Neurosci Bull June 1, 2015, 31(3): 338–350. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1508-2

·Review·

Hypothalamic-pituitary-adrenal axis function during perinatal depression

Phillipe Leff Gelman[1], Mónica Flores-Ramos[2,3], Margarita López-Martínez[1], Carlos Cruz Fuentes[3], Juan Pablo Reyes Grajeda[4]

[1]*National Institute of Perinatology, Mexico City, Mexico*

[2]*National Council of Sciences and Technology (CONACyT), Mexico City, Mexico*

[3]*National Institute of Psychiatry, Mexico City, Mexico*

[4]*National Institute of Genomic Medicine, Mexico City, Mexico*

Corresponding author: Phillipe Leff Gelman. E-mail: pleff@ymail.com

Abnormal function of the hypothalamic–pituitary–adrenal (HPA) axis is an important pathological finding in pregnant women exhibiting major depressive disorder. They show high levels of cortisol pro-inflammatory cytokines, hypothalamic-pituitary peptide hormones and catecholamines, along with low dehydroepiandrosterone levels in plasma. During pregnancy, the TH2 balance together with the immune system and placental factors play crucial roles in the development of the fetal allograft to full term. These factors, when altered, may generate a persistent dysfunction of the HPA axis that may lead to an overt transfer of cortisol and toxicity to the fetus at the expense of reduced activity of placental 11β-hydroxysteroid dehydrogenase type 2. Epigenetic modifications also may contribute to the dysregulation of the HPA axis. Affective disorders in pregnant women should be taken seriously, and therapies focused on preventing the deleterious effects of stressors should be implemented to promote the welfare of both mother and baby.

Keywords: brain; depression; neuroendocrine; pregnancy; stress; glucocorticoids

Introduction

Mood disorders arise from complex interactions between genetic, developmental, and environmental factors. Extensive studies have demonstrated that early life stressors produce changes in behavior and enhance the sensitivity of the stress response systems[1-4]. Although the genetic background has been implicated in the development of mood-related disorders, and genetic research has identified some chromosomal regions and genes that are involved in susceptibility to mood disorders, the etiology of anxiety and depressive disorders is still not clear in humans, particularly in women with major depressive disorder (MDD)[1].

The pathogenesis of perinatal depression is an emerging field. Although considerable progress has been made in this area in the last few years, there still remain unanswered questions and gaps in our knowledge of the underlying pathogenesis, the long-term impact of perinatal depression on the developing fetus, and the best methods for counseling pregnant women concerning the risks of untreated MDD *versus* the risks of psychopharmacologic treatment during pregnancy and lactation[5]. Meta-analysis studies have reported that the mean prevalence rate of prenatal depression is ~12% (this varies greatly according to location, mode of assessment, and socioeconomic conditions), and show that a large percentage of pregnant women displaying major depression remain depressed in the postpartum period and/or continuously[6, 7]. Anxiety, depressive disorder, and stress during pregnancy are risk

factors for negative outcomes in newborns, like preterm birth or low birth weight; also, insecure attachment and impaired child development could be a consequence of mental disorders during pregnancy[6, 8-10]. The mechanisms by which maternal depression impacts fetal and neonatal development are currently under investigation; there is some evidence that depressive symptoms impact the infant's hypothalamic-pituitary-adrenal (HPA) axis, enhancing the levels of catecholamines and cortisol in the newborn[6,10].

The HPA axis, along with the sympathetic-adrenal-medullary axis, is one of the major biological stress response systems in humans[11]. Many of the hallmark symptoms of depression reflect processes of hypothalamic dysfunction, such as disturbances of mood, appetite, sleep, sex-drive, and motivation. Although there is considerable evidence that three monoaminergic systems (serotonin, norepinephrine, and dopamine), as well as the glutamate and γ-aminobutyric acid systems are involved in the pathogenesis of depression, other circuits are clearly involved, such as the arginine-vasopressin (AVP)/ corticotrophin-releasing hormone (CRH) peptide system, which has been shown to regulate the functional activity of the HPA axis[12, 13].

