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Endocrinology of human parturition

Les hormones de l’accouchement

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Abstract

The mechanisms involved in human pregnancy maintenance and parturition are highly complex and involve mother, fetus and placenta. The “final common pathway” to delivery is composed by inflammatory and endocrine interactive paths that tip the balance in favor of coordinated uterine contractility and cervical dilation. These mechanisms involve a shift from progesterone to estrogen dominance, CRH action, increased sensitivity to oxytocin, gap junction formation, and increased prostaglandins activity. Complementary changes in the cervix involve a decrease in progesterone dominance and the actions of prostaglandins and relaxin, via connective tissue alterations, leading to cervical softening and dilation. Neuronal, hormonal, inflammatory and immune pathways participate in initiation of labor and the utero-placental unit plays a major role in the synthesis and release of parturition mediators.

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Keywords: Parturition; Placenta; Estrogens; Progesterone; CRH; Urocortin; Prostaglandins; Relaxin

Résumé


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1. Introduction

Parturition is a coordinated process of transition from a quiescent myometrium to an active rhythmically contractile state requiring complex interplay between placental, fetal and maternal compartments. The precise mechanisms involved in initiation of labor are thought to involve functional progesterone withdrawal, increased estrogen bioavailability, corticotrophin releasing hormone (CRH) and neuroendocrine mediators and finally, increased responsiveness of the myometrium to prostaglandins and oxytocin [1]. Labor at term may be regarded best physiologically as a release from the inhibitory effects of pregnancy on the myometrium rather than as an active process mediated by uterine stimulants [2]. It involves an integrated set of changes within the maternal tissues of the uterus (myometrium, decidua, and uterine cervix), which occur gradually over a period of days to weeks. Such changes include an increase in prostaglandin synthesis and release within the uterus, an increase

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in the myometrial gap junction formation, and up-regulation of myometrial oxytocin receptors. Indeed, endocrine or paracrine-autocrine factors from the feto-placental unit bring about a switch in the pattern of myometrial activity [3]. In fact, human parturition is an inflammatory and endocrine event, where the two systems interact modulating labor onset and progression [4].

In the past, the placenta was believed to be a largely passive organ mainly responsible for delivering nutrients to the fetus. With progress in obstetric research, this concept has gradually shifted to one that recognizes the placenta as a transient endocrine organ and a central regulator of maternal–placental–fetal physiology. Thus, the placenta ensures appropriate physiologic milieu for normal growth and development of fetal, placental, and maternal tissues necessary for a successful pregnancy. Indeed, the placenta represents a very metabolically active organ during parturition. It is a source of a large number of “information” molecules that, when released, can exert their biologic effects on the placenta itself but can also enter the maternal and fetal circulation, thus acting as autocrine, paracrine, and endocrine factors [5,6].

Placenta produces a large variety of molecules including steroid hormones, hypothalamic-pituitary hormones, neuropeptides, growth factors and cytokines, involved in parturition [7]. Steroid hormones include the common female gonadal steroid hormones, progesterone and estrogens. It is noteworthy that the placenta produces also hormones that are known to be produced by neuroendocrine organs, such as oxytocin, gonadotrophin-releasing hormone (GnRH), opioids and CRH. However, the fetus itself plays a role in initiation of labor, through the secretion of neurohormones and other stimulators of prostaglandin synthesis [8].

Thus, inflammation, mechanical distension of the uterus at term and hormonal paracrine and autocrine signalling between the feto-placental unit and the mother seem to promote the initiation of human parturition through coordinated activation of stimulatory pathways and loss of uterine quiescence, which enables contractions to occur.

2. Phases of human parturition

Pregnancy may be considered as consisting of four parturitional phases (Fig. 1). During the first parturitional phase (phase 0 – quiescent phase) the uterus is kept in a quiescent state through the action of progesterone and other minor factors such as prostacyclin (PGI2), relaxin, parathyroid hormone-related peptide (PTHRP), calcitonin gene-related peptide, vasoactive intestinal peptide and nitric oxide (NO). All these agents act mediate an increased intracellular concentrations of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) which inhibit the release of intracellular calcium for myometrial contractility.

