A SZÜLÉS BEINDULÁSA: MECHANIZMUS ÉS JELENTŐSÉG (Összefoglaló)

INITIATION OF LABOUR: MECHANISMS AND SIGNIFICANCE (Review)
Presented in part: Hungarian Paediatric Association, Annual National Paediatric Congress, 22-24 September, 2016 Szeged, Hungary. [Abstract in Hungarian]

Kérdések:
• mi indítja be a szülést?
• hogy miért pont 40 hét múlva? – A szülés megindulásának titkai
• egyáltalán: mi az, ami megismerhető?
• van-e a témának különlegessége a koraszülés vonatkozásában?

Válaszok:
• háromféle alap-mechanizmus különböztethető meg (mechanikai, „magzati tüdő” és a Corticotropin Releasing Hormone (placenta)
• ma sem tudjuk pontosan, hogy van-e egy közvetlen kiváltó mozzanat, de egyre több tényező szerepe igazolódik (pl. méret – érett, ösztrogén, oxitocin, idegek és hormonok)
• tudomány-filozófiai szempontból helyesebb az elsődleges „primum movens” **(initiatio)** helyett az okok láncolatának, az elősegítő folyamat **(promotio)** lépéseinek tisztázása
• maga a koraszülés (és/vagy „koraszülöttség”) egy sajátságos szindróma, számos okkal és tényezővel (pl. infectio/inflammatio, relaxin, oxidatív stressz, sima izom cytoskeleton). Ennek „előre jelzése” **(praedictio)** a – népegészségügyi, epidemiológiai jelentőségű – megelőzés **(praeventio)** lehetőségét rejti magában.

További adatok:

Az első nagyobb – az endokrin szabályozás szerepét hangsúlyozó – összefoglaló (1983) óta eljutottunk **a genetika, molekuláris biológia, a computeres modellezés** területére, és jórészt tisztázódott a magzati, az anyai és a placentáris tényezők szerepe. Mindezek akárcsak lista-szerű felsorolása itt most nem lehetséges; a megtett út **mérföldköve**inek (pl. az érett és koraszülés biológiai alapjainak és tényezőinek állat-élettani és humán vonatkozásai, inflammatio, biokémiai aspektusok, méhizom kontraktilitás és cytoskeleton, az endokrin, parakrin és autokrin mechanizmusok, a szülés endokrinológiájának és élettanának modern összefoglalói, a magzati tüdő surfactant hormonja, a pulmonális collectinek, a foeto-maternális jelátvitel, a mikroRNS-ek szerepe) vázlatos ismertetése mellett két fontos „állomás”-ra azonban érdemes a figyelmet külön is felhívni.

Az ausztrál szülész-fiziológus (Brennecke SP, Parkington HC) kutató csoport [általam már ismertetett (In: Gyermekgyógyászati Klinika honlapja, Továbbképzések, Ioncsatornák – betegségek) témában] kimutatta **a méh izomzatában egy K+ csatorna** jelenlétét, amely a kontraktilitást befolyásolja. Ennek zavara vezethet – többek között, leegyszerűsítve – túlhordáshoz, fájásgyengeséghez, amely megfelelő „antagonista” szerrel hatékonyan befolyásolható. Az ellenkező irányból megközelítve, elképzelhető, hogy (távlatilag) a myometrium „korai” aktivitásának gyógyszeres befolyásolásával a koraszülés megelőzhető.

A texasi (Mendelson CR) munkacsoport vetette fel és igazolta a **magzat** szerepét a szülés beindulásában. Igazolták a szteroid receptor koaktivátor **(SRC-1 és -2)** transzkripciós regulátorok, s a hatásukra keletkező felületaktív fehérje **(SP-A)**, valamint a – hasonló bioszintézis útvonalon keletkező – proinflammatorikus vérlemezke aktiváló faktor **(PAF)** jelentőségét. Ezek ugyanis – a közfelfogásban nem eléggé ismert – immunfunkciójuk révén a magzatvíz-méhizom gyulladásos útvonalon át, továbbá a progeszteron receptor funkció csökkentésével fokozzák a kontraktilitási gének expresszióját „Minél inkább megértjük a normál lefolyású 40 hetes terhesség során a szülés beindításában szerepet játszó tényezőket, annál nagyobb eséllyel tudjuk a koraszülést megakadályozni”. (Mendelson CR)

What initiates labour?

Kerry Anderson

Foetal Lung Theory

- SP-A is a signaling protein found in the lungs that also aids macrophage action. It is thought that levels rise when the lungs are developed and this activates foetal macrophages to embed in the uterus and initiate contraction.
- Evidence comes from the fact that many pre-term labours are associated with infection of membranes and that bacteria bind to the same receptor on macrophages as SP-A
- Research in mice shows induction of labour by SP-A and delayed labour by giving antibody

Mechanical Theory

- Uterine Distension Theory: supported by the fact that multifoetal pregnancies and those with polyhydaminos are at greater risk for pre-term labour.
- Ferguson's reflex: increases PGF2a, mechanism unclear.

CRH Theory

- CRH from the placenta (anencephaly) is stimulated by glucocorticoids.
- Increased CRH seems to increase foetal ACTH and cause placental vasodilatation, prostaglandin production and myometrial contractility.
- It also enables the placenta to convert oestrogen to progesterone which has been shown to induce labour at any stage.

Currently three big theories ...

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Ferguson reflex

The **Ferguson reflex** is the name given to the neuroendocrine reflex comprising the self-sustaining cycle of uterine contractions initiated by pressure at the cervix or vaginal walls. It is an example of positive feedback in biology. The Ferguson reflex occurs in mammals.

Mechanism

Upon application of pressure to the internal end of the cervix, oxytocin is released, which stimulates uterine contractions, which in turn increases pressure on the cervix (thereby increasing oxytocin release, etc.), until the baby is delivered. Sensory information regarding mechanical stretch of the cervix is carried in a sensory neuron, which synapses in the dorsal horn before ascending to the brain in the anterolateral columns (ipsi and contralateral routes). Via the median forebrain bundle, the efferent reaches the PVN and SON of the hypothalamus. The posterior pituitary releases oxytocin due to increased firing in the hypothalamo-hypophyseal tract. Oxytocin acts on the myometrium, on receptors which have been upregulated by an increasing estrogen-progesterone ratio. This causes myometrial contraction and further positive feedback on the reflex.

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Hogy miért pont 40 hét múlva? - A szülés megindulásának titkai
Szerző: Máriáss Márta
2008. március 8. | Frissítve: 2015. augusztus 9. **Forrás:** hazipatika.com

Hogy mi váltja ki a szülés megindulását, egyelőre nem ismert pontosan, de néhány történésben már biztosak lehetünk.

Méretes és érett baba, egyre több ösztrogén hormon
A szülés egyik megindítója a gyermek kellő mérete. A kilencedik hónapban súlya hetente mintegy 250 grammot nő. Az a nyomás, amit a baba belülről fejt ki a méhfalra, egyszer csak eléri azt a határt, mellyel a baba jelt ad az anya szervezetének a szülés megindítására.
A szülés időpontját a baba érettsége, fejlettsége is befolyásolja. Döntő ideg- és hormonrendszerének, főként agyalapi mirigyének (hipofízis) és mellékveséjének fejlettsége. Ha hipofízise kellően fejlett, ösztrogénhez igen hasonló hormon termelésébe kezd. Márpedig meghatározó a progeszteron és ösztrogén hormonok egymáshoz képesti arányának megváltozása. A várandósság végén csökken a progeszteron (sárgatest-hormon) jelenléte. Magas vérbeli koncentrációjának a terhesség fenntartása volt a feladata: meggátolta a méhösszehúzódásokat. Koncentrációja nem csökken lényegesen, de az ösztrogén hatásai kerülnek túlsúlyba, s lesznek meghatározók. Az ösztrogének aktiválják az anyaméh izomzatában termelődő két másik hormonra, az oxitocinra és prolaktinra érzékeny receptorokat.
A fejlett magzat által kibocsátott hormonok is hatnak a méhlepényre, a méhlepény anyagai, enzimei pedig az anyai ösztrogén-, adrenalin- és noradrenalin hormon termelését fokozzák, majd pedig ezek visszahatnak a magzat hormonháztartására, érésére. Akkor hát hol is kezdődik a szülés? Apránként, az anyai és magzati szervezet kölcsönhatásaiból egy önerősítő folyamat veszi kezdetét.

Itt is, ott is gyűlik az oxitocin

Az anya hipofízisének hátsó lebenyében a terhesség alatt egyre több lesz az oxitocin, a méh simaizomzatának összehúzását beindítani képes hormon. Az oxitocin a magzat hipofízisében is termelődik. A magzati mellékvese egyszer csak az oxitocin előalakjait kezdi termelni. Oxitocin a méhlepény anyai eredetű szöveti rétegében (decidua) is termelődik. A szülés megindulásához szükséges oxitocin az anya szervezetében és a méhlepényben végbementő változások, a születendő baba mozgása, a méhnyakra gyakorolt hatása nyomán áll elő.

A terhesség végén a méhlepényben prosztaglandin hormonok is képződnek. A prosztaglandin-termelés növekedése közvetetten azt eredményezi, hogy a méhizomzat érzékenyebben reagál az oxitocinra, ahogy méhszáj érése felpuhulása is ennek köszönhető.

A rendszertelen vagy jósló fájások idején, amikor a hasfal megkeményedik, még alig van oxitocin a vérben, de mennyisége egyre nő.