The extensive literature published over the last several decades indicates that abnormal HPA axis activity in adults with MDD is among the most consistent and robust biological findings in psychiatry to date[14-16]. Adults with depression disproportionately show chronic hyperactivity of the HPA axis and an inability of this system to return to a normal rhythm following long-term exposure to stressors[17]. Indeed, at least 50% of depressed adults show evidence of deregulated activity of the HPA axis[18]. Prolonged elevation of cortisol levels in serum can result in exhaustion and irritability, which are classic physiological symptoms of depression[19], and adults with the most severe depression exhibit high levels of cortisol[20]. Nonetheless, it is not clear whether the observed deregulation of the HPA axis is a consequence of stressful experiences or, as suggested by some human studies, results from a pre-existing vulnerability. Animal studies have shown that the activity of the HPA axis changes in response to extreme and/or chronic stress and that these changes may be part of the causal mechanisms by which environmental stress contributes to the development of depression, the persistence of symptoms, and the recurrence of depressive disorders[21, 22]. However, the latter hypothesis is based on pre-existing differences in HPA axis functioning in certain individuals that result in increased susceptibility to stress-inducing "depressionergic effects"[23, 24]. Irrespective of whether these hypotheses are convincing, they both highlight the importance of the putative role of adrenocortical deregulation in depression.

Limbic structures and the HPA axis are co-regulated in order to diminish the stress response, and the prefrontal cortices play a critical role in control over the HPA axis. *In vivo* studies have demonstrated that fronto-limbic dysregulation of HPA-axis dysfunction is related to difficulties in emotion regulation, a characteristic of depression[25]. Moreover, limbic-frontal connectivity could be different in responders or non-responders to drugs, and in responders to cognitive behavioral therapy compared with pharmacotherapy responders[26].

With regard to depression and human reproduction, the precise etiology of depression in pregnancy and the postpartum period remains elusive. However, studies have shown that depressive episodes may differ during pregnancy and the postpartum period, suggesting that abnormal function of the HPA axis, hypercortisolemia during pregnancy, and/or cortisol withdrawal in the postpartum period may contribute to depression during these periods. In addition, women with different genetic predispositions (e.g., glucocorticoid (GC) receptor polymorphisms) are reported to be at risk of becoming ill with a depressive episode at various times in the perinatal period[10].

By understanding the functional roles of a wide range of stress mediators, cell receptors, and signaling systems in the hippocampus, hypothalamus, pituitary gland, and placenta during pregnancy, it may be feasible to conceptualize the interactions of this complex neuroendocrine network and determine how maternal and placental secreted factors influence the physiological activity of the HPA axis and respond to perpetuating stressors that eventually lead to the expression of affective disorders during pregnancy.

Moreover, the epigenetic modulation of genes encoding hormones and target receptors involved in stress-mediated responses may provide links and clues to the gestational and transgenerational transmission of depressive disorders in a woman's offspring. Thus, changes

in the circulating levels of soluble mediators or in the functioning of target receptors during persistent stressful challenges may contribute to the abnormal function and reactivity of the HPA axis to stressors, eventually leading to depression and negative outcomes for both mother and fetus during pregnancy as well as for the neonate and child in postnatal life.

The primary aim of this review is to discuss the key roles of distinct endocrine factors released from neurosecretory tissues and the central nervous system (CNS), as well as the placenta, which all together may contribute to the dysregulation of the HPA axis during perinatal depression.

Perinatal Depression and the HPA Axis

Several pieces of evidence documented recently show that abnormal function of the HPA axis plays a key role in the etiology of MDD during pregnancy and postpartum[5, 6, 27, 28]. Recent work has demonstrated that the reproductive steroids estrogen and progesterone interact with the HPA axis and may trigger HPA axis abnormalities in susceptible women. Critical hormonal changes occur during the transition from pregnancy to the postpartum period[29]. During the third trimester of a normal pregnancy, high estrogen and progesterone levels and high plasma cortisol are associated with hyperactivity of the HPA axis due to the increased levels of hormone stimulation[29, 30]. During childbirth and transition to the postpartum period, reproductive hormone levels rapidly decline, facilitating the blunting of HPA axis activity due to the suppression of the increased levels of CRH released from hypothalamic paraventricular nucleus (PVN) cells during pregnancy[5, 29]. The suppression of CRH seems to depend on the length of time it takes for the hypertrophic adrenal cortex of pregnancy to gradually return to its normal size[5, 29]. Similar to non-puerperal women exhibiting MDD, women with postpartum depression (PPD) display a disturbed HPA axis. However, although the triggering factors for PPD are still unknown, human and animal studies suggest that its onset may be determined by both genetic factors and stressful life events[31, 32]. Consistent with these studies, the inability of the HPA axis to respond to stressors and to maintain homeostatic regulation is a robust biological finding in MDD and PPD. This inability is due to the impaired negative feedback mediated by cortisol receptors in the anterior pituitary, hypothalamus, and hippocampus, as well as ACTH (adrenocortical hormone) receptors in the anterior pituitary and CRH autoreceptors in the hypothalamus[5, 33, 34]. Women with PPD and non-puerperal women with MDD display similar abnormalities in HPA axis activity and exhibit high baseline cortisol levels and exaggerated responses to the dexamethasone/CRH test. Furthermore, women with PPD display an ongoing blunting of the ACTH response to CRH administration at 6 to 12 weeks postpartum compared with non-depressed women, reflecting an ongoing hyporeactive HPA axis[5, 33]. In the same context, euthymic women with a past history of PPD who undergo a protocol consisting of high-dose gonadal steroid administration followed by abrupt withdrawal exhibit an increased cortisol response and onset of significant depressive symptoms compared to normal women. Such results posit that a vulnerability trait related to the onset of PPD does exist or may develop as a consequence of a previous depression[34].

