therefore endometrial CRH, in addition to its direct decidualizing effect, may also alter the decidualizing action of progesterone via its influence on the locally produced modulators, including prostaglandin E2. In addition, CRH stimulates the production of both IL-1 and IL-6 in human endometrial stromal cells (Zoumakis et al., 2000). IL-1 is an important modulator of the decidualization process, blocking the differentiation of human endometrial stromal cells induced by ovarian steroids or cAMP (Frank et al., 1995). The stimulatory effect of CRH on stromal IL-1 indicates that the former may exert its decidualizing effect either directly or indirectly as a modulator of progesterone, which is the classical decidualizing effector. Therefore, a close interaction occurs within the human endometrium involving CRH, prostaglandins and cytokines, which act as an endometrial network of decidualization.

3.1.3. The role of CRH in implantation, early maternal tolerance and trophoblast invasion

The fundamental process of implantation involves a series of steps leading to an effective “cross-talk” between invasive trophoblast cells and the maternal endometrium. The success of implantation depends on achieving the appropriate embryo development to the blastocyst stage and the invasion of the latter into the decidualized endometrium (Makrigiannakis et al., 2006). During blastocyst implantation, the maternal endometrial response to the invading fetal semi-allograft has characteristics of an acute, aseptic inflammatory response (Makrigiannakis et al., 2001). However once implanted, the embryo suppresses this response and prevents rejection. Simultaneously, the mother’s immune system prevents a graft vs. host reaction deriving from the fetal immune system (Makrigiannakis et al., 2001).

Early in pregnancy, the implantation sites in rat endometrium contain 3.5-fold higher concentrations of CRH compared to the interimplantation regions (Makrigiannakis et al., 1995b), indicating that CRH might participate in implantation. Embryonic trophoblast and maternal decidua cells produce CRH and express Fas ligand (FasL), a proapoptotic molecule (Makrigiannakis et al., 2001). Fas and its ligand play an important role in the regulation of immune tolerance. The major function of the Fas–FasL interaction is the induction of apoptosis in activated cells carrying Fas, that is, in cells located at the interface between the fetal placenta and maternal endometrium.

CRH induces the expression of apoptotic FasL on invasive extravillous trophoblast and maternal decidual cells at the fetal–maternal interface (Makrigiannakis et al., 2001). Furthermore, CRH increases the apoptosis of activated T lymphocytes through FasL induction, participating in the processes of both implantation and early pregnancy tolerance. This effect of CRH is specifically mediated through CRH–R1 (Makrigiannakis et al., 2001). These findings suggest that CRH participates in the processes of both implantation and early pregnancy immune tolerance.

The trophoblast is the first tissue to differentiate in the mammalian conceptus and its normal development is important for implantation and further survival of the embryo. Indeed, trophoblast invasion and regulation
is a prerequisite for a successful pregnancy. The placenta has the unique ability to proliferate and invade the endometrium in a controlled manner. We have shown that CRH inhibits in vitro the invasion of human extravillous trophoblast cells (Bamberger et al., 2006). This effect is mediated by CRH-R1 and involves downregulation of the synthesis of the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) by extravillous trophoblast cells. CEACAM1 is a member of the carcinoembryonic antigen (CEA) family and the immunoglobulin superfamily, which is expressed in the normal human placenta with a specific localization in the extravillous trophoblast cell (Bamberger et al., 2006). Thus, early in pregnancy, locally produced CRH appears to have a dual effect on trophoblast implantation and invasion, mediated via the R1 receptor: (1) it promotes implantation and maintenance of early pregnancy, by killing activated T lymphocytes, and (2) it controls proper trophoblast invasion, by regulating CEACAM1 expression.