A fájások helye - előkészületek a méhizomzatban

A fájások főszereplője az anyaméh falának középső rétegét alkotó, mintegy két centiméter vastag simaizom, vagyis a méhizomzat (miometrium). A várandósság idején az ösztrogének készítik elő arra, hogy képes legyen erőteljes összehúzódásokra. A méhben kiépülnek olyan adrenerg receptorok, melyek egyik csoportjának segítségével a méhizomzat összehúzódásra, másik részükkel elernyedésre késztethető. A szülés idejére készen állnak a miometriumban az oxitocint fogadni képes és a prosztaglandin-receptorok, melyek az összehúzódásokra adott parancsot közvetítik.

A méhnyak a terhesség alatt a fertőzésektől védett, és nem enged a rá nehezedő nyomásnak. A progeszteron hatására a méhnyak sejtjei nyákdugóvá összeálló váladékot választottak ki. A méhnyak vérellátása megnő, a szülés idejére percenként 750 ml vér tud megfordulni szövetében. Élénk mirigyműködése nyomán vastagabb, duzzadt lett. A terhesség végére ösztrogén-hatásra megérik, vagyis rugalmas kollagén rostjai lebomlanak. A méhnyak falának szilárdsága a nem várandós állapothoz képest mintegy 10-12-szer gyengébb, ez a felpuhulás a nagymérvű tágulás feltétele.

Idegek és hormonok unszolása

A méhizomzatot számtalan idegi és hormonhatás egyidejűleg szinte bombázza, így az nem kerülheti el sorsát, az összehúzódásokat. A szülés beindulásában résztvevő hormonok termelődnek a méhlepényben, az anya petefészkében, agyában, a hipofízisben, a mellékvese-kérgében, s ugyanúgy a magzat azonos szerveiben is. Még a magzat tüdejében is termelődnek olyan molekulák, amelyek áttételesen hatnak a méhizomzatra, annak összehúzódására. A résztvevő hormonok puszta felsorolása is hosszadalmas, vazopresszin, ösztrogén, progeszteron, kortizol, adenocorticotropin (ACTH), jónéhányuk magzati párja, valamint a lepényi hormonok, például a CRH és a relaxin.

A vazopresszin nevű hormont például a hipofízis "gyártja", s az oxitocinhoz hasonlóan a méhizomzatot készteti összehúzódásra. A havi ciklusok idején a méhizomzat főleg erre reagál. A szülés idejére a vazopresszint megkötni képes receptorokból is jóval több található a méhizomzatban. E hormon szerepe jó példa arra, hogy az anya fizikai és lelki állapota miként befolyásolja a történéseket. Ha az anya elfárad, kevés folyadékot iszik, só- és vízhiányos a szervezete, vízháztartása helyreállítására vazopresszint kezd termelni. Igen ám, csakhogy ezzel többek között a méhizomzatra is hat. A lelki terhek adrenalinszintjét növelve vezetnek fájásokhoz.

Időjárás és egyéb bizonytalan tényezők

Tietze 1984-ben egy New York-i orvospáros adatait publikálta, akik 1948 és 1957 közötti adatokból azt az eredményt kapták, hogy a legtöbb gyermek egyértelműen holdtölte után, a legkevesebb pedig újholdat követően születik. Az időjárás, légnyomás is befolyásolhatja a születést. Dr. Geréb Ágnes, szülészorvos például megfigyelte, hogy olyan időjárási viszonyok esetén, amikor egy-két napon belül esősre fordul az idő, gyakoribb a fájások nélküli, idő előtti burokrepedés. Magyarázat nincs rá, de egy biztos, az időjárási és nyomásviszonyok is hatással vannak a szülésre, annak beindulására.

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Ahogy sejtettük is, nyoma sincs egyfajta biológiai gongütésnek, melynek egyértelmű hangjára hirtelen beindul a szülés. A baba és a mama testének párbeszéde, környezetük jeleinek értékelés nyomán együttes döntés eredménye a szülés megindulása, mely óvatosan, apránként veszi kezdetét, mintha csak anya és gyermeke együtt figyelnék, alkalmas-e az idő a nagy pillanatra, s készen állnak, hogy bármely pillanatban beavatkozzanak, leálljanak, vagy gyorsítsák a csoda lezajlását, az új élet születést.

Ignoramus et ignorabimus

The Latin maxim ***ignoramus et ignorabimus***, meaning "we do not know and will not know", stood for a position on the limits of scientific knowledge, in the thought of the nineteenth century. It was given credibility by Emil du Bois-Reymond, a German physiologist, in his *Über die Grenzen des Naturerkennens* ("On the limits of our understanding of nature") of 1872.

Emil du Bois-Reymond (1818–1896)

Hilbert's reaction

David Hilbert suggested that such a conceptualization of human knowledge and ability is extremely pessimistic. We can find answers to many of these questions, and by considering them unsolvable, we limit our understanding. In 1900, in an address to the International Congress of Mathematicians in Paris, Hilbert suggested that answers to the problems of mathematics are possible with human effort. He declared that, "In mathematics there is no *ignorabimus*." „We must not believe those, who today, with philosophical bearing and deliberative tone, prophesy the fall of culture and accept the *ignorabimus*. For us there is no *ignorabimus*, and in my opinion none whatever in natural science. In opposition to the foolish *ignorabimus* our slogan shall be: *Wir müssen wissen — wir werden wissen*. ('We must know - we

David Hilbert

Physiology of parturition

Errol R Norwitz, MD, PhD

Parturition cascade — It is likely that a "parturition cascade" exists at term which removes the mechanisms maintaining uterine quiescence and recruits factors promoting uterine activity. Given its teleological importance, such a cascade would likely have multiple redundant loops to ensure a fail-safe system of securing pregnancy success (and thus preserving the species). In such a model, each element is connected to the next in a sequential fashion, and many of the elements demonstrate positive feed-forward characteristics typical of a cascade mechanism.

The sequential recruitment of signals that serve to augment the labor process suggest that **it may not be possible to single out any one signaling mechanism** as being responsible for the initiation of labor. Therefore, it is prudent to describe such mechanisms as being responsible for **"promoting",** rather than **"initiating",** the process of labor.

The Scientist
May 2013 Issue

Why So Soon?

Researchers are using modern experimental tools to probe the mysterious molecular pathways that lead to premature labor and birth.

By Bob Grant | May 1, 2013

It is a surprise that a phenomenon such as labor is essential for the survival of our species, and yet we know very little about the mechanisms that control it.

Roberto Romero, Wayne State University

In virtually every nonhuman mammalian species levels of progesterone decline dramatically at the end of pregnancy. In humans, however, circulating progesterone levels do not drop off. For human labor to begin there must be changes involving progesterone receptors within myometrial cells that make the receptors less responsive to the flood of progesterone, a phenomenon called “functional progesterone withdrawal.”

Work centers on interactions between a family of microRNAs (miRNAs), miR-200, and the target transcription factors, called zinc finger E-box binding homeobox proteins, ZEB1 and ZEB2. First using gene expression arrays and more recently with human tissues in vitro and mouse models of preterm labor, miR-200 miRNAs, ZEB1, and ZEB2 act as genetic switches in uterine tissues during the transition from pregnancy to labor.[1]
Here’s how it works: during pregnancy, when progesterone binds to progesterone receptors, myometrial cells begin producing more ZEB1, which inhibits the expression of genes coding for contractile proteins essential for the uterine contractions that define labor. ZEB1 and ZEB2 also inhibit the expression of the miR-200 family, and their decline further upregulates the ZEBs. This feedback loop maintains the uterus in a quiescent, noncontractile state for the full duration of pregnancy. But when progesterone receptor function becomes altered, levels of the ZEBs drop, contractile proteins are expressed, and miR-200 levels rise rapidly. This cascade ultimately leads to the wholesale uterine contractions of labor.

Lancet. 2008 Jan 5;371(9606):75-84.
Epidemiology and causes of preterm birth.
Goldenberg RL et al,

Abstract
This paper is the first in a three-part series on preterm birth, which is the leading cause of perinatal morbidity and mortality in developed countries. Infants are born preterm at less than 37 weeks' gestational age after: (1) spontaneous labour with intact membranes, (2) preterm premature rupture of the membranes (PPROM), and (3) labour induction or caesarean delivery for maternal or fetal indications. The frequency of preterm births is about 12-13% in the USA and 5-9% in many other developed countries; however, the rate of preterm birth has increased in many locations, predominantly because of increasing indicated preterm births and preterm delivery of artificially conceived multiple pregnancies. Common reasons for indicated preterm births include pre-eclampsia or eclampsia, and intrauterine growth restriction. Births that follow spontaneous preterm labour and PPROM – together called spontaneous preterm births – are regarded as a syndrome resulting from multiple causes, including infection or inflammation, vascular disease, and uterine overdistension. **Risk factors** for spontaneous preterm births include a previous preterm birth, black race, periodontal disease, and low maternal body-mass index. A short cervical length and a raised cervical-vaginal fetal fibronectin concentration are the strongest predictors of spontaneous preterm birth.