HPA Axis: Physiological and Cellular Mechanisms

Corticotrophin-Releasing Hormone

CRH is recognized as a major hypothalamic neurohormone that regulates ACTH release from the anterior pituitary, which in turn stimulates cortisol secretion from the adrenal cortex[35]. CRH molecules comprise a large family of structurally-related molecules that are found in all mammalian species[36–42]. In mammals, the CRH/Ucn (urocortin) family comprises at least four ligands: CRH, Ucn1, Ucn2, and Ucn3[43, 44]. All of these peptides have been found in human placenta and fetal membranes and are thought to be involved in the mechanisms of parturition[45-47]. In the brain, CRH-synthesizing neurons are located in the PVN; release of the peptide into the hypophyseal-portal blood system conveys the hormone to the anterior pituitary. Within the CNS, CRH has also been detected in many regions outside the PVN, including the central nucleus of the amygdala, dorsal raphe, locus coeruleus, inferior olivary nucleus, prefrontal cortical area, and Barrington's nucleus, where it may act as a modulator of various neurotransmitter systems[48].

Arginine Vasopressin

There are two major vasopressinergic systems in the brain. The first involves the hypothalamic magnocellular

neurons in the PVN and supraoptic nucleus (SON). AVP acting through its peripheral cognate V1a receptor[49, 50], a G-protein-coupled receptor signaling *via* phospholipase C[51-52], is largely responsible for regulating water homeostasis and blood pressure[49, 53]. The second system consists of parvocellular neurons within the PVN; these neurons produce both AVP and CRH peptide hormones[55]. At least 50% of CRH-synthesizing cells in the PVN co-express AVP[56]. Acting through its cognate V1b receptor expressed on pituitary corticotrophs, AVP stimulates ACTH release[53, 55, 57]. The V1b receptor is largely responsible for regulating HPA-axis activity and responding to acute and chronic stressors in mammals[53, 55].

Stimulatory Activity of CRH and AVP

Activation of the HPA axis not only regulates bodily functions such as metabolism and immunity but also has profound effects on the brain[58]. Some CRH neurons in the PVN co-express and release AVP. When released together into the hypophyseal-portal system, AVP strongly potentiates the ACTH-releasing activity of corticotrophs[59, 60]. In addition, AVP released from the SON may induce ACTH release from the pituitary[59]. CRH and AVP stimulate ACTH secretion from pituitary corticotrophs by interacting with the CRH type 1 (CRHR1) and Avpr1b or V1b receptors, respectively[62].

Behavioral studies in mutant mice have shown that, although CRH appears to be the dominant ACTH secretagogue in response to acute stressors (e.g., restraint stress)[55], AVP seems to be sufficient to maintain adequate HPA activity for survival in CRH- and CRHR1-deficient mice[63, 64]. These studies demonstrated that mutant mice exhibit a compensatory increased activity of the basal hypothalamic vasopressinergic system in CRHR1-knockout animals[65].

CRH/AVP Receptor Signaling Systems

Both the CRHR1 and the Avpr1b receptor subtypes belong to the extensive family of seven membrane-spanning G protein-coupled receptors (GPCRs), which have been shown to activate signaling systems in pituitary corticotrophs. Thus, CRH induces ACTH release, which activates GPCR signaling systems coupled to adenylate cyclase, cAMP formation, and the activation of protein kinase A. In contrast, AVP responses mediated through the Avpr1b receptor subtype activate the phospholipase C signaling system[57, 66]. The Avpr1b receptor signaling system is required for normal pituitary and adrenal responses to acute stressful stimuli and is crucial for the ACTH-release response to chronic stressors[62, 66]. Moreover, previous studies have shown that AVP responses to chronic stress are stimulated by GCs, which enhance the expression of Avpr1b receptor mRNA in the hypothalamus.