The second phase (phase 1 – activation phase) of parturition is associated with activation of uterine function. A rise in estrogen and CRH together, possibly, with mechanical stretch may lead to up-regulation of a panel of genes required for contractions. These CAPs include connexin 43, prostaglandin and oxytocin receptors (OTRs).

In the third phase of parturition (phase 2 – stimulation phase), the uterus can be stimulated by uterotonics including prostaglandins, oxytocin and CRH. The biochemical events within the uterus resemble an inflammatory reaction, with increased synthesis of cytokines.

The fourth phase of parturition (phase 3 – involution phase) includes the uterine involution that follows the delivery of the fetus and the placenta. It has been primarily attributed to the effects of oxytocin [9].

3. Hormones involved in parturition

3.1. Estrogens

Estrogens are essential for uterine development and function, playing a key role in uterine contractility. Human pregnancy is characterized by a typical hyperestrogenic state. The placenta is the primary source of estrogens, and concentrations of estrogens increase in the maternal circulation with increasing
Fig. 2. Biosynthesis and metabolism of estrogens in maternal and feto-placental unit.

Both DHEA and estradiol concentrations increase towards term [10]. However, lower DHEA levels and estradiol/estriol ratio are reported in postterm patients who are non-responsive to induction of labor [11,12] suggesting that their myometrium has not been primed and production of DHEA is critical. Glucocorticoids may influence this step increasing the conversion of dehydroepiandrosterone to estrogen via induction of aromatase expression in human placenta [13]. Hence, there is no reciprocal fall in plasma progesterone and rise in plasma estrogen, rather both estrogen and progesterone increase progressively towards term but the ratio of estrogen/progesterone begins to favor estrogen [14,15].

Estrogens do not themselves cause uterine contractions in parturition, but do promote a series of myometrial changes, including increasing the number of prostaglandin receptors, oxytocin receptors, and up-regulating the enzymes responsible for muscle contractions (myosin light chain kinase, calmodulin) [10,16] that enhance the capacity of the myometrium to generate contractions. Indeed, estrogens increase connexin 43 synthesis and gap junction formation in the myometrium, allowing for coordinated uterine contractions. Estrogens control also cervical ripening, by the rearrangement and realignment of collagen, elastin, and glycosaminoglycans, mediated by the induction of collagenase and elastase [17] (Fig. 3).

3.2. Progesterone

Progesterone is one of the main hormones of pregnancy. It is produced by corpus luteum and later in pregnancy by placental conversion of cholesterol coming from maternal circulation through the activity of two specific enzymes, cytochrome P450 side-chain cleavage (P450scc) and 3beta-hydroxysteroid dehydrogenase (3BHSD) [17]. Progesterone sustains the state of pregnancy and maintains uterine quiescence throughout gestation. In fact, it decreases myometrial contractility and inhibits myometrial gap junction formation. Indeed, progesterone activity stimulates the uterine NO synthetase, which is a major factor in uterine quiescence, and down-regulates prostaglandin production, as well as the development of calcium channels and oxytocin receptors (Figs. 4 and 5). In the cervix, progesterone
increases tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), inhibiting collagenolysis [18,19].

Serum progesterone levels do not vary significantly in the late third trimester of pregnancy and there is no evidence of a fall in maternal plasma or uterine tissues progesterone at labor. In pregnancy, progesterone is in dynamic balance with estrogen in the control of uterine activity. The factors that result in parturition must overcome the progesterone effect that predominates during the early pregnancy period of uterine quiescence [20]. The activity of 17,20 hydroxysteroid dehydrogenase in fetal membranes increases around the time of parturition, leading to an increase in net 17β-estradiol and 20-dihydroprogesterone, altering the estrogen/progesterone balance.

Thus, a functional progesterone withdrawal at the receptor level is believed to be involved in the process of parturition [21]. There have been several different mechanisms proposed for this, including decrease in progesterone receptors expression, switch in progesterone receptor isoforms [22], local metabolism of progesterone [23], changes in levels of cofactors affecting progesterone receptor (PR) function [24].