Adv Clin Exp Med. 2013 Mar-Apr;22(2):283-8.
Initiation of preterm labor.
Pawelec M et al

Abstract
Preterm births are still a major problem in obstetrics. It is estimated that preterm births occur in about 12% of all pregnancies. Due to advances in medical technology and better care of fetuses and premature babies, the preterm mortality rate has been falling (as recently as 1995 the survival rate in the US for premature infants born at 34 weeks amounted to only a fraction of the corresponding rate for those born after 37 weeks). In the US in 2005, preterm births cost society approximately $26 billion, and medical care for premature babies cost more than $51 billion. Only the richest countries can afford such costly medical care. That is why it is not only the individual aspects but also the social aspects that are important when studying preterm birth mechanisms and ways of preventing them. The existing research indicates that both spontaneous mature birth and preterm birth begin and proceed in a similar manner. This is confirmed by the similar involvement in both processes of corticotropin-releasing hormone, urocortin, extracellular stress protein HSP70 (amniotic fluid heat shock protein), prostaglandins, proinflammatory cytokines or glucocorticosteroids. Apparently, at the beginning of either a preterm birth or a term birth, there is a stimulus that ends the development of the fetus or initiates birth. This stimulus works via feedback through placental hormones and through substances present in the fetal membranes, ultimately leading to functional progesterone withdrawal (FPW), thus leaving the uterus sensitive to contractive factors.

Science. 2014 Aug 15;345(6198):760-5.

Preterm labor: one syndrome, many causes.

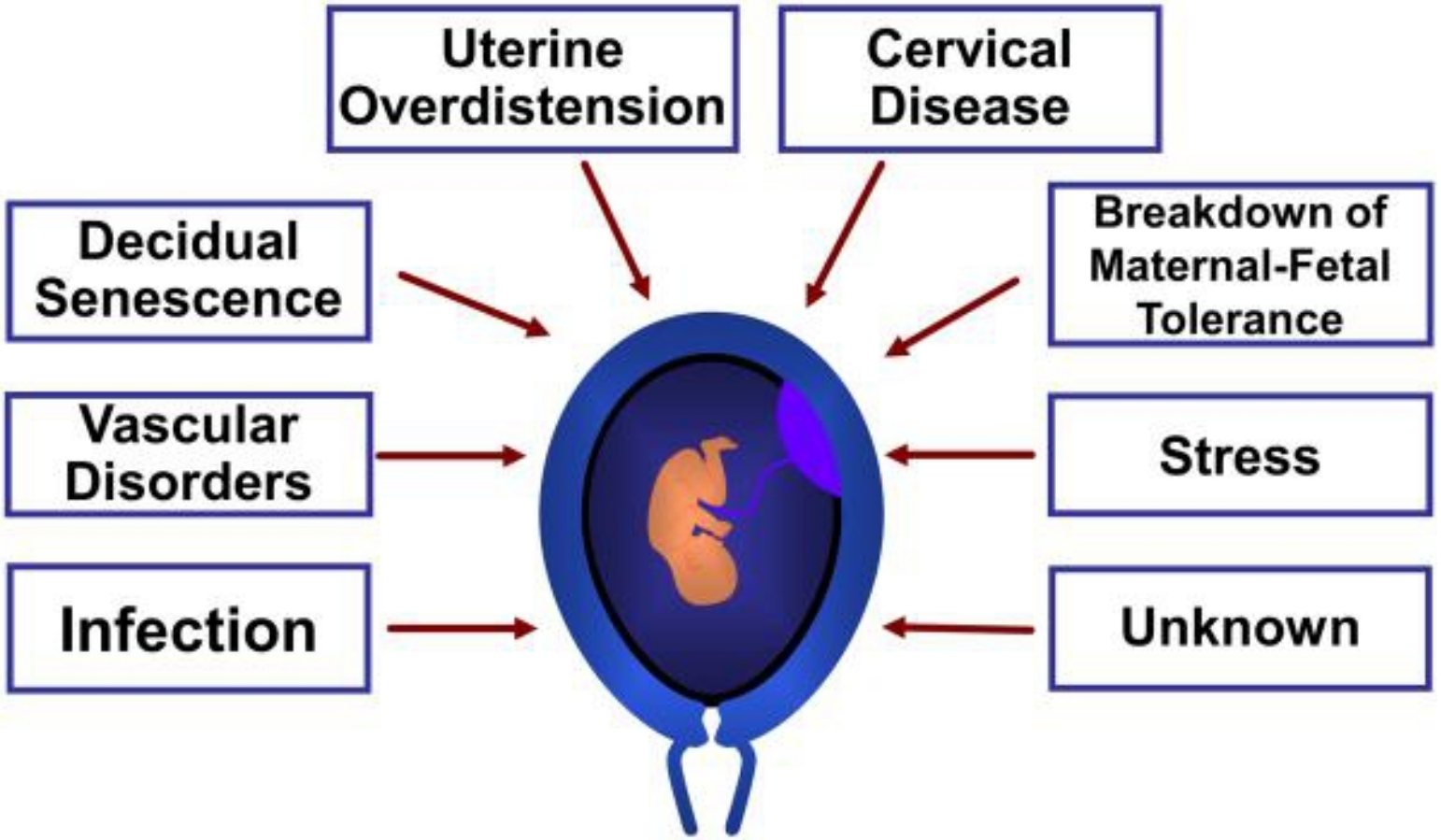
Romero R, Dey SK, Fisher SJ.

Abstract

Preterm birth is associated with 5 to 18% of pregnancies and is a leading cause of infant morbidity and mortality. Spontaneous preterm labor, a syndrome caused by multiple pathologic processes, leads to 70% of preterm births. The prevention and the treatment of preterm labor have been long-standing challenges.

We summarize the current understanding of the mechanisms of disease implicated in this condition and review advances relevant to intra-amniotic infection, decidual senescence, and breakdown of maternal-fetal tolerance.

The success of progestogen treatment to prevent preterm birth in a subset of patients at risk is a cause for optimism. Solving the mystery of preterm labor, which compromises the health of future generations, is a formidable scientific challenge worthy of investment.



Proposed mechanisms of disease implicated in spontaneous preterm labor. Genetic and environmental factors are likely contributors to each mechanism.

Am J Obstet Gynecol. 2012 Feb;206(2):119-23.
The preterm birth syndrome: a prototype phenotypic classification.

Villar J et all

Abstract
Preterm birth is a syndrome with many causes and phenotypes. We propose a classification that is based on clinical phenotypes that are defined by ≥ 1 characteristics of the mother, the fetus, the placenta, the signs of parturition, and the pathway to delivery. Risk factors and mode of delivery are not included. There are 5 components in a preterm birth phenotype: (1) maternal conditions that are present before presentation for delivery, (2) fetal conditions that are present before presentation for delivery, (3) placental pathologic conditions, (4) signs of the initiation of parturition, and (5) the pathway to delivery. This system does not force any preterm birth into a predefined phenotype and allows all relevant conditions to become part of the phenotype. Needed data can be collected from the medical records to classify every preterm birth. The classification system will improve understanding of the cause and improve surveillance across populations.

In Vivo. 2012 Sep-Oct;26(5):799-812.

Review: Impact of mediators present in amniotic fluid on preterm labour.

Vrachnis N et al.

Abstract

Preterm birth continues to be one of the most important issues in current obstetric medicine, being the single largest cause of perinatal morbidity and mortality. The signals that initiate preterm and term labour remain a mystery. Intrauterine inflammation with the secretion of cytokines is one of the accepted explanations for the mechanism of initiation of preterm labour. This review discusses the current understanding of the molecular mechanisms for the initiation of preterm labour, focusing chiefly on the role of intra-amniotic fluid mediators, whether endogenous or infection-induced, in the regulation of inflammatory response pathways associated with spontaneous preterm labour. Prostaglandins (PGs) are considered to be one of the key mediators of preterm labour, with the concentration of biologically active PGs in the amniotic fluid, particularly PGE(2) and PGF(2α), being significantly higher in women with preterm labour. Cytokines, such as interleukins and tumour necrosis factor alpha, additionally play a dominant role in preterm labour, particularly in association with infection. Elevated amniotic fluid concentrations of extracellular matrix mediators, including metalloproteases, are also implicated in the process of foetal membrane rupture in preterm labour. Allelic variations in the main amniotic fluid mediators may be the key to understanding the disparity in the rates of preterm

J Steroid Biochem Mol Biol. 2014 Jan;139:159-65.

Progesterone, inflammation and preterm labor.

Pařízek A1, Koucký M, Dušková M.

Abstract

The initiation of human parturition is not fully understood to date. The data from **animal** experiments demonstrate that the primary impulse for the initiation of physiological labor arises from the fetal hypothalamo-pituitary-adrenal axis (HPA). HPA is responsible for the stimulation of steroid synthesis and prostaglandin production and, in turn, the cervical dilation and the beginning of myometrial contractions. Animal experiments, however, are only partly suitable for understanding the mechanism of human labor due to substantial species-specificity. In **human,** the changing levels of placental CRH control the production of fetal and placental steroids. The fundamental pathogenic manifestation of spontaneous preterm labor is inflammation and similar processes also underlie the full term one. While in full term labor it is not yet precisely known what starts this process, in the preterm one, several factors have been discussed like infection, uteroplacental ischemia, and hormonal abnormalities (progesterone- or CRH-related). Inflammatory processes affect both the mother and the fetus. Fetal inflammatory response (FIRS), which can be expected for children born preterm, is frequently associated with long-term complications, in particular neurological and pulmonary. Research in this field is therefore aimed at predicting preterm labor, and on predicting the fetal inflammatory response. The role of progesterone and its receptors in the pathophysiology of preterm labor are likewise intensively studied. Clinical results on the use of additive doses of progesterone in secondary prevention of preterm labor and current experimental studies point to progesterone and its receptors playing a key role in the pathophysiology of preterm labor.

Front Immunol. 2014 Dec 1;5:574.

Preterm birth, intrauterine infection, and fetal inflammation.