Thus, AVP-mediated stress responses are responsible for up-regulation of the pituitary release of ACTH by activating its cognate Avpr1b/V1b receptor; in contrast to oxytocin, which has been shown to inhibit ACTH release[67], AVP plays a critical role in sustaining corticotrophic responsiveness in the presence of high levels of GCs during chronic stress and depression[68].

Glucocorticoids

GCs have long been considered the interface between stress and brain function, explaining why cortisol resistance and dysfunction of the HPA axis are implicated in affective disorders, with major impact on MDD[69]. Patients exhibiting MDD show increased cortisol levels in saliva, plasma, and urine and increased function and size of both the pituitary and the adrenal glands[70]. The sustained activity of the HPA axis is thought to be related, at least in part, to a reduction of the feedback inhibition mediated by GCs on their cognate cell receptors[69]. Recent studies have emphasized the importance of epigenetic modification of GC receptors and suggested that such modification might explain the reduced inhibitory responses of GCs in the brain and neuroendocrine tissues[71]. Nonetheless, other factors such as cytokines (e.g., IL-1β and IL-6) also modulate GC responses to stressors in the hippocampus, hypothalamus, and pituitary[72, 73]. In fact, cellular studies have shown that the activation of cytokine-dependent signal transduction pathways by pro-inflammatory cytokines contributes to the GC-dependent deregulation of the HPA axis and to the altered feedback regulation of CRH and AVP peptides in the hypothalamus as well[74, 75].

Interestingly, antidepressant treatment has been extensively reported to restore the normal activity of the HPA axis and to improve the inhibitory negative feedback responses of target tissues to GCs. These observations led some authors to suggest that the HPA axis might be the final common pathway that drives most of the symptomatology in depressive disorders, as well as several

acute symptoms of other psychiatric disorders[76].

Animal models of anxiety and depression have been used to elucidate how chronic stress and depression impact HPA axis activity, GC receptors, and intracellular signaling systems implicated in the observed morphological changes in limbic and cortical structures of the brain[2, 69, 76]. Thus, HPA axis hyperactivity should not be regarded merely as an epiphenomenon of depression, but as a crucial risk factor that predisposes individuals to the development of this affective disorder and that may be produced by early-life experiences that induce molecular changes in target tissues in association with genetic vulnerability and liability[69].

Neurosecretory cells, as well as metabolic tissues such as liver and adipose tissue express the NADPH-dependent 11β-hydroxysteroid dehydrogenase type 1 enzyme (11β-HSD1), which is the major determinant and limiting factor controlling GC concentration and their access to their cognate receptors in target cells[77, 78]. 11β-HSD1 has been localized in the mouse and rat hippocampus, hypothalamus, and pituitary, demonstrating its importance in the negative feedback regulation of endogenous GCs within the HPA axis. Mutant mice with deficiencies in 11β-HSD1 display adrenocortical hypertrophy and increased adrenal responses to ACTH *in vitro*[79]. GCs are key regulators of brain development and metabolic, neurotransmitter, and structural functions, most notably influencing neurons[79]. Chronic GC administration has deleterious effects on several regions of the brain, particularly in the hippocampus[80, 81].

Glucocorticoid Receptors

GC receptors have an extensive range of actions in cells and tissues throughout the organism. These actions have long been recognized to elicit both rapid and delayed effects on physiological and behavioral responses[76, 82-84]. GC actions are mediated primarily by the activation of two specific receptors: the mineralocorticoid receptor (MR) and the corticosteroid type II or GC receptor[84, 85]. Both MR and GC receptors mediate rapid non-genomic effects *via* the binding of cortisol to cell membranes[86]. In the CNS, MRs bind very low levels of GCs *in vivo*[87, 88] against the 100–1000-fold molar excess of GCs that circulate in the blood[85].

The acute effects of GCs on target cells in the HPA axis are predominantly mediated *via* their rapid action at their receptor sites. This action produces a rapid negative feedback response of the HPA axis that suppresses its own stress-induced hyperactivity. Within the pituitary, GCs suppress CRH-induced ACTH secretion within minutes *via* a rapid, transcription-independent mechanism[89]. The rapid GC effect on the pituitary accounts for about half of the rapid feedback inhibition of ACTH release that occurs *in vivo*[90]; the remaining half occurs within the brain (i.e., PVN cells in the hypothalamus, CA1-CA3 pyramidal cells and the granular cell layer in dentate gyrus of the hippocampus).