Progesterone actions are mediated by two functionally different but structurally highly related intranuclear proteins, progesterone receptor (PR) A and PRB. Functional progesterone withdrawal is mediated by an increase in the myometrial PRA:PRB expression ratio, inducing functional estrogen activation by effecting the expression of estrogen receptor [25,26]. Changes in the level of some of these cofactors may account for the functional progesterone withdrawal, such as a decline in the levels of cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB)-binding protein and steroid receptor coactivators 2 and 3 in human fundal myometrium thus reducing PR transcription [24]. Indeed, progesterone can be metabolized to a less active metabolite, 20-dihydropregesterone that increases after the initiation of labor [23], presenting another potential mechanism for functional progesterone withdrawal.

### 3.3. Oxytocin

Oxytocin, a peptide hormone produced by hypothalamic neurons, and its receptor (OT and OTR) play an important role in
parturition, although their precise role is as yet incompletely understood [27]. An increased pulsatile secretion of oxytocin by neurohypophysis and an increased receptors expression and affinity in myometrium and decidua are observed in labor. Circulating oxytocin does not increase in late pregnancy, but concentration of uterine oxytocin receptors increases toward the end of pregnancy [28], resulting in increased efficiency of oxytocin action as pregnancy progresses. Estrogen increases oxytocin receptor expression and progesterone suppresses such estrogen-induced increase in cultured human myometrial cells. Placental oxytocin acts directly on the myometrium to cause contractions and indirectly by up-regulating prostaglandin production, especially prostaglandin F2α (PGF2α) by the decidua (Fig. 6). PGF2α, in turn, is produced primarily by the maternal decidua and acts on the myometrium to up-regulate oxytocin receptors and gap junctions, thereby promoting uterine contractions [29]. However, OT appears not to be an essential participant in labor as oxytocin (−/−) null mice can deliver normally [30].

### 3.4. Relaxin

The 6-kDa polypeptide hormone relaxin (RLX) belongs to the insulin-like-growth factor family (IGF) and the major protein consists of 57 amino acids and two polypeptide chains (A and B). Relaxin has numerous effects on the reproductive system including endometrial vascularization and remodelling of connective tissue leading to structural changes, regarding loosening of joints and tendons as well as softening of the cervix in preparation for birth [31].

Circulating relaxin is a product of the corpus luteum of pregnancy, which is present in the ovary for the duration of pregnancy. However, relaxin is also a product of the placenta and decidua and acts locally [32,33]. Some of the effects of relaxin include stimulation of procollagenase and prostromelysin, (proMMP-1, proMMP-2) for cervical ripening, as well as a decrease in TIMP-1 [34]. Relaxin is also capable of inhibiting contractions of nonpregnant human myometrial strips, but, paradoxically, relaxin does not inhibit contractions of pregnant human uterine tissue, may be due to the competitive effects of progesterone [35].

### 3.5. Prostaglandins

Prostaglandins (PG) are thought to play a central role in human parturition, acting to stimulate myometrial contractility and ripen the cervix (Fig. 7) [36]. The major precursor for PGs is arachidonic acid, which is stored in glycerophospholipids. The fetal membranes are enriched with two major glycerophospholipids, phosphatidylinositol and phosphatidylethanolamine. As gestation advances, the progressively increasing levels of estrogen stimulate the storage, in fetal membranes, of these glycerophospholipids containing arachidonic acid. A series of fetal membrane lipases, including phospholipase A2 and phospholipase C control the release of arachidonic acid from storage in fetal membrane phospholipids. Once in a free state, arachidonic acid is available for conversion to PG. The second step involves the free arachidonic acid being converted to the PG intermediate, PGH2, in a reaction catalysed by COX enzymes. Finally, PGH2 is converted to prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), PG12, PGD2 and thromboxane by specific synthase enzymes [36].