Kemp MW

Abstract

Preterm birth (PTB) (delivery before 37 weeks' gestation) is a leading cause of neonatal death and disease in industrialized and developing countries alike. Infection (most notably in high-risk deliveries occurring before 28 weeks' gestation) is hypothesized to initiate an intrauterine inflammatory response that plays a key role in the premature initiation of labor as well as a host of the pathologies associated with prematurity. As such, a better understanding of intrauterine inflammation in pregnancy is critical to our understanding of preterm labor and fetal injury, as well as on-going efforts to prevent PTB. Focusing on the fetal innate immune system responses to intrauterine infection, the present paper will review clinical and experimental studies to discuss the capacity for a fetal contribution to the intrauterine inflammation associated with PTB. Evidence from experimental studies to suggest that the fetus has the capacity to elicit a pro-inflammatory response to intrauterine infection is highlighted, with reference to the contribution of the lung, skin, and gastrointestinal tract. The paper will conclude that pathological intrauterine inflammation is a complex process that is modified by multiple factors including time, type of agonist, host genetics, and tissue.

J Leukoc Biol. 2016 Jan;99(1):67-78.

Inflammation and preterm birth.

Cappelletti M et al.

Abstract

Preterm birth is the leading cause of neonatal morbidity and mortality. Although the underlying causes of pregnancy-associated complication are numerous, it is well established that infection and inflammation represent a highly significant risk factor in preterm birth. However, despite the clinical and public health significance, infectious agents, molecular trigger(s), and immune pathways underlying the pathogenesis of preterm birth remain underdefined and represent a major gap in knowledge. Here, we provide an overview of recent clinical and animal model data focused on the interplay between infection-driven inflammation and induction of preterm birth. Furthermore, here, we highlight the critical gaps in knowledge that warrant future investigations into the interplay between immune responses and induction of preterm birth.

Obstet Gynecol. 1993 Nov;82(5):821-8.

Elevated first-trimester serum relaxin concentrations in pregnant women following ovarian stimulation predict prematurity risk and preterm delivery.

Weiss G et al

Abstract

OBJECTIVE: To determine whether ovarian stimulation would result in higher circulating relaxin concentrations and whether this hyperrelaxinemia would be associated with prematurity.

METHODS: Two groups of women were studied: 1) women achieving pregnancy after ovarian stimulation (n = 114) and 2) women achieving pregnancy without treatment (n = 37). Serum was obtained at 6-12 weeks' gestational age; fetal number was determined by transvaginal ultrasound. Prematurity risk or preterm delivery was determined from the obstetric record. A specific human relaxin enzyme-linked immunosorbent assay was used to measure serum relaxin concentrations. Hyperrelaxinemia was defined as levels greater than 3 standard deviations above the weighted mean of levels in normal unstimulated singleton pregnancies at 6-12 weeks' gestation.

RESULTS: An association was found between prematurity risk or premature delivery and peripheral relaxin concentrations during weeks 6-12 of pregnancy in women having ovarian stimulation and in women having multiple gestations. Circulating relaxin concentrations greater than 16 ng/mL in women having ovarian stimulation and levels greater than 7 ng/mL in women who had multiple gestations predicted prematurity risk or premature delivery in 50% of the women.

CONCLUSIONS: These data demonstrate that after ovarian stimulation, some women have highly elevated circulating first-trimester relaxin concentrations. First-trimester hyperrelaxinemia identifies a group of women at risk for prematurity who can be monitored aggressively.

Ann N Y Acad Sci. 2005 May;1041:345-50.

Mechanisms of relaxin-mediated premature birth.

Weiss G, Goldsmith LT.

Abstract

In women, circulating relaxin is produced by the corpus luteum of pregnancy. The levels of relaxin are predominantly determined by the luteal mass, the number of corpora lutea present. Relaxin levels are highest after ovulation induction, which stimulates formation of many corpora lutea. Elevated relaxin levels in the first trimester of pregnancy are maintained throughout pregnancy and are linearly related to preterm birth. In an in vitro model of late human pregnancy cervix, relaxin increases MMP-1 and MMP-3 and decreases TIMP-1 levels, thus acting as a positive regulator of matrix metalloproteinases. In an in vivo rhesus monkey model of early pregnancy, relaxin decreases cervical collagen content, decreases cervical lumican levels, and stimulates MMP-7 levels. Early effects of relaxin in the uterus include increasing endometrial arteriole number and increasing the number of leukocytes, uterine natural killer cells, macrophages, and neutrophils. These cells release many cytokines which contribute to changes that stimulate and facilitate uterine contractility. If these changes persist in late pregnancy, relaxin may be a mediator of labor. Excess relaxin may produce these changes at an accelerated rate, causing preterm birth.

Front Immunol. 2014 Nov 12;5:567.
Oxidative stress damage as a detrimental factor in preterm birth pathology.
Menon R.

Abstract
Normal term and spontaneous preterm births (PTB) are documented to be associated with oxidative stress (OS), and imbalances in the redox system (balance between pro- and antioxidant) have been reported in the maternal-fetal intrauterine compartments. The exact mechanism of labor initiation either at term or preterm by OS is still unclear, and this lack of understanding can partially be blamed for failure of antioxidant supplementation trials in PTB prevention. Based on recent findings from our laboratory, we postulate heterogeneity in host OS response. The physiologic (at term) and pathophysiologic (preterm) pathways of labor are not mediated by OS alone but by OS-induced damage to intrauterine tissues, especially fetal membranes of the placenta. OS damage affects all major cellular elements in the fetal cells, and this damage promotes fetal cell senescence (aging). The aging of the fetal cells is predominated by p38 mitogen activated kinase (p38MAPK) pathways. Senescing cells generate biomolecular signals that are uterotonic, triggering labor process. The aging of fetal cells is normal at term. However, aging is premature in PTB, especially in those PTBs complicated by preterm premature rupture of the membranes, where elements of redox imbalances and OS damage are more dominant. We postulate that fetal cell senescence signals generated by OS damage are likely triggers for labor. This review highlights the mechanisms involved in senescence development at term and preterm by OS damage and provides insight into novel fetal signals of labor initiation pathways.

Exp Physiol. 2014 Mar;99(3):525-9.

The importance of the smooth muscle cytoskeleton to preterm labour.

Morgan KG.

Abstract

Multiple mechanisms have been shown to regulate the onset of labour in a co-operative and complex manner. One factor, myometrial stretch and associated increases in wall tension, has been implicated clinically in the initiation of labour and especially the aetiology of preterm labour. Recent work on the mechanisms involved has led to the finding that the intracellular Ca(2+) requirement for activation of the myometrial contractile filaments increases during gestation. The decreased Ca(2+) sensitivity correlates with an increase in the expression of caldesmon, an actin-binding protein and inhibitor of myosin activation, during pregnancy. In late pregnancy, an increase in extracellular signal-regulated kinase-mediated caldesmon phosphorylation occurs, which appears to reverse the inhibitory action of caldesmon during labour. Force generated by the myometrial contractile filaments is communicated across the plasmalemma to the uterine wall through focal adhesions. Phospho-tyrosine screening and mass spectrometry of stretched myometrial samples identified several stretch-activated focal adhesion proteins. This Src-mediated focal adhesion signalling appears to provide a tunable, i.e. regulated, tension sensor and force transmitter in the myometrial cell. In other parallel studies, biophysical measurements of smooth muscle compliance at both the cellular and tissue levels suggest that decreases in cellular compliance due to changing interactions of the actin cytoskeleton with the focal adhesions may also promote increases in uterine wall tension. These results, taken together, suggest that focal adhesion proteins and their interaction with the cytoskeleton may present a new mode of regulation of uterine contractility.

Dis Markers. 2015;2015:435014.

Predicting Preterm Labour: Current Status and Future Prospects.

Georgiou HM et al.

Abstract

Preterm labour and birth are a major cause of perinatal morbidity and mortality. Despite modern advances in obstetric and neonatal management, the rate of preterm birth in the developed world is increasing. Yet even though numerous risk factors associated with preterm birth have been identified, the ability to accurately predict when labour will occur remains elusive, whether it is at a term or preterm gestation. In the latter case, this is likely due to the multifactorial aetiology of preterm labour wherein women may display different clinical presentations that lead to preterm birth. The discovery of novel biomarkers that could reliably identify women who will subsequently deliver preterm may allow for timely medical intervention and targeted therapeutic treatments aimed at improving maternal and fetal outcomes. Various body fluids including amniotic fluid, urine, saliva, blood (serum/plasma), and cervicovaginal fluid all provide a rich protein source of putative biochemical markers that may be causative or reflective of the various pathophysiological disorders of pregnancy, including preterm labour. This short review will highlight recent advances in the field of biomarker discovery and the utility of single and multiple biomarkers for the prediction of preterm birth in the absence of intra-amniotic infection.

J Reprod Immunol. 2011 Mar;88(2):176-84.
Pharmacological inhibition of inflammatory pathways for the prevention of preterm birth.
Keelan JA

Abstract

The major cause of spontaneous preterm birth (sPTB) at less than 32 weeks of gestation is intrauterine inflammation as a consequence of colonisation of the gestational membranes by pathogenic microorganisms which trigger activation of the local innate immune system. This results in release of inflammatory mediators, leukocytosis (chorioamnionitis), apoptosis, membrane rupture, cervical ripening and onset of uterine contractions. Recent PCR evidence suggests that in the majority of cases of inflammation-driven preterm birth, microorganisms are present in the amniotic fluid, but these are not always cultured by standard techniques. The nature of the organism and its cell wall constituents, residence time in utero, microbial load, route of infection and extent of tissue penetration are all factors which can modulate the timing and magnitude of the inflammatory response and likelihood of progression to sPTB. Administration of anti-inflammatory drugs could be a viable therapeutic option to prevent sPTB and improve fetal outcomes in women at risk of intrauterine inflammation. Preventing fetal inflammation via administration of placenta-permeable drugs could also have significant perinatal benefits in addition to those related to extension of gestational age, as a fetal inflammatory response is associated with a range of significant morbidities. A number of potential drugs are available, effective against different aspects of the inflammatory process, although the pathways actually

JAMA Pediatr. 2015 Mar;169(3):220-9.