3.1.4. Placental CRH

During human pregnancy, the placenta and fetal membranes produce large amounts of CRH (McLean et al., 1995). Synthesis of CRH in these tissues increases with advancing gestation and by term, it is present in high concentrations in the maternal and fetal blood, and in amniotic fluid (Frim et al., 1988). The biologic activity of CRH in maternal plasma is attenuated by the presence of a circulating CRH-binding protein (CRH-BP), produced by the liver and placenta (Linton et al., 1993). CRH-BP concentrations decrease during the last 6 weeks of pregnancy, leading to elevations of free CRH (Linton et al., 1993). Thus, placental CRH is responsible for the hypercortisolism observed during the latter half of pregnancy. This hypercortisolism is followed by a transient suppression of hypothalamic CRH secretion in the postpartum period, which may explain the blues/depression and autoimmune phenomena seen during this period (Chrousos et al., 1998).

Placental CRH induces dilation of uterine and fetal placental vessels through nitric oxide synthetase activation (Chrousos, 1999; Smith, 2007). At term pregnancy, placental CRH promotes myometrial contractility by stimulating progaglandin production from the decidua and fetal membranes (Jones and Challis, 1989) and potentiates the contractile effects of oxytocin and progaglandins on the myometrium (Benedetto et al., 1994).

Placental CRH is also released into the fetus and stimulates the production of dehydroepiandrosteredione from the fetal zone of the adrenal gland during pregnancy (Sirianni et al., 2005). Because the placenta cannot directly synthesize estradiol, the fetal adrenal gland is the predominant source of its precursor, dehydroepiandrosteredione. This positive loop may also mediate other components of labor, such as expression of oxytocin receptor, gap junctions and progaglandins (Grammatopoulos and Hillhouse, 1999).

Placental CRH secretion is stimulated by glucocorticoids, inflammatory cytokines, and anoxic conditions, including the stress of preeclampsia or eclampsia (Robinson et al., 1988; Goland et al., 1995).

3.1.5. The role of CRH in normal parturition and preterm delivery

Placental CRH appears to play an important role in coordinating the transition of the uterus from a relaxation state to a contraction state during labor (Grammatopoulos and Hillhouse, 1999). During the final 3 weeks of the gestation, the process of parturition takes place. Parturition – the process by which the fetus is expelled from the uterus to the extrauterine environment – is a result of a complex interplay of fetal and maternal factors. This process requires that the uterus develops coordinated contractility and the cervix dilates, in order to allow passage of the fetus through the birth canal. CRH and its related peptide urocortin 1 (Ucn1), may control human parturition not only by affecting myometrial contractility, but also by increasing local matrix metalloproteinase-9 (MMP-9) activity in placenta and fetal membranes (Li and Challis, 2005), thus contributing to membrane rupture with the onset of labor.

It has been demonstrated that CRH plasma levels are significantly higher in women delivered preterm and significantly lower in women delivered after term than in women delivered at term (McLean et al., 1995). It should be pointed out that in nonprimate mammals, end of pregnancy is associated with a fall in maternal progesterone concentration, which contributes to the initiation of labor (Karalis et al., 1996). In the human placenta cortisol is able to compete with the action of progesterone in CRH regulation (Yang et al., 2006). Therefore, cortisol blockade of progesterone is a possible mechanism in labor initiation.

The etiology and initiation of preterm labor is a complex phenomenon. Factors such as genital tract infection, spontaneous rupture of membranes and premature activation of normal parturition may all be involved in preterm delivery. In some women with idiopathic preterm labor, concentrations of CRH increase up to 10 weeks before the development of any symptoms or signs (McLean et al., 1995). Indeed, it has been suggested that there is a “CRH placental clock” which is active from the early stages of human pregnancy and determines the length of gestation and the timing of parturition and delivery (McLean et al., 1995). These data suggest that the timing of labor is related to processes that occur early in pregnancy and that parturition is the final step of a longitudinal process in the feto-placental unit, activated at a predetermined stage of gestation. We have shown that increased plasma CRH and ACTH levels may be associated with idiopathic preterm labor (Makrigiannakis et al., 2007); thus maternal CRH and ACTH levels may be useful predictors for the timing of parturition in a woman who has been diagnosed with preterm labor.