Prostaglandin levels are increased before and during labor in the uterus and membranes [37]. Many factors affect their production: levels are decreased by progesterone and increased by estrogens, inflammatory cytokines and CRH [38–40]. PGE2 and PGF2α are produced by fetal membranes and other intrauterine tissues and their levels are elevated in the amniotic fluid at term, as well as in labor. This increase in prostaglandin levels is thought to be a critical step in human parturition and fetal membranes obtained from term human pregnancies may show marked increases in PG2 output, and in the expression of COX 2 before labor. PG metabolism plays an important role in altering bioactive PG output in the uterus. PG2 and thromboxane are spontaneously inactivated, while PGE2 and PGF2 are metabolically inactivated by the enzyme 15-hydroxy-PG dehydrogenase (PGDH), which is also subject to regulation in uterine tissues. The net effect of PGs in human labor may be
Regulated by changes at different steps in PG synthesis and metabolism [41,42].

It has been shown that COX-2 mRNA and protein levels increase in intrauterine tissues at term before and during labor. The labor-associated up-regulation of COX-2 involves amnion-derived factors that stimulate and maintain COX-2 transcription, leading to accumulation of COX-2 mRNA and increasing enzyme activity throughout the onset and progression of labor until delivery. Pro-inflammatory cytokines induce COX-2 expression in amnion, chorio-decidual and myometrial cells. Human amnion is a major source of PGs and exhibits a substantial increase in the synthesis of PGE2 with the onset of labor [40].

Prostaglandins, mainly PGE2 and to a lesser extent PGF2α, seem to be the endpoint of the CRH cascade and characterize the action of most of the molecules that participate in term and preterm labor mechanisms. However, they also enhance their own production. They decrease the activity of placental 11β-HSD-2, the enzyme that converts cortisol to cortisone, resulting in a further increase in local cortisol concentrations, this representing another positive feedback mechanism. Moreover, PGE2 stimulates fetal CRH production, yet a further positive feedback loop [41,42,39].

3.6. CRH and ucorortins

Corticotrophin releasing hormone (CRH) is one of the most prominent neuropeptides involved in parturition, acting on stress induced hormonal, vascular and inflammatory responses. Urocortins (Ucn, Ucn2, Ucn3) share sequence homologies with CRH and show similar biological effects. In fact, placenta is capable of synthesizing and releasing several neurohormones and neuropeptides, which act locally in modulating the release of the pituitary-like hormones, resembling the organization of the hypothalamus–pituitary–target gland axes; moreover, they are chemically identical to, and have the same biologic activities as, their neuronal counterparts [31].

CRH stimulates pituitary ACTH secretion and adrenal cortisol production. In the mother, cortisol inhibits hypothalamic CRH and pituitary ACTH release, creating a negative feedback loop [43]. In contrast, cortisol stimulates CRH release by the decidual, trophoblastic, and fetal membranes. CRH, in turn, further drives maternal and fetal HPA activation, thereby establishing a potent positive feed-forward loop [44]. In normal pregnancy, the increased production of CRH from decidual, trophoblastic, and fetal membranes leads to an increase in circulating cortisol beginning in mid gestation. The effects of CRH are enhanced by a fall in maternal plasma CRH-binding protein near term. At term and in labor, circulating levels of CRH, ACTH and cortisol are increased, although they are not necessarily indicative of maternal HPA axis activation. The human placenta and endometrium synthesize and secrete CRH, which drives fetal ACTH and cortisol secretion [45,46]. Placental CRH has complex effects including a role in the onset of labor, resembling the timer of a biologic clock counting from the early stages of gestation and signaling the timing of labor [47,48]. A longitudinal measurement of CRH throughout pregnancy suggests that the placental clock may be set to run fast or slow as early as the first or second trimester of pregnancy. Once the speed of the placental clock is set, the timing of delivery may be predetermined.