In the pituitary, GCs regulate the expression of pro-opiomelanocorticotropic hormones such as ACTH, β-endorphin, and α-melanocyte-stimulating hormone[91], and the expression of CRH and AVP receptors on pituitary corticotrophs[92, 93] and in the hypothalamus[94,95]. They also modify the inhibitory GABAergic inputs targeting PVN/CRH neurons[96-98]. Thus, GCs display an intrinsic control of both CRH and AVP activity, including ACTH secretion from corticotrophs[99]. Genomic actions of GCs are mediated by the transcriptional activation or repression of target genes after translocation of the intracellular (ligand-bound) receptor to the nucleus and binding of the receptor complex to a GC response element sequence located in the promoter region of GC-regulated genes[84, 100-101].

Glucocorticoids and Pregnancy

GCs readily cross barriers such as the placenta and are potent mediators in determining fetal growth and development, in addition to late-life pathologies[102]. Similar to 11β-HSD1, placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) serves as a GC barrier enabling tight regulation of materno-fetal GC transfer[102] particularly near term, when this enzyme is highly expressed in the syncytiotrophoblast (the interface tissue between maternal and fetal circulation)[103]. Considering the extremely high maternal GC levels compared to the fetal levels and the increase in placental 11β-HSD2 activity that occurs throughout gestation, subtle changes in 11β-HSD2 activity during pregnancy may induce dramatic GC effects on the fetus due to GC toxicity[102]. Placental 11β-HSD2 falls during late gestation, facilitating the passage of GCs to the fetus and permitting maturation of the lungs[104,105]. 11β-HSD2 is broadly and highly expressed in both rat and human fetal brains during mid-gestation, especially in the neuroepithelium, where its level decreases abruptly at the

terminal stage of neurogenesis[106]. Animal studies have shown that a relative deficiency of 11β-HSD2 may lead to overexposure of the fetus to GCs, producing fetal growth retardation, low birth weight, and altered programming responses that may exacerbate later-life diseases[102, 107]. Similar consequences of abnormally low placental 11β-HSD2 have been demonstrated in humans[108] although human deficiencies in 11β-HSD2 are rarely reported[102]. GCs are crucially important in the development of the mammalian brain, conferring long-lasting effects on brain structures and neurons, remodeling axons and dendrites, and affecting cell survival[74]. Thus, fetal exposure to GCs is likely to have widespread effects on neural organization and synapse formation, leading to changes in hippocampal structure and function, and affecting memory and behavior in adult life, as demonstrated in human and animal studies[102, 109]. In addition, it seems that the effects of stress during fetal life may differ according to sex, females being more sensitive to fetal stress than males. This effect seems to persist into adulthood[110].

Placental Factors Involved in Depressive Disorder: HPA Axis Relationship

The mammalian placenta is an essential interface between the maternal and fetal circulations; it carries oxygen-rich blood and nutrients and is endowed with an endocrine function that produces peptide hormones such as CRH, human chorionic gonadotropin hCG, growth hormone (hGH), human placental lactogen (hPL), cytokines (IL-6, IL-11, and IL-1), chemokines (CCL4 and CCL11), growth factors (heparin-binding EGF, IGF1, VGF), cortisol/cortisone, prostaglandins (PGE2), estrogens, and progesterone[111]. These hormones play pivotal roles in metabolic, energetic, and growth-associated functions, blastocyst implantation, trophoblast invasion, and the placentation process, facilitating recognition of the fetal allograft during pregnancy. Moreover, these factors have been implicated in mood and/or depressive-like behaviors[5, 10, 11]. The wide and varied activities displayed by such factors suggest that the endocrine placenta interacts with both the brain and the HPA system to produce homeostatic balance and optimal metabolic, energetic, and growth-related activity in order to bring a pregnancy to full term with a successful neonatal outcome (Fig. 1).

Placental CRH

CRH has been shown to play a crucial role in the mechanisms responsible for embryo implantation and the maintenance of human pregnancy[76]. Both the rat and human uterus express the CRH gene[76,112]. Cellular studies show that epithelial cells constitute the primary source of endometrial CRH[113] and its cognate receptor, CRH-R1[114], is widely distributed in epithelial and stromal cells of the human endometrium[113, 115] and myometrium[111]. During stromal decidualization, progestins stimulate the expression of endometrial CRH in a cAMP-dependent manner[115], resulting in the production of large amounts of CRH[114,116]. Furthermore, animal studies have shown that the rat endometrium and the adjacent trophoblast-implantation site contain CRH concentrations 3.5-fold higher than the inter-implantation regions during early pregnancy[116]. These findings suggest that CRH binding to its cognate receptor is involved in both implantation and early pregnancy immune tolerance[116]. CRH levels increase during gestation and at term; high concentrations of placental CRH (pCRH) are present in maternal and fetal blood, including the amniotic fluid[113, 116]. CRH activity in maternal plasma is attenuated by the presence of a circulating CRH-binding protein (CRH-BP) produced by the liver and placenta. CRH-BP levels decrease during the last 6 weeks of pregnancy, leading to an elevation in free CRH[115,117]. Thus, pCRH appears to be responsible for the hypercortisolism during the latter half of pregnancy (Fig. 1). This hypercortisolism leads to the transient suppression of hypothalamic CRH secretion in the postpartum period, a biological mechanism that could explain the occurrence of depression and autoimmune phenomena during this period[118]. It is important to note that GCs, pro-inflammatory cytokines, anoxic conditions, and stress conditions of pregnancy (i.e., preeclampsia) stimulate the secretion of pCRH[115, 119]. This correlates with the high circulating levels of CRH in women delivered preterm compared to the low levels in women delivered at or after term[119, 120].