3.1.6. The potential role of CRH in spontaneous abortions

Human reproduction is remarkably inefficient, with more than half of spontaneous conceptions failing to complete the first trimester. We demonstrated that abortive decidua contain leukocytes that are positive for FasL and extravillous trophoblasts, which show increased expression of Fas and increased rates of apoptosis (Minas et al., 2007). We hypothesized that CRH, and its related peptide Ucn1, may mediate these phenomena. Indeed, we found that CRH and Ucn1 expression was up-regulated in abor-
tions (Minas et al., 2007). In vitro, these peptides induced the expression of Fasl in decidual lymphocytes obtained from elective termination of pregnancy placentas and thus potentiated the cells’ ability to induce Fas-mediated apoptosis in an extravillous trophoblast-choriocarcinoma hybrid cell line. Finally, decidual lymphocytes from abortion sites effectively induced apoptosis of extravillous trophoblasts without prior treatment. It is possible that these events may impede successful early placentation and thus contribute to the pathophysiology of human abortion. These effects were mediated by CRH-R1, since the addition of a CRH-R1 antagonist completely reversed these events.

3.1.7. The potential role of CRH in placental dysfunction associated with preeclampsia and intrauterine growth retardation

Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality, characterized by hypertension, proteinuria, and edema. In severe cases, impaired liver function, activation of the clotting system, renal failure or pulmonary edema may also be present. Intrauterine growth restriction (IUGR) is another major cause of perinatal morbidity and mortality, characterized by failure to attain optimal intrauterine growth and development. Shallow trophoblast invasion and subsequently deficient remodeling of spiral arteries have been associated with preeclampsia and/or IUGR (Schiessl, 2007).

Normally, the pregnant uterus exerts remarkable vascular remodeling and the most important change is the transformation of the uterine spiral arteries into low-resistance flow vessels that allow large volumes of blood to enter the placental intervillous space (Rusterholz et al., 2007). CRH participates in the maintenance of vascular tone by activating a guanylate cyclase/nitric oxide pathway in the human placenta (Clifton et al., 1995). Indeed during blastocyst implantation, EVT invasion leads to replacement of the endothelium of the uterine arteries, thus modifying the high-resistance, non-pregnant circulation to a low-resistance system in order to facilitate nutrient exchange (Rusterholz et al., 2007). In pre-eclamptic and growth-restricted pregnancies, the maternal plasma levels of CRH are significantly elevated (Perkins et al., 1995), whereas placental CRH-R1 expression is reduced (Karteris et al., 2003). The pathophysiologic basis of the inverse correlation between CRH and CRH-R levels in these complicated pregnancies is unknown. One possibility is that elevated levels of placental CRH may down-regulate its own receptor. Alternatively, defects causing preeclampsia and/or IUGR may result in reduced CRH-R expression, and the concomitant increase in CRH production may represent a regulatory mechanism to compensate for the decreased signaling efficiency. Indeed, dysregulation of the CRH/CRH-R1 system has been suggested to play a role in the pathophysiology of placental ischemia, which is observed in preeclampsia (Karteris et al., 2005). Thus it is possible that abnormal first trimester trophoblast invasion due to a dysregulated CRH/CRH-R1 system may lead to placental dysfunction associated with preeclampsia and/or IUGR.

It is tempting to speculate on the pathophysiologic network system between first trimester improper trophoblast invasion, CRH and Fas–FasL interaction, IUGR and preeclampsia that might underlie these findings. A large scale prospective study, evaluating pregnant women from the first trimester and throughout pregnancy, will be required to determine the clinical implication of this relationship.

3.2. CRH in the male reproductive system

3.2.1. Testicular CRH

CRH is present in the testis of several animal species, localized in Leydig and germ cells and in spermatozoa (Fabbri et al., 1990). A major stimulus for Leydig-cell derived CRH is luteinized hormone, which results in CRH secretion in a dose-dependent fashion (Fabbri et al., 1990). In the rat testis, CRH acts as an anti-reproductive hormone, exerting autocrine inhibitory actions on Leydig cell steroidogenesis (Fabbri et al., 1990; Dufau et al., 1993).

