Activation of simultaneous pathways in the initiation of parturition in humans

G Ventolini*

Abstract

Introduction
Despite of numerous studies and remarkable progress in the understanding of human reproduction, the pathways by which parturition is initiated in humans remain unclear. This paper discusses the activation of pathways in the initiation of parturition in humans.

The Hypothesis

Human parturition is a physiological reaction process initiated by the simultaneous activation of pro-labour inflammatory pathways in the utero-placental and cervicovaginal domains.

Evaluation of Hypothesis

Progesterone controls uterine quiescence by reducing myometrial responsiveness to cytokines. Following anti-progestinic effect. Cervical ripening has been associated with the activation of pathways sharing a pro-inflammatory physiological reaction that includes the expression of the inducible isoform of the nitric oxide synthase. Oxytocin seems to be the trigger for uterine contractions because there is a maximal oxytocin receptor formation and concentration and gap junction formation in the myometrium in parturition. The steroids have a crucial role in controlling oxytocin receptor formation. Oxytocin is also one of the stimuli that increase uterine prostaglandin synthesis. Coupling of oxytocin receptor occupancy and PG synthase activity in the myometrium contributes to the progression of parturition. The foetus may be involved in the coordination of placental oestrogen production, through mechanical distention of the uterus, and through its secretion of neuro-hypophysial hormones as well as other stimulators of prostaglandin synthesis. Glucocorticoids, prostaglandins, oestrogen and placental corticotropin-releasing hormone are facilitators in the onset of parturition.

Conclusion

Human parturition is a physiological reaction process initiated by the simultaneous activation of pro-labour inflammatory pathways in the utero-placental and cervicovaginal domains.

Introduction

Liggins1 reported 32 years ago that foetal maturation was promoted by corticosteroids and hindered by hypophysectomy. In addition, Liggins observed that an increase in corticosteroid concentration, in the foetal circulation preceding parturition, was producing speedy organ maturation, therefore enhancing foetal viability and contributing to the parturition mechanisms. He called the above changes “preparation for birth”.

Despite of numerous studies and remarkable progress in the understanding of human reproduction since then, the pathways by which parturition is initiated in humans remain unclear.

We may consider pregnancy as a state characterized by a complex interaction of important synchronized factors involved in maintaining uterine quiescence, then preparing the female body for birth by initiating the process of parturition2.

In addition, we may view parturition as the result of composite, partially defined events that are tightly regulated by a variety of pathways and mediators of endocrine, nervous and immune systems3. Among them are changes in hormonal levels of oestrogen and progesterone, corticotropin-releasing hormone (CRH) and cortisol; pro-inflammatory cytokine (PIC) reactions; increased production of prostaglandins (PGs) and oxytocin; connective tissue remodelling and myometrical preparation for contracility. This paper discusses the activation of simultaneous pathway in the initiation of human parturition.

Hypothesis

Human parturition is a physiological reaction process initiated by the simultaneous activation of pro-labour inflammatory pathways in the utero-placental and cervico-vaginal domains of a pregnant woman. This activation allows parturition to take place through cervical ripening followed by myometrical stimulation.
Nuclear factor κB seems to modulate these functions by regulating the expression of PGs, chemokines and PICs involved in both term and preterm labour.

**Evaluation of Hypothesis**

Progestosterone controls uterine quiescence by reducing myometrial responsiveness to cytokines. Following anti-progestin treatment, polymorphonuclear granulocytes, macrophages and mast cells infiltrate into the cervix. Anatomical regionalization in labour promotion supports a strong association between inflammatory activation and onset of preterm labour. Nuclear factor κB seems to modulate these functions by regulating the expression of PGs, chemokines and PICs involved in both term and preterm labour. In guinea pigs, during late pregnancy, the cytokines, interleukin-8 (IL-8) and IL-1 beta induce a cervical ripening that is morphologically similar to the anti-progestin effect. Cervical ripening has been associated with the activation of pathways, sharing a pro-inflammatory physiological reaction that includes the expression of inducible isoform of the nitric oxide synthase (NOS). Oxytocin seems to be the trigger for uterine contractions because there is a maximal oxytocin receptor formation and concentration in the myometrium in parturition. The steroids have a crucial role in controlling oxytocin receptor formation. Oxytocin is also one of the stimuli that increase uterine PG synthesis. Coupling of oxytocin receptor occupancy and PG synthase activity in the myometrium contributes to parturition progression. The foetus may be involved in the coordination of placental oestrogen production, through mechanical distention of the uterus, and through its secretion of neuro-hypophysial hormones as well as other stimulators of PG synthesis.