The distribution of clinical phenotypes of preterm birth syndrome: implications for prevention.

Barros FC et al

Abstract

IMPORTANCE: Preterm birth has been difficult to study and prevent because of its complex syndromic nature.

OBJECTIVE: To identify phenotypes of preterm delivery syndrome in the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project.

DESIGN, SETTING, AND PARTICIPANTS: A population-based, multiethnic, cross-sectional study conducted at 8 geographically demarcated sites in Brazil, China, India, Italy, Kenya, Oman, the United Kingdom, and the United States. A total of 60,058 births over a 12-month fixed period between April 27, 2009, and March 2, 2014.

MAIN OUTCOMES AND MEASURES: The main study outcomes were clusters of preterm phenotypes and for each cluster, we analyzed signs of presentation at hospital admission, admission rates for neonatal intensive care for 7 days or more, and neonatal mortality rates.

RESULTS: Twelve preterm birth clusters were identified using our conceptual framework. Eleven consisted of combinations of conditions known to be associated with preterm birth, 10 of which were dominated by a single condition. Only 22% (n = 1284) of all the preterm births occurred spontaneously without any of these severe conditions. The prevalence of preterm birth ranged from 8.2% in Muscat, Oman, and Oxford, England, to 16.6% in Seattle, Washington.

CONCLUSIONS AND RELEVANCE: We identified 12 preterm birth phenotypes associated with different patterns of neonatal outcomes. In 22% of all preterm births, parturition started spontaneously and was not associated with any of the phenotypic conditions considered. We believe these results contribute to an improved understanding of this complex syndrome and provide an empirical basis to focus research on a more homogenous set of phenotypes.

Can Med Assoc J. 1983 Feb 15;128(4):387-92.

Initiation of parturition in humans.

Drover JW, Casper RF.

Abstract

The mechanism by which parturition is initiated in humans is largely unknown. The placenta and fetal membranes appear to play the major role in the initiation of labour, and the fetus may influence the timing of labour. Clinical observations and experiments with animals have revealed that placental neuropeptides may be able to control steroid metabolism and trigger the onset of labour, while the fetus may be able to interact with such events to initiate parturition at an appropriate time. However, further study is needed to determine the role of placental releasing factors and glycoprotein hormones and their ability to control placental steroid metabolism.

Ann Med. 2008;40(3):167-95.

Genetic contributions to preterm birth: implications from epidemiological and genetic association studies.

Plunkett J, Muglia LJ.

Abstract
Infants born before term (<37 weeks) have an increased risk of neonatal mortality as well as other health problems. The increasing rate of preterm birth in recent decades, despite improvements in health care, creates an impetus to better understand and prevent this disorder. Preterm birth likely depends on a number of interacting factors, including genetic, epigenetic, and environmental risk factors. Genetic studies may identify markers, which more accurately predict preterm birth than currently known risk factors, or novel proteins and/or pathways involved in the disorder. This review summarizes epidemiological and genetic studies to date, emphasizing the complexity of genetic influences on birth timing. While several candidate genes have been reportedly associated with the disorder, inconsistency across studies has been problematic. More systematic and unbiased genetic approaches are needed for future studies to examine the genetic etiology of human birth timing thoroughly.

A spontán koraszülés, mint multifaktoriális terhespathológiai kórkép

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	Dr. Bátorfi József, Ph.D.

Budapest

2012

ÖSSZEFOGLALÁS

A koraszülés kialakulása, miként számos fejlődési rendellenesség, illetve krónikus betegség létrejötte genetikai tényezők és környezeti hatások összjátékára vezethető vissza. A tartós hypooxigenizáció az IGF-rendszer befolyásolásán keresztül valószínűsíthető hatást gyakorol az újszülött energiaforgalmára, anyagcseréjére is, ezenkívül a placentaris 11β-HSD2-génaktivitás, s az anyai glükokortikoid hatással szembeni barrier atékonyságának csökkenéséhez vezet.

Az idő előtti burokrepedést követő koraszülés megindulása, melyben a Bcl-2 és Bax apoptotikus gének hatására aktiválódott metalloproteináz enzimek is fontos szerepet játszanak, az esetek többségében méhűri felszálló fertőzésre vezethető vissza, ami a gyulladásos mediátorok megnövekedett mennyiségén keresztül csökkenti az IGF-rendszer működésének hatékonyságát. Vizsgálataim révén igazolódott, hogy a koraszülés megindulásában szerepet játszó apoptózis folyamatában elsősorban az azt stimuláló Bax-gén túlműködése és kevésbé a gátló hatású Bcl-2-gén alulműködése játszhat szerepet.

A 11β-HSD2 gén lepényi aktivitása is csak a 28. terhességi hét után lezajló koraszülések kapcsán mutat csökkenést, az anyai glükokortikoidokkal szembeni csökkent védettség elsősorban az e terhességi korcsoportba tartozó koraszülések esetén jön kóroki tényezőként szóba. A 11β-HSD2-génaktivitás csökkenésének hátterében állhat mutáció, de lehet a következménye krónikus distresst eredményező magzati állapotnak is.

AZ ÉRTEKEZÉS ALAPJÁUL SZOLGÁLÓ KÖZLEMÉNYEK:

1.Demendi C, Börzsönyi B, Nagy ZB, Rigó J Jr, Pajor A, Joó JG.
Gene expression patterns of insulin-like growth factor 1, 2 (IGF-1, IGF-2) and insulinlike growth factor binding protein 3 (IGFBP-3) in human placenta from preterm deliveries: influence of additional factors.
Eur J Obstet Gynecol Reprod Biol, 2012; 160: 40-44. **IF: 1.764**

2. **Demendi C**, Börzsönyi B, Végh V, Nagy ZB, Rigó J Jr, Pajor A, Joó JG.
Gene expression patterns of the Bcl-2 and Bax genes in preterm birth.
Acta Obstet Gynecol Scand (in press), **IF: 1.860**

3. Joó JG, **Demendi C**, Börzsönyi B, Csanád M, Pajor A, Rigó J Jr, Nagy ZB.
A fetomaternalis glükokortikoid-anyagcsere egyensúlyzavarának kóroki szerepe a koraszülés hátterében; a lepényi 11β-hidroxiszteroid dehidrogénáz 2 enzim génjének expressziós mintázata.
Magy Nőorv L, 2012; 75: 14-21.

MOLECULAR MODELS OF BIRTH

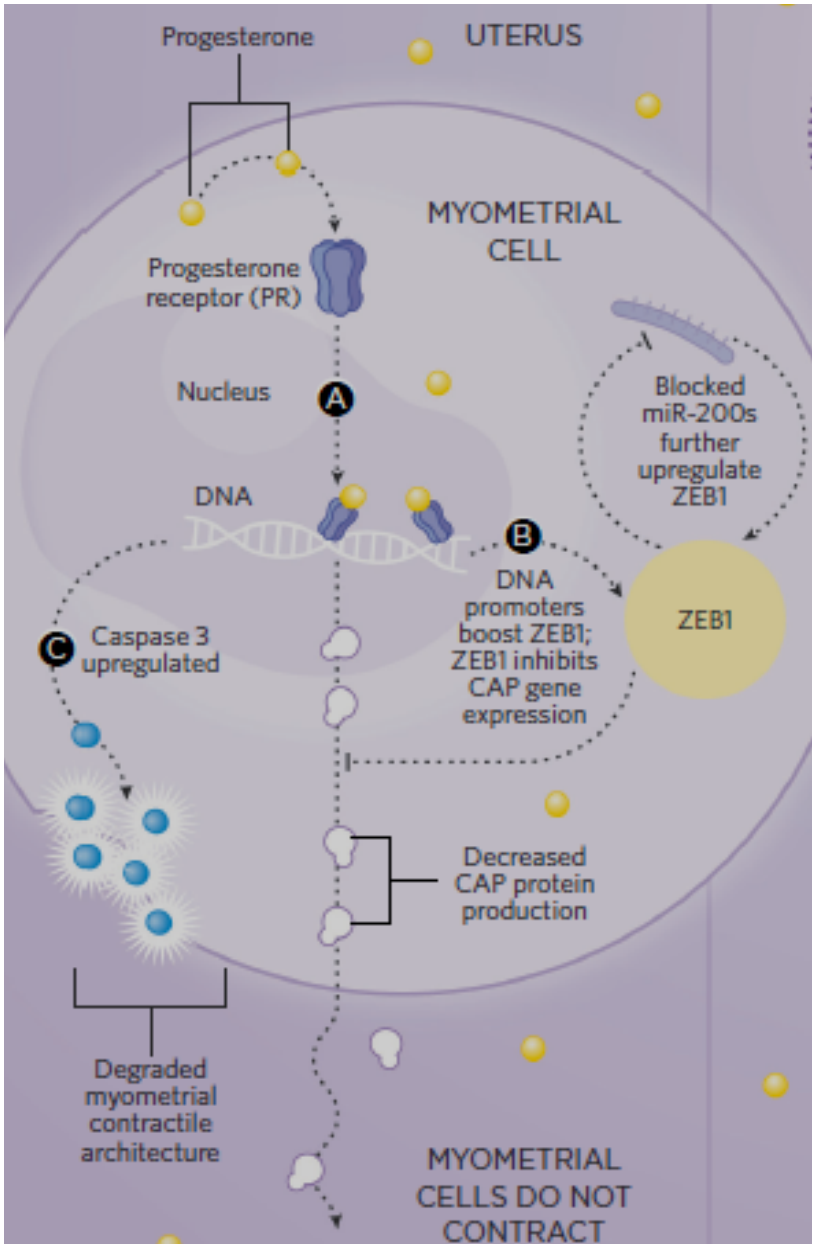
MAINTAINING PREGNANCY

Progesterone interacts with progesterone receptors (PRs) in the cytoplasm of myometrial cells, causing the complex to translocate to the nucleus ν

A . There, the activated receptor binds to the promoter of the ZEB1 gene, which leads to upregulation of the transcription factors and subsequent inhibition of genes that code for contraction-associated proteins (CAPs) ν

B . PRs in the nucleus also upregulate caspase 3, an enzyme that degrades the contractile architecture of the cell ν

C . All of this results in a quiescent uterus that is allowed to stretch and grow as the fetus develops.