Recent studies have shown that pregnant women with depression display high levels of pCRH that may contribute to serious medical complications or outcomes in mother and baby[5]. pCRH has been shown to be a crucial peptide hormone in fetal development, and increased levels of this peptide in the fetal circulation correlate with altered distribution and expression of GC receptors in the fetal

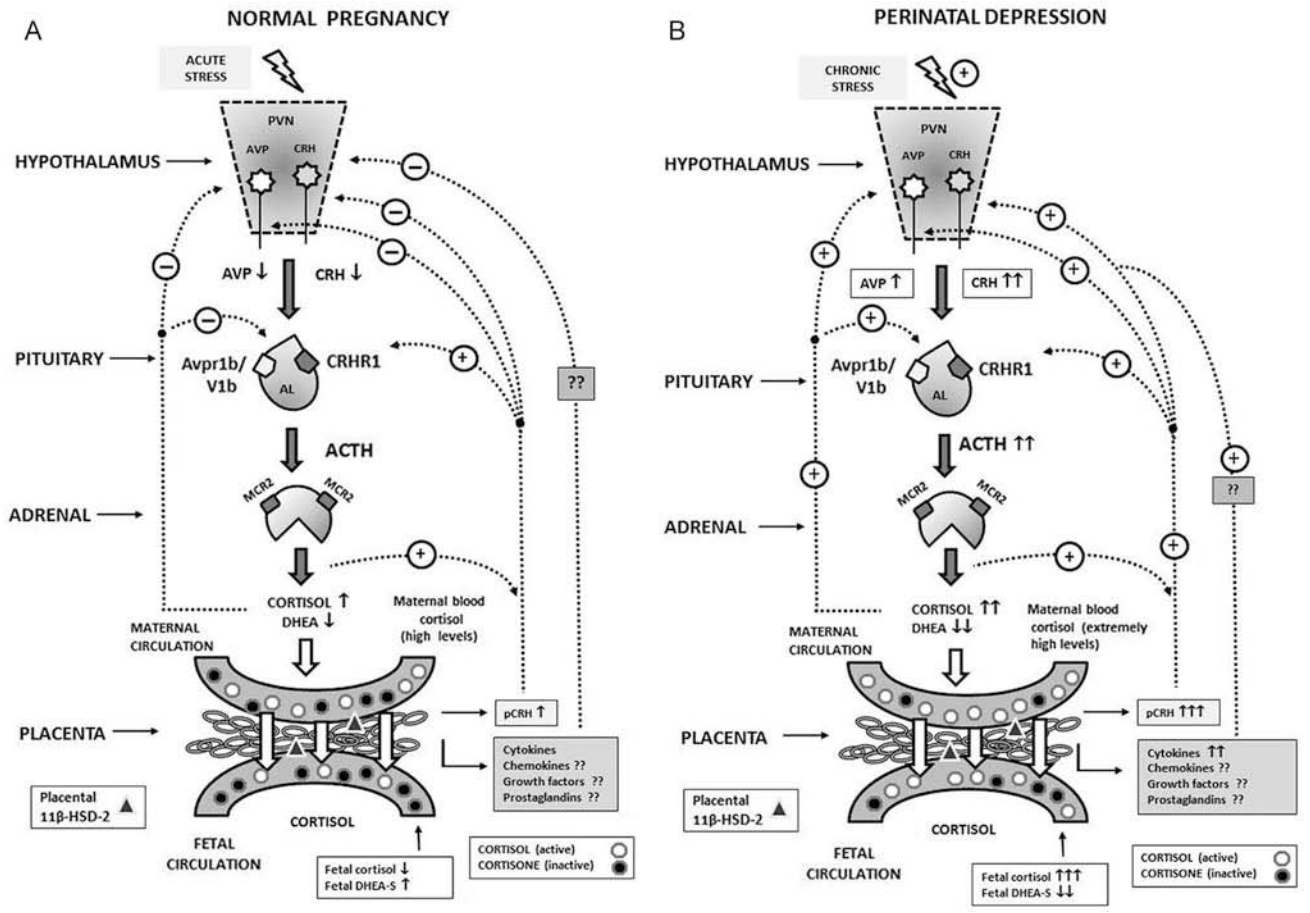

Fig. 1. Interaction between the HPA axis and the endocrine placenta during normal pregnancy (A) and during chronic stress leading to perinatal depression (B). A: During normal pregnancy physiological stressors impinge on the hypothalamus inducing the release of arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH) from PVN neurons into the hypophyseal-portal system (median eminence). This in turn, enhances the release of adrenocorticotropic hormone (ACTH) from corticotrophs located in the anterior lobe (AL) of the hypophysis. Corticotrophs express both cognate AVP and CRH binding receptors, Avpr1b/V1b and CRHR1. ACTH enhances the secretion of cortisol and dehydroepiandrosterone (DHEA) from the adrenals after binding their cognate melanocortin receptor type 2 (MCR2 receptor). Cortisol drives the negative inhibitory feedback on hypothalamic (PVN) CRH and AVP-producing cells and on corticotrophs in the pituitary. During normal pregnancy, most circulating levels of ACTH, cortisol (diurnal levels, 140–700 nmol/L; midnight levels, 80–350 nmol/L) and DHEA (not shown) in maternal blood are driven by placental CRH (pCRH), whose high serum levels during the 3rd trimester (30–32 gestational weeks) could mitigate the activity of hypothalamic CRH and AVP (CRH ↓, AVP↓) responses on the HPA axis. The physiological "*cortisolemia*" found in maternal blood contrasts to the low cortisol levels *versus* high cortisone and dehydroepiandrosterone sulfate (DHEA-S) levels found in the fetal circulation. Cortisol permeating the placental and fetal membranes is enzymatically converted into inactive cortisone by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), avoiding the glucocorticoid toxicity to fetal tissues, particularly to the developing CNS. Released cortisol from the adrenals and placenta from early to late pregnancy appears to drive the secretion of pCRH (synthesized by endometrial cells), and is used as a biological marker to determine the timing of spontaneous (preterm, term) birth (not shown)[123] (see text for details). B: During perinatal depression a different panorama is seen. High circulating