**Empirical Data**

The myometrial quiescence is maintained by progesterone. Progesterone antagonists and progesterone synthase inhibitors induce parturition in species showing no spontaneous progesterone withdrawal before parturition. In guinea pigs, all anti-progestinics increased myometrial responsiveness to oxytocin and PGs markedly increasing myometrial gap junctions. Progesterone may control uterine quiescence by reducing myometrial responsiveness to cytokines.

Glucocorticoids, PGs, oestrogen and placental CRH are facilitators in the onset of parturition. The presence of CRH produced by the placenta and myometrium in the circulation is a unique feature of primate pregnancy. Anatomical regionalization in labour promotion supports a strong association between inflammatory activation and onset of preterm labour.

Following anti-progestin treatment, polymorphonuclear granulocytes, macrophages and mast cells infiltrate into the cervix therefore cytokines and other chemotactic agents may mediate this effect. In guinea pigs, during late pregnancy, the cytokines IL-8 and IL-1 beta induce a cervical ripening that is morphologically similar to the anti-progestin effect.

Cervical ripening has been associated with the activation of pathways, sharing a pro-inflammatory physiologic reaction that includes the expression of inducible isoform of NOS. Nitric oxide (NO) is assumed to be the ultimate mediator in the mechanisms of cervical ripening. A reduction of NO activity in the uterus, concomitant with its activation in the cervix, facilitates human parturition. Local application of NO donors induces similar structural changes observed during cervical ripening. In addition, NO donors are clinically effective in enabling first trimester dilation and curettage. Furthermore, an increased activity of NO in the cervix is associated with shortening.

A complex interaction between cytokines, PGs and NO is the key biochemical pathway accounting for the preterm ripening of the cervix. Cervical competence is a key feature in parturition. Cervical ripening (modification in collagen fibres, water content, proteoglycans and hyaluronic acid levels) precedes myometrial contractions by several weeks, signifying that parturition is a protracted process in which uterine contractions are late events.

The stimulation of the uterine muscle during labour results from an interaction between oxytocin and PGF2 alpha. Recent evidence suggests that oxytocin is most important for the initial phase of labour, whereas increased synthesis of PGF2 alpha is essential for the progression of labour. PGE2 may have an important role in the ripening of the cervix.

Oxytocin seems to be the trigger for uterine contractions because there is a maximal oxytocin receptor formation and concentration and gap junction formation in the myometrium in parturition. The steroids have a crucial role in controlling oxytocin receptor formation. Oxytocin is also one of the stimuli that increase uterine PG synthesis. Coupling of oxytocin receptor occupancy and PG synthase activity in the myometrium contributes to progression of parturition. The foetus may be involved in the coordination of placental oestrogen production, through mechanical distention of the uterus, and through its secretion of neuro-hypophysial hormones as well as other stimulators of PG synthesis.

In parturition, PICs, IL-1 beta, IL-6, IL-8 and tumour necrosis factor alpha (TNF-alpha) are present independently of an infection. The uterus is activated by PIC through stimulation of expression and production of uterine activation proteins (UAPs). One action is to stimulate PG synthesis, predominantly of PGF2 alpha and its receptor, PTGFR.
In addition, PIC increases the synthesis of matrix metallo-proteinases (MMPs), vascular endothelial growth factor (VEGF) and progesterone receptor C isoform, consequently decreasing myometrial progesterone sensitivity. PGF2 alpha may act through its receptor in the amplification cytokine functions. Sequentially, VEGF augments uterine leukocyte recruitment, and MMP-9 promotes activation of cytokines. PIC also decreases the activity of 11beta-hydroxysteroid dehydrogenase responsible for increasing intrauterine cortisol concentrations. Cortisol drives PG synthesis. In coordination, all these pathways activate the myometrium and trigger uterine contractions and promote parturition 10.

Nuclear factor κB seems to be a key modulator of these pathways and functions by regulating the expression of PGs, chemokines and PICs involved in both term and preterm labour 1.

Consequences of Hypothesis

The clue in the initiation of parturition in humans seems to stand in the simultaneous activation and coordination of PIC pathways in the utero-placental and cervico-vaginal domains. In our current research study, we are actively collecting vaginal samples in pregnant patients before and at parturition to more precisely identify cytokines, proteins and lactobacillus implicated in that process.

Discussion

Liggins 1 reported thirty-five years ago that foetal maturation was promoted by corticosteroids and hindered by hypophysectomy. In addition, Liggins observed that an increase in corticosteroid concentration, in the foetal circulation preceding parturition, was producing speedy organ maturation, therefore enhancing foetal viability and contributing to the parturition mechanisms. He called the above changes “preparation for birth”.