The very rapid rise of CRH in late pregnancy is associated with an estriol (E3) surge and critically altered P/E3 and estriol/estradiol (E3/E2) ratios that create an estrogenic environment at the onset of labor [49]. CRH and its related peptides act on CRH receptors (CRH-R1 and CRH-R2) to stimulate E2 and inhibit P4 production in placental cells. CRH-R1 and CRH-R2 stimulated divergent signalling pathways. CRH-R1 increased E2 production via adenyl-cyclase/protein kinase A (AC-PKA) and phospholipase C/protein kinase C (PLC-PKC) signaling and decreased P4 production via PLC-PKC signaling. CRH-R2 increased E2 production and inhibited P4 production via PLC-PKC signaling [50]. CRH regulates myometrial contractility, exerting diverse roles at different stages of gestation. In fact, CRH is involved in both relaxation and contraction of
myometrium and this has been demonstrated to be likely dependent on different patterns of expression and biologic effects of CRH receptors. CRH-R1 contributes to the maintenance of myometrial relaxation during pregnancy through activation of the adenylyl cyclase/cAMP pathway. In contrast, at term CRH-binding induces phosphorylation of CRH-R2 variants, with subsequent stimulation of the phospholipase C/inositol triphosphate, ERK1/2, and RhoA pathways and increase of myosin light chain (MLC20) phosphorylation, promoting myometrial contractility [51–53].

CRH induces the production of chemokines and cytokines in myometrium at term and subsequently results in the cascade of inflammation. The inflammation induced by CRH can lead to activation of uterine contractility. In fact, CRH stimulates the output of chemokines and pro-inflammatory cytokines in human pregnant myometrium, which could induce chemotaxis of monocytes to myometrium and promote inflammation, confirming that human parturition is an inflammatory event [54–56].

CRH modulates prostaglandin production by the fetal membranes and placenta, induces vasodilation of the feto-placental circulation by activating nitric oxide synthase, and stimulates fetal adrenal DHEAS output directly or indirectly via fetal pituitary ACTH, suggesting a role for this neurohormone in fetal lung maturation and adaptive mechanisms in response to the stress of parturition (Fig. 8). Stimulation of the fetal pituitary by CRH increases corticotropin production and, consequently, the synthesis of cortisol by the fetal adrenal gland and maturation of the fetal lungs. In turn, the rising cortisol concentrations in the fetus further stimulate placental CRH production. The maturation of the fetal lungs as a result of increasing cortisol concentrations is associated with increased production of surfactant protein A and phospholipids, both of which have pro-inflammatory actions and may stimulate myometrial contractility through increased production of prostaglandins by fetal membranes and the myometrium itself [57–60].

Placental CRH synthesis is stimulated by the produced fetal cortisol (positive feedback mechanism). A difference exists between placental and hypothalamic CRH, since placental secretion is stimulated and fetal hypothalamic secretion is depressed by cortisol. Thus, although fetal CRH production may be
reduced, placental CRH is increased. Moreover, the potential for fetal cortisol negative feedback action on fetal ACTH production is reduced by increased production of corticosterone-binding globulin (CBG) at the end of pregnancy. Placental estrogens also induce the expression of prostaglandin synthase and, in turn, the production of prostaglandins in chorion and amnion cells. Furthermore, placental estrogens enhance placental CRH production, this forming a second positive feedback loop [61–64] (Fig. 9).

Concerning urocortins [65], Ucn is synthesized and secreted by placenta and fetal membranes, similarly to CRH. However, the secretion patterns of these two peptides are different, as maternal plasma CRH levels keep increasing until term, whereas Ucn levels remain relative constant during gestation and increase only after onset of parturition [66–68]. Ucn has similar effects as CRH, augmenting matrix metalloproteinase, ACTH, and prostaglandin secretion from cultured human placental cells, enhancing myometrial contractility [69,70]. Similarly, Ucn2 is a neuroendocrine factor that is up-regulated at time of parturition and acts as a pro-inflammatory agent in placenta and in myometrium [71]. In fact, Ucn2 is up-regulated by TNF- via nuclear factor-B (NF-kB) in myometrium cell lines and increased pro-inflammatory mediators and prostaglandin F receptor expression via CRH-R2, influencing uterine contractility [72] (Fig. 9).

4. Conclusion

The mechanisms involved in human pregnancy maintenance and parturition are highly complex and involve mother, fetus and placenta. Despite extensive research, the integrated mechanisms underlying the onset of human parturition are not yet fully elucidated [73]. Inflammation is central in the process of labor, while prostaglandins, CRH, Ucns and oxytocin are key placental factors which mediate both endocrine (metabolism, immune function, cardiovascular changes) and paracrine (uterine contractility, local hormone production) mechanisms.

Disclosure of interest

The authors declare that they have no competing interest.

References