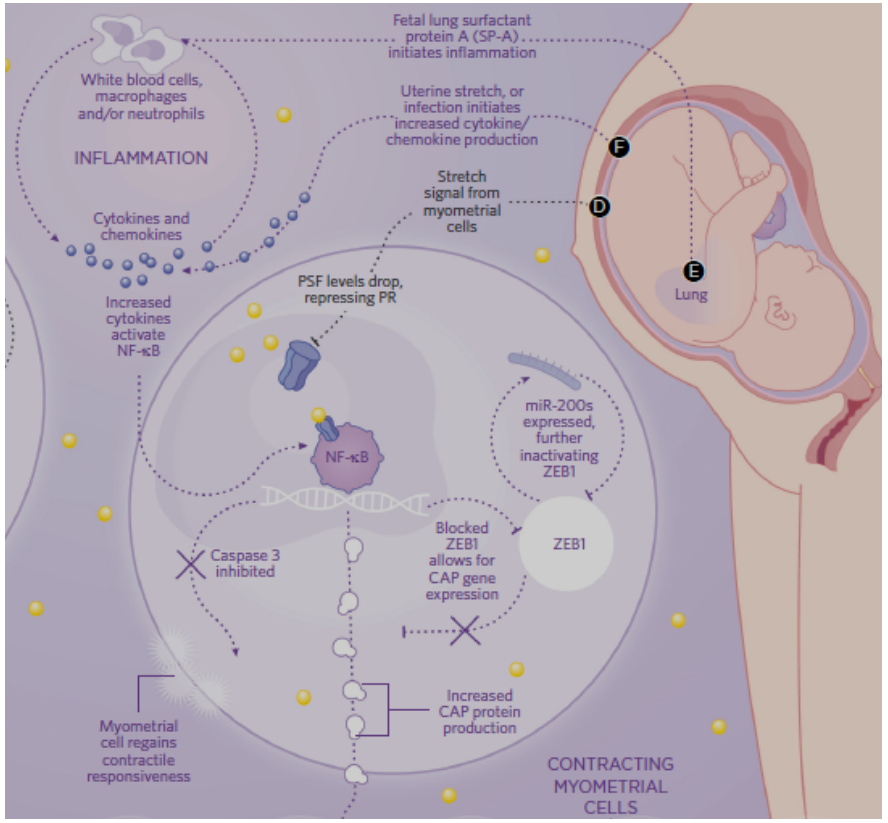
MOLECULAR MODELS OF BIRTH

INITIATING LABOR

Mechanical stretch forces in the uterus cause a drop in polypyrimidine tract binding protein-associated splicing factor (PSF), a coregulator of the progesterone receptor. This leads to the increased expression of proteins involved in contraction

D . As the fetal lung matures, it produces an abundance of surfactant protein A (SP-A), which activates macrophages in the amniotic fluid, promoting their migration to the uterus where they release proinflammatory cytokines. Increased cytokine production activates NF-κB, which translocates to the nucleus of the myometrial cell, where it binds to CAP gene promoters, activating CAP expression. It also binds to PRs, blocking their binding with DNA. This decreases ZEB1 expression, therefore increasing expression of CAPs and decreasing caspase 3 levels

E . Signals from uterine stretch forces and intraamniotic infection can also increase proinflammatory cytokines and chemokines, which can result in increased CAP expression



Cold Spring Harb Perspect Med. 2015 Sep 3;5(11).

Molecular Regulation of Parturition: A Myometrial Perspective.

Renthal NE et al.

Abstract

The molecular mechanisms that maintain quiescence of the myometrium throughout most of pregnancy and promote its transformation to a highly coordinated contractile unit culminating in labor are complex and intertwined. During pregnancy, progesterone (P4) produced by the placenta and/or ovary serves a dominant role in maintaining myometrial quiescence by blocking proinflammatory response pathways and expression of so-called "contractile" genes. In the majority of **placental mammals**, increased uterine contractility near term is heralded by an increase in circulating estradiol-17β (E2) and/or increased estrogen receptor α (ERα) activity and a sharp decline in circulating P4 levels. However, in **women**, circulating levels of P4 and progesterone receptors (PR) in myometrium remain elevated throughout pregnancy and into labor. This has led to the concept that increased uterine contractility leading to term and preterm labor is mediated, in part, by a decline in PR function. The biochemical mechanisms for this decrease in PR function are also multifaceted and interwoven. In this paper, we focus on the molecular mechanisms that mediate myometrial quiescence and contractility and their regulation by the two central hormones of pregnancy, P4 and estradiol-17β. The integrative roles of microRNAs also are considered.

Mol Hum Reprod. 2013 Nov;19(11):711-7.

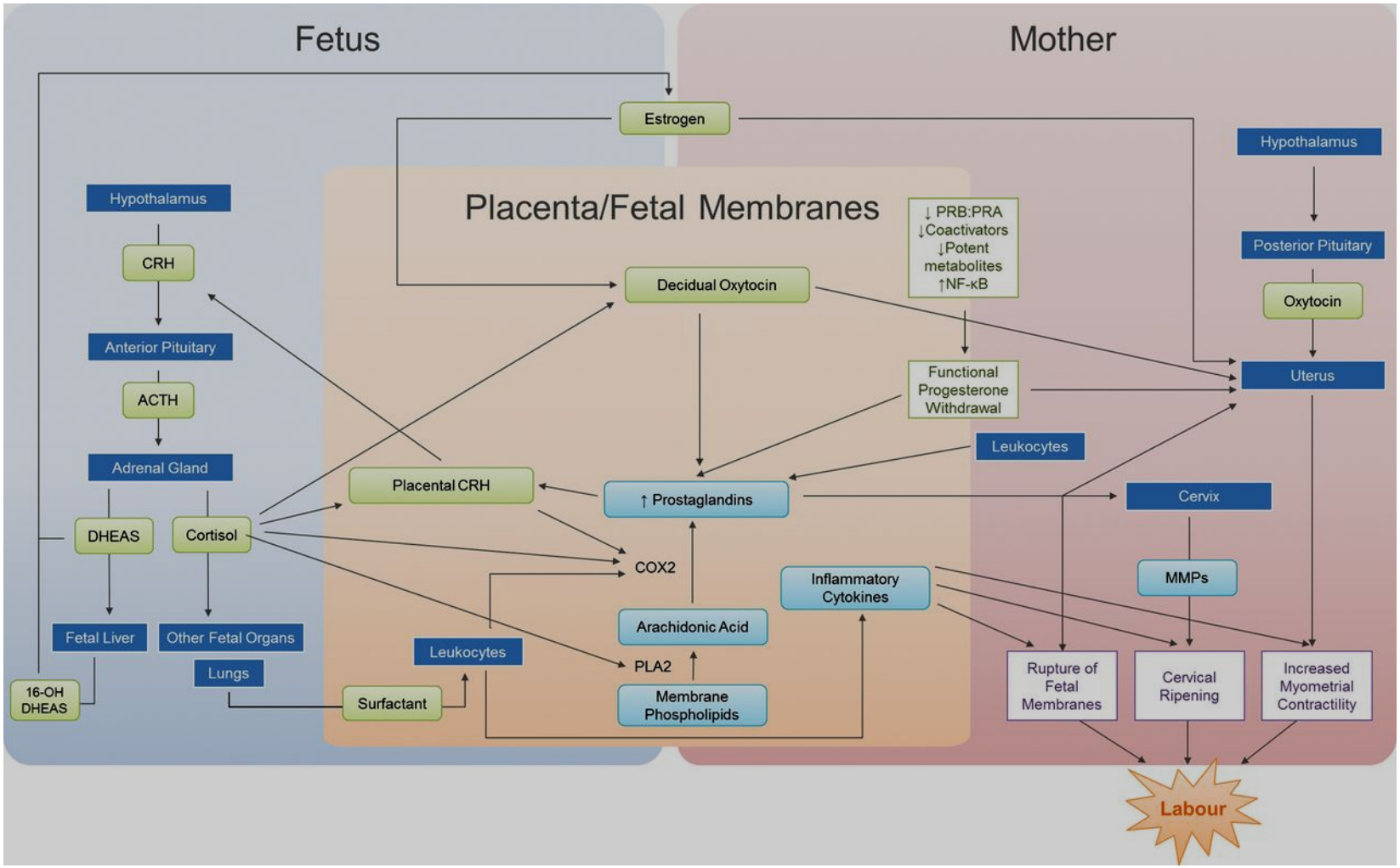
Computer models to study uterine activation at labour.