Later, 11 put forward the concept that the coordination of oxytocin receptors and gap junction formation with PG synthesis was important for initiating and maintaining labour in humans. In addition, they concluded that the foetus itself was involved through influencing placental oestrogen production, mechanical uterine expansion and secretion of neuro-hypophysial hormones as well as PG synthesis.

Mammals (other than humans) in late pregnancy initiate parturition by progesterone withdrawal using the following pathways: luteolysis, variations in function of progesterone receptor and up-regulation of placentale P450c17 hydroxylase 4.

Conversely in hemochorial placentation, that does not happen in species like humans. Other factors like anti-inflammatory cytokines, steroid and polypeptide hormones and PGs have primary pregnancy-associated functions, including facilitation of parturition 1. Macrophages and non-antigen-specific natural killer cells that provide innate immunity are abundant and highly specialized in the maternal-foetal interface. Moreover, the human placenta produces hormones, growth factors and cytokines. Two of these hormones, CRH and uroctin (new ligand of CRH receptor), are also secreted by choriion, amnion and uterine decidua 6.

The role of progesterone in parturition has received a lot of attention. Progesterone antagonists, like Mifepristone (RU486), and progesterone synthase inhibitors, like epostane, have labour-inducing activity, increase myometrial responsiveness to PGs and oxytocin as well as induce cervical ripening. These activities were studied in animal model species (guinea pigs and Tupaja belangeri) that do not exhibit progesterone withdrawal before parturition; they effectively induce pre-term parturition although they did not in mid-pregnancy. It has been reported that following anti-progestinic treatment, there is an infiltration of polymorphonuclear granulocytes, mast cells and macrophages into the cervix, which suggests that cytokines may be the mediators of this effect. In late-pregnant guinea pigs, it has been observed that IL-8 and IL-1 beta induce cervical ripening that is comparable to the one caused by anti-progestins. Chwalisz 10 reported that progesterone maintains uterine quiescence by down-regulating gap junctions and inhibiting cervical ripening.

Furthermore, a role for IL-1 beta, IL-6, IL-8 and TNF-alpha was noticed to be manifested independently of the presence of infection in preterm and term births. Uterine tissues advance through sequential alterations that initiate towards the end of pregnancy from relative uterine quiescence to uterine stimulation. The uterine activity is triggered by PIC through stimulation of the expression and production of UAPs.

One of these actions is the stimulation of PG synthesis. PGF2 alpha and its receptor, PTGFR, are particularly important for labour. In addition, PICs are able to increase the synthesis of MMPs, VEGF and the progesterone receptor C isoform, which leads to decreased tissue progesterone responsiveness. Some of these effects are replicated by PGF2 alpha, suggesting that it may act via its receptor to amplify the direct actions of cytokines.

In turn, VEGF may enhance leukocyte recruitment to the uterus, and MMP-9 may promote activation of inactive pro-form cytokines. PICs also decrease the activity of 11beta-hydroxysteroid dehydrogenase, which is likely to increase intrauterine cortisol concentrations. In turn, cortisol may drive PG synthesis.

Together these feed-forward mechanisms activate the uterus, trigger the production of uterine contractile stimulants and lead to labour and delivery 10-12.
The local application of NO donors in both animals and humans induces ultra-structural changes similar to those occurring during physiological cervical maturation. NO donors have proven to be clinically effective in facilitating first trimester dilation and curettage. Preliminary data also suggest that in women presenting with threatening preterm labour, there is increased activity of NO in the cervix, which is associated with shortening. A complex interaction between cytokines, PGs and NO is the key biochemical pathway accounting for the preterm ripening of the cervix.

Recently, MacIntyre proposed that pregnancy could be characterized by a complex interplay of inflammatory events regulated by both the acquired and innate immune systems. He suggested that parturition could be described as the activation of "pro-labour" inflammatory pathways that promote myometrial activation and cervical ripening. In addition, he put out that a premature activation by infection of the described pathways could cause preterm labour and birth. He also identified nuclear factor κB as the principal moderator of these functions by regulating the expressions of PGs chemokines and PICs involved in preterm and term labour.

**Conclusion**

Human parturition is a physiological reaction process initiated by the simultaneous activation of pro-labour inflammatory pathways in the utero-placental and cervico-vaginal domains.

**Abbreviations list**

CRH, corticotropin-releasing hormone; IL, interleukin; MMP, matrix metalloproteinase; NO, nitric oxide; NOS, nitric oxide synthase; PG, prostaglandin; PIC, pro-inflammatory cytokine; PTGFR, prostaglandin F receptor; TNF alpha, tumour necrosis factor alpha; UAP, uterine activation protein; VEGF, vascular endothelial growth factor.

**References**