levels of pCRH released from the placenta, could have (although not fully established) stimulatory effects on hypothalamic AVP and CRH, altering their production and secretion. Both hypothalamic peptides and pCRH could enhance the non-physiological high circulating levels of cortisol (hypercortisolemia) *versus* the low levels of DHEA detected during depression, reflected in the high cortisol/DHEA ratio [>1.0 (1.5-2.5)] and low cortisol/DHEA ratio [< 1.0 (0.05-0.08)] in depressed *versus* healthy individuals[124]. Persistent chronic stressors impinging on the HPA axis promote the secretion of both CRH and AVP from the hypothalamus, which in turn leads to the high secretion of ACTH and cortisol. The high pCRH levels found in the maternal bloodstream during perinatal depression could override the aberrant dysfunction of the HPA axis, once this hormone targets several brain structures

(i.e, hippocampus, prefrontal cortex, and amygdala). Although the effects of other mediators secreted from the immune system (proinflammatory cytokines; IL-6, IL-1β, IL-11, and TNF-α) (not shown) on HPA axis responses during perinatal depression have been extensively documented (see text for details), the effects of placental mediators, such as cytokines [i.e., leukemia inhibitory factor (IL-6/LIF)], growth factors (IGF1, heparin-binding EGF, and VGF), chemokines (CCL4 and CCL11), and prostaglandins (PGE2)], in altering HPA axis activity during perinatal depression have not been completely elucidated, an issue that needs to be explored. Nonetheless, the high circulating pCRH and cortisol levels in the maternal bloodstream that permeate placental membranes and which escape the enzymatic catabolism of placental 11β-HSD2 are crucial for the negative outcomes on both fetal neurodevelopment and the reprogramming of fetal stress-responsive endocrine systems. +, stimulatory response; –, inhibitory response; ??, uncertain response or non-defined response; ↑, increased response; ↓, decreased response.

brain[5, 74]. Furthermore, in studies focused on screening for potential biomarkers of stress and depression during pregnancy, pCRH has been suggested as a functional biomarker for the risk of developing perinatal depression and postpartum depression[5, 61]. However, due to the short half-life of this peptide hormone, which falls to undetectable levels within hours after childbirth[5, 117], its use as a potential biomarker seems limited[5], so its use as a marker during mid-pregnancy for increased risk of developing MDD or PPD is still controversial[5].