Sharp GC, Saunders PT, Norman JE.

Abstract

Improving our understanding of the initiation of labour is a major aim of modern obstetric research, in order to better diagnose and treat pregnant women in which the process occurs abnormally. In particular, increased knowledge will help us identify the mechanisms responsible for preterm labour, the single biggest cause of neonatal morbidity and mortality. Attempts to improve our understanding of the initiation of labour have been restricted by the inaccessibility of gestational tissues to study during pregnancy and at labour, and by the lack of fully informative animal models. However, computer modelling provides an exciting new approach to overcome these restrictions and offers new insights into uterine activation during term and preterm labour. Such models could be used to test hypotheses about drugs to treat or prevent preterm labour. With further development, an effective computer model could be used by healthcare practitioners to develop personalized medicine for patients on a pregnancy-by-pregnancy basis. Very promising work is already underway to build computer models of the physiology of uterine activation and contraction. These models aim to predict changes and patterns in uterine electrical excitation during term labour. There have been far fewer attempts to build computer models of the molecular pathways driving uterine activation and there is certainly scope for further work in this area. The integration of computer models of the physiological and molecular mechanisms that initiate labour will be particularly useful.

Key endocrine and inflammatory factors associated with the initiation of human parturition.



G.C. Sharp et al. Mol. Hum. Reprod. 2013;19:711-717

MHR
Basic science of reproductive medicine

Clin Perinatol. 1993 Mar;20(1):9-28.

Biologic basis of term and preterm labor.

Myers DA1, Nathanielsz PW.

Abstract

Normal parturition in **sheep and nonhuman primates** appears to be initiated by signals from the fetus. These signals involve the fetal hypothalamo-hypophyseal-adrenal axis and are closely integrated with the control of maturation of the fetal organs such as the lungs, gut, and kidneys that are indispensable for extrauterine life. The integrated set of changes in fetal and maternal myometrial, decidual, and cervical tissues are gradual and occur over several days. When the myometrium and cervix have been appropriately prepared, endocrine and paracrine factors in the fetal membranes, decidua, and the myometrium bring about a change in the pattern of myometrial activity from contractures to contractions. This switch occurs at night, and recurs and augments over several nights until eventually cervical dilation occurs to allow the fetus to be born.

Gynecol Endocrinol. 2015;31(9):679-83.

Factors implicated in the initiation of human parturition in term and preterm labor: a review.

Ravanos K et al.

Abstract

After accommodating the pregnancy for an average of 40 weeks, the uterus expels the fetus, the placenta and the membranes through the birth canal in a process named parturition. The absolute sequence of events that trigger and sustain **human** parturition are not yet fully clarified. Evidence suggests that spontaneous preterm and term labor seem to share a common inflammatory pathway. However, there are several other factors being involved in the initiation of human parturition. Placental corticotropin releasing hormone production seems to serve as a placental clock that might be set to ring earlier or later determining the duration of pregnancy and timing of labor. Estrogens do not cause contractions but their properties seem to capacitate uterus to coordinate and enhance contractions. Cytokines, prostaglandins, nitric oxide and steroids seem also to induce ripening by mediating remodeling of the extracellular matrix and collagen. Infection and microbe invasion resulting in chorioamnionitis also represents a common cause of early preterm labour. This review provides an overview of all these factors considered to be implicated in the initiation of human parturition.

Hum Reprod. 1999 Jan;14(1):229-36.

Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process.

Thomson AJ et al.

Abstract

Inflammatory mediators in the cervix, placenta and fetal membranes play a crucial role in human parturition. The aim of this study was to determine whether the upper and lower segments of the myometrium are infiltrated by inflammatory cells during pregnancy and parturition. Myometrial biopsies were obtained from non-pregnant women, and pregnant women at term before and after the onset of spontaneous labour. Subpopulations of inflammatory cells were identified using immunocytochemistry. The intercellular adhesion molecules, 1 and 2, platelet endothelial cell adhesion molecule, vascular cell adhesion molecule and E-selectin were immunolocalized to investigate their involvement in leukocyte accumulation. Histological analysis demonstrated that inflammatory cells, predominantly neutrophils and macrophages, infiltrate human myometrium during spontaneous labour at term. The infiltrate is predominant in the lower uterine segment but is also present in the upper segment. Increased expression of E-selectin was found on the vascular endothelium of biopsies obtained during labour, suggesting a role for this molecule in the accumulation of leukocytes. These results suggest that inflammatory cell infiltration is part of the physiological mechanisms that occur in the myometrium during parturition. Further understanding of this process may suggest new strategies aimed at preventing preterm delivery.

BJOG. 2003 Apr;110 Suppl 20:39-45.
Mechanisms of labour – biochemical aspects.
López Bernal A

Abstract
The mechanism of labour is not fully understood and further research into this important physiological process is needed. In some species, notably sheep, parturition is due to activation of the fetal hypothalamic-pituitary-adrenal axis. However, in primates, this axis appears to have a supportive, rather than essential role. Successful parturition requires an increase in coordinated uterine contractility together with changes in connective tissue that allow cervical ripening and dilatation. In most mammals, however, these changes are synchronised by a fall in maternal progesterone levels and a rise in oestrogens. This is not the case in women in whom the onset of labour occurs without apparent changes in circulating steroid levels.
The basis of uterine contractility is the interaction between actin and myosin in myometrial smooth muscle cells. This is driven by **calcium** through Ca(2+)-calmodulin-dependent myosin light chain kinase (MLCK) activity. Moreover, calcium sensitisation occurs via activation of Rho kinase, a calcium-independent pathway that promotes contractility by inhibiting myosin phosphatase and probably by phosphorylating myosin on the same site as MLCK.
Uterine activity can be modulated by many G-protein coupled receptors (GPCRs). For example,
receptors coupled to Galpha(q) (oxytocin-, prostanoid FP and TP, endothelin-receptors) stimulate contractility by activating the phospholipase C/Ca(2+) pathway;
receptors coupled to Galpha(s) (beta(2)-adrenoceptors, prostanoid EP2 and IP, some 5-hydroxytryptamine receptors e.g. 5-HT(7)) relax the uterus by increasing myometrial cyclic AMP levels; and
receptors coupled to Galpha(i) (alpha(2)-adrenoceptors, muscarinic, 5-HT(1)) potentiate

Semin Cell Dev Biol. 2007 Jun;18(3):296-304. Epub 2007 May 18.

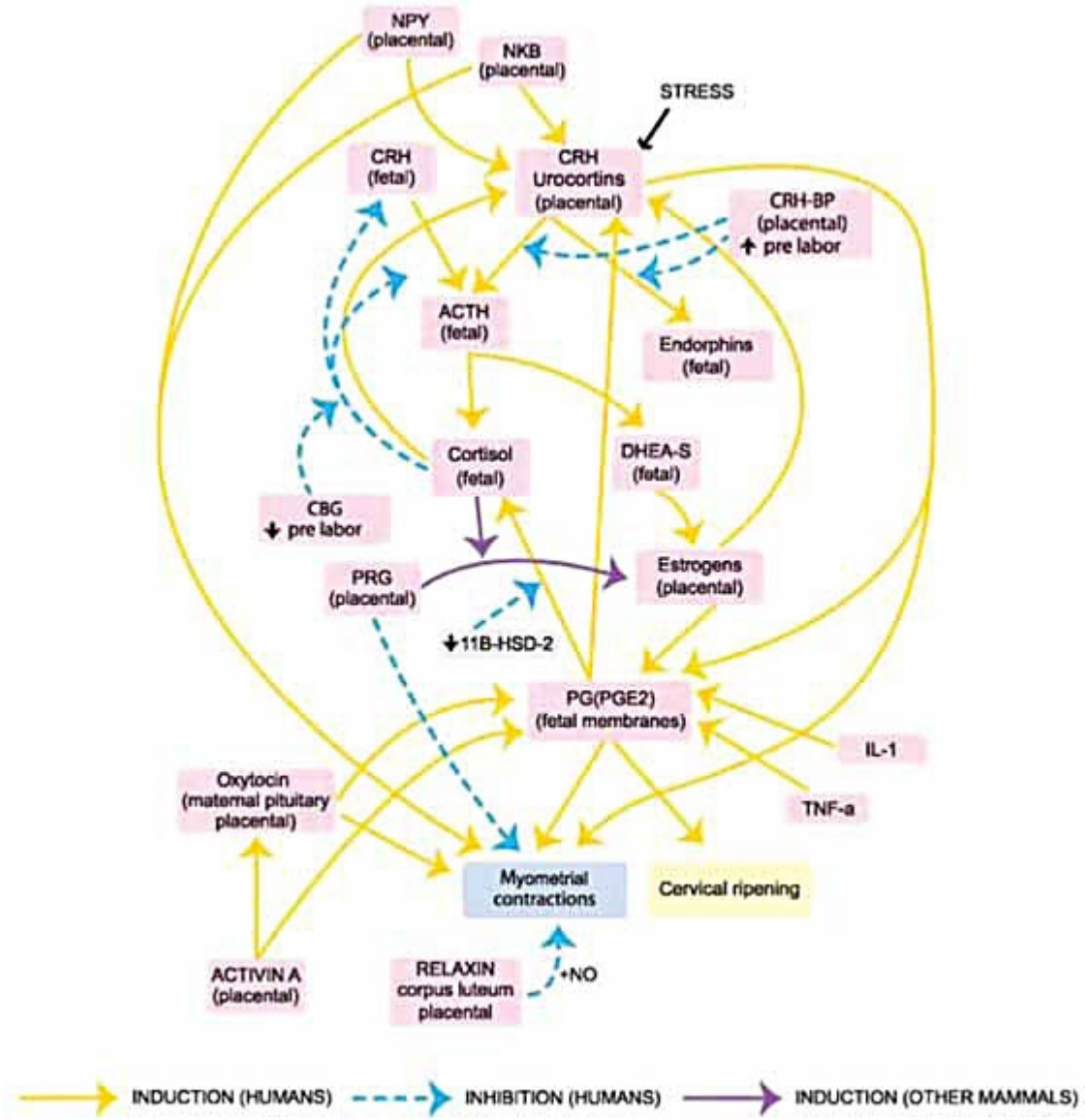
Regulation of the uterine contractile apparatus and cytoskeleton.