4. Interactions between the mother and the fetus: influence of maternal stress and adverse intrauterine environment on the development of the offspring

Epidemiological and experimental studies suggest that environmental events acting in the developing embryo in utero are crucial determinants for disorders later in life (Fowden et al., 2006), a phenomenon known as “fetal programming”.

Life exists through maintenance of a dynamic equilibrium called homeostasis, which is constantly challenged by adverse forces, the stressors. Stress is defined as a state of threatened homeostasis. Abnormal trophoblast invasion, deficient remodeling of spiral arteries with high-resistance placental vessels and subsequent placental dysfunction, leading to preterm labor and/or fetal growth restriction and/or preeclampsia, may reflect a state of threatened homeostasis for the fetus that responds to intrauterine stressors by increasing its CRH levels. However, a fundamental question that remains to be answered is whether the elevated concentrations in CRH are a cause of preterm labor and/or fetal growth restriction and/or preeclampsia or consequence of an underlying pathophysiology. It has been suggested that the fetus might respond to an adverse intrauterine circumstance through increased placental CRH levels. Inappropriate elevations of fetal cortisol generate a common pathway to growth restriction and to elevations of placental CRH. In addition, abnormally increases in fetal cortisol may impair fetal growth and predispose to later life diseases, such as insulin resistance and cardiovascular disease. Indeed, this relationship is exacerbated in cases of placental or uteroplacental dysfunction. Interestingly, a recent epidemiological study suggested that preterm birth is associated with diminished long-term survival and reproduction (Swamy et al., 2008).

It is possible that abnormal endometrial environment during implantation and trophoblast invasion may predispose to placental dysfunction associated with later appearance of preeclampsia and/or IUGR and/or preterm labor. Determining the mechanisms that control implantation and invasion may have implications for therapeutic
intervention in preeclampsia, intrauterine growth retardation, infertility and spontaneous abortions.

Apart from the adverse intrauterine stressors, maternal gestational stress has also been linked to development of insulin resistance and cardiovascular disease, as well as to development of a diverse range of neurodevelopmental disorders in later life (Reynolds et al., 2007) have been associated with preterm delivery (Ruiz et al., 2003), low birth weight (Kinsella and Monk, 2009), and adult offspring insulin resistance (Entringer et al., 2008). In humans, low birth weight has been correlated with adult increased plasma cortisol levels and risk for developing glucose intolerance, hypertension and dyslipidemia, i.e. components of the metabolic syndrome (Chrousos and Kino, 2007). In addition, prenatal maternal stress and anxiety have been associated with increased risk for impaired cognitive development, behavioral problems, autism and schizophrenia (O’Donnell et al., 2009). Animal data indicate that prenatal maternal stress alters the activity of the placental barrier 11-betahSD2 enzyme, which metabolizes cortisol (O’Donnell et al., 2009). Future studies are needed to elucidate the mechanisms by which in utero stress hormones affect fetal programming and to investigate the potential use of CRH-antagonists in the prevention of adult offspring long-term diseases, from metabolic syndrome to psychiatric disorders.

5. Conclusions

Hypothalamic CRH, the principal regulator of stress, has suppressive effects on female and male reproductive function. CRH has been identified in both the female and male reproductive systems. CRH participates in various reproductive functions that have an inflammatory component, where it serves as an autocrine and paracrine modulator. CRH has a fundamental role in the mechanisms responsible for embryo implantation and maintenance of human pregnancy. It has been suggested that there is a “CRH placental clock” which is active from the early stages of human pregnancy and defines the length of gestation and the onset of parturition and delivery. Abnormalities of decidual, trophoblast and placental CRH have been implicated in several common disease processes of pregnancy, including spontaneous abortions, preeclampsia and intrauterine growth restriction. Further study is required into the clinical applications of CRH-receptor antagonists in the management of pathophysiological states associated with abnormal CRH levels during pregnancy, such as preeclampsia/eclampsia, intrauterine growth restriction, and preterm labor. In addition, more research is needed to elucidate the mechanisms by which in utero stress hormones affect fetal programming and to investigate the potential use of CRH-receptor antagonists in the prevention of adult offspring long-term diseases, from metabolic syndrome to psychiatric disorders.


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