Monoamines and their relationship with the HPA axis must also be considered in the field of perinatal depression. Early-life GC exposure affects the serotonergic system in different ways (for review, see Wyrwoll and Holmes, 2012[121]). For instance, increased serotonin output and decreased reuptake, decreased hippocampal 5-HT_{1A} receptor binding, and increased hippocampal serotonin levels and turnover have been reported in animals exposed to stress. In addition, it seems that changes in serotonergic and catecholaminergic systems may, at least in part, underlie the altered expression and activtity of 11β-HSD2[121].

Conclusions

Abnormal function of the HPA axis, along with the sympathetic-adrenal-medullary axis explains the pathology in pregnant women exhibiting MDD. Cumulative research carried out over the last few decades has shown that the HPA axis is driven by the secretion of hypothalamic AVP and CRH hormones in response to acute stressors, where cortisol mediates a negative feedback loop after binding their GC receptors in the hypothalamus, pituitary, and hippocampus, turning off the signals that otherwise could lead to a perpetual imbalance of several endocrine parameters as demonstrated in the long-term dysregulation of this axis in MDD[122] or in animals exhibiting stress-associated depressive behaviors[2].

The maternal HPA axis activity leads to a sustained hypercortisolism resulting in an overt transfer of GCs to the fetus at the expense of the reduced activity of placental 11β-HSD2, and GC toxicity that enhances the reprogramming of fetal limbic functions associated with changes in forebrain structures that are relevant for the expression of mood-associated behaviors[74]. 11β-HSD2 is downregulated in pregnant women exhibiting stress and anxiety disorders[123]. GCs are crucial for neural development and for metabolic, neurotransmitter, and synaptic functions, especially during the period of maximal fetal growth. Epigenetic modifications of hormone and trophic factor receptors appear to be responsible for the repertoire of stress responses and particularly for shaping and orchestrating the structural anatomy and distribution of neurotransmitters in the brain[124, 125]. Perhaps the most relevant factor is the effect of the transgenerational transmission of epigenetic changes on brain molecules, due to the modified responses after the reprogramming of bodily stress systems during both prenatal and postnatal life[71, 126]. Such epigenetic changes in molecules and neurotransmitter systems play crucial roles in the future development of psychiatric disorders in susceptible individuals. For instance, DNA methylation of the promoter sites of genes encoding forebrain receptors involved in hippocampal plasticity, such as the GC receptor, tachykinin receptor 3, neurotrophin 3, brain-derived neurotrophic factor, and vascular endothelial growth factor, is reduced in limbic areas of the brain in adult individuals exhibiting major depression[124, 125].

Although non-pregnant and pregnant women share the key elements and epigenetic modifications that are crucial for developing MDD, pregnant women also exhibit increased expression of placental mediators (pCRH,

leukemia inhibitory factor, and IGF1-2, among many others yet to be explored) whose role in perinatal stress is still emerging, and whose contributions to the exacerbation of depressive symptoms could be assumed from targeting their cognate receptors in the mother's brain. For instance, insulin-like growth factor 1 (IGF1) has been reported to ameliorate anxiety, depression, and memory deficits, whereas deficiency of IGF1 in the adult brain has been shown to contribute to the expression of anxiety and depressive behaviors, as shown in mutant animals lacking the IGF1 gene. Although the contribution of placental IGF1 to depressive disorder has not been fully explored, reduced gene expression could be assumed to impinge on fetal neurodevelopment and produce negative neonatal outcomes and altered stress-related responses and cognitive functions in children later in life.

Thus, MDD during pregnancy is a particular manifestation of mood-related disorder, due to the development and growth of the endocrine-placenta which produces paracrine and endocrine factors during early and late pregnancy, and whose dysfunction in affective disorders could promote dysfunction of both the HPA axis and associated maternal limbic structures, leading to fetal reprogramming of the CNS as well as of the systems responding to bodily stress (Fig. 1). Ultimately, such effects may lead to altered behavioral responses and psychiatric disorders.

New perspectives on the treatment of perinatal depression suggest that CRH receptor antagonists and potentiators of CRH secretion/action may be useful[126]. However, further studies are needed to either validate or support such therapies.

ACKNOWLEDGEMENTS

This review was supported by the National Institute of Perinatology, Mexico (212250-07311).

Received date: 2014-06-28; Accepted date: 2014-09-24

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