Taggart MJ, Morgan KG.

Abstract
Parturition at term, the end stage of a successful pregnancy, occurs as a result of powerful, co-ordinated and periodic contractions of uterine smooth muscle (myometrium). To occur in a propitious manner, a high degree of control over the activation of a myometrial cell is required. We review the molecular mechanisms and structural composition of myometrial cells that may contribute to their increased contractile capacity at term. We focus attention on pathways that lead to the activation of filamentous networks traditionally labeled 'contractile' or 'cytoskeletal' yet draw attention to the fact that functional discrimination between these systems is not absolute.

Hormones (Athens). 2012 Oct-Dec;11(4):397-409.
Endocrine, paracrine, and autocrine placental mediators in labor.
Iliodromiti Z et al.

Abstract
Considering that preterm birth accounts for about 6-10% of all births in Western countries and of more than 65% of all perinatal deaths, elucidation of the particularly complicated mechanisms of labor is essential for determination of appropriate and effective therapeutic interventions. Labor in humans results from a complex interplay of fetal and maternal factors, which act upon the uterus to trigger pathways leading gradually to a coordinated cervical ripening and myometrial contractility. Although the exact mechanism of labor still remains uncertain, several components have been identified and described in detail. Based on the major role played by the human placenta in pregnancy and the cascade of labor processes activated via placental mediators exerting endocrine, paracrine, and autocrine actions, this review article has aimed at presenting the role of these mediators in term and preterm labor and the molecular pathways of their actions. Some of the aforementioned mediators are involved in myometrial activation and preparation and others in myometrial stimulation leading to delivery. In the early stages of pregnancy, myometrial molecules, like progesterone, nitric oxide, and relaxin, contribute to the retention of pregnancy. At late stages of gestation, fetal hypothalamus maturation signals act on the placenta causing the production of hormones, including CRH, in an endocrine manner; the signals then enhance paracrinically the production of more hormones, such as estrogens and neuropeptides, that contribute to cervical ripening and uterine contractility. These



Pathways leading to labor. The main pathway starts from placental CRH, exploits fetal DHEA-S to produce estrogen environment and, through prostaglandins, results in myometrial contractions and cervical ripening, thus inducing labor. A variety of mediators interact in complex ways producing positive feedback loops of the main pathway:
- placental CRH → fetal ACTH → fetal cortisol → placental CRH
- placental CRH → fetal ACTH → fetal DHEA-S → estrogens → placental CRH
- placental CRH → fetal ACTH → fetal DHEA-S → estrogens → PGE2 → placental CRH
- placental CRH → fetal ACTH → fetal DHEA-S → estrogens → PGE2 → fetal cortisol → placental CRH.

These mediators feed-forward enhancing roots of the main pathway (NPY, NKB, IL-1, TNF-α, stress mediators, like catecholamines) or the endpoint of labor (NPY, NKB, oxytocin, activin A, IL-1, TNF-α).

CONCLUSION

Human placenta is seen to be both an intermediary barrier and an active messenger in the maternal-fetal dialog. It releases endocrine, paracrine, and autocrine factors which control secretion of regulatory or terminal-effector molecules. Coordinated action results in cervical ripening, myometrial contractility, and labor, placenta also being implicated in initiation of labor and in preterm labor. Meanwhile, placental CRH acts on the fetal pituitary-adrenal axis, stimulating adrenal production of DHEA-S and cortisol, while myometrial activation, achieved via activation of estrogen derived from fetal DHEA-S through placental enzymes, causes uterine contractions. Subsequently, with onset of late-gestation "functional" progesterone withdrawal, fetal cortisol production, developing in an estrogenic environment, leads to labor. Placental CRH also acts directly on myometrial cells via its receptors. Other placental mediators (e.g. neuropeptides produced before labor), binding to their own receptors in myometrium, enhance uterine contractility. Placental CRH-induced prostaglandin and molecules (e.g. oxytocin, placental neuropeptides), regulatory cytokines, and growth factors cause cervical ripening, rupture of fetal membranes, myometrial stimulation, and regular contractions. Cytokines (e.g. IL-1, IL-6, and TNF-α) are involved in positive feedback of placental CRH production, while stress or infection can trigger the placental "clock" and prematurely initiate the cascade of labor.

Despite extensive research into the extremely complicated mechanisms of labor in numerous animal models and humans, full elucidation is still lacking because of broad human v. animal divergence of physiology. Future progress in this area will enable development of effective treatments for preterm delivery thereby reducing neonatal morbidity and mortality.

Endocrinology of Pregnancy.

Tal R et al

Source Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2015 Dec 7.

Excerpt

A coordinated sequence of events must occur in order to establish and successfully maintain a healthy pregnancy. Synchrony between the development of the early embryo and establishment of a receptive endometrium is necessary to allow implantation and subsequent progression of pregnancy. The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus. Known as the feto-placental unit (FPU), this interface is a major site of protein and steroid hormone production and secretion. Many of the endocrine and metabolic changes that occur during pregnancy can be directly attributed to hormonal signals originating from the FPU. The initiation and maintenance of pregnancy depends primarily on the interactions of neuronal and hormonal factors. Proper timing of these neuro-endocrine events within and between the placental, fetal, and maternal compartments is critical in directing fetal growth and development and in coordinating the timing of parturition. Maternal adaptations to hormonal changes that occur during pregnancy directly affect the development of the fetus and placenta. Gestational adaptations that take place in pregnancy include establishment of a receptive endometrium; implantation and the maintenance of early pregnancy; modification of the maternal system in order to provide adequate nutritional support for the developing fetus; and preparation for parturition and subsequent lactation.

Physiology of parturition
Errol R Norwitz, MD, PhD

INTRODUCTION — Labor is a physiological event involving a sequential, integrated set of changes within the myometrium, decidua, and uterine cervix that occur gradually over a period of days to weeks. Biochemical connective tissue changes in the uterine cervix appear to precede uterine contractions and cervical dilation, and all of these events usually occur before rupture of the fetal membranes.

PHYSIOLOGICAL PHASES OF MYOMETRIAL ACTIVITY — The regulation of uterine activity during pregnancy can be divided into four distinct physiologic phases:

Phase 0: inhibitors active — During pregnancy the uterus is maintained in a state of functional quiescence through the action of various putative inhibitors including, but not limited to:

- Progesterone
- Prostacyclin (prostaglandin I-2)
- Relaxin
- Parathyroid hormone-related peptide
- Nitric oxide
- Calcitonin gene-related peptide
- Adrenomedullin
- Vasoactive intestinal peptide.

Phase 1: myometrial activation — As term approaches the uterus becomes activated in response to uterotopins, such as estrogen. This phase is characterized by increased expression of a series of contraction-associated proteins (CAPs) (including myometrial receptors for prostaglandins and oxytocin), activation of specific ion channels, and an increase in connexin-43 (a key component of gap junctions). An increase in gap junction formation between adjacent myometrial cells leads to electrical synchrony within the myometrium and allows for effective coordination of contractions.

Phase 2: stimulatory phase — Following activation, the "primed" uterus can be stimulated to contract by the action of uterotonic agonists, such as the stimulatory prostaglandins E2 and F2 alpha and oxytocin.

Phase 3: involution — Involution of the uterus after delivery occurs during phase 3 and is mediated primarily by oxytocin.

Proc Natl Acad Sci U S A. 2004 Apr 6;101(14):4978-83.

Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition.

Condon JC et al.

Abstract

Parturition is timed to begin only after the developing embryo is sufficiently mature to survive outside the womb. It has been postulated that the signal for the initiation of parturition arises from the fetus although the nature and source of this signal remain obscure. Herein, we provide evidence that this signal originates from the maturing fetal lung. In the mouse, secretion of the major lung surfactant protein, surfactant protein A (SP-A), was first detected in amniotic fluid (AF) at 17 days postcoitum, rising progressively to term (19 days postcoitum). Expression of IL-1beta in AF macrophages and activation of NF-kappaB in the maternal uterus increased with the gestational increase in SP-A. SP-A stimulated IL-1beta and NF-kappaB expression in cultured AF macrophages. Studies using Rosa 26 Lac-Z (B6;129S-Gt(rosa)26Sor) (Lac-Z) mice revealed that fetal AF macrophages migrate to the uterus with the gestational increase in AF SP-A. Intraamniotic (i.a.) injection of SP-A caused preterm delivery of fetuses within 6-24 h. By contrast, injection of an SP-A antibody or NF-kappaB inhibitor into AF delayed labor by >24 h. We propose that augmented production of SP-A by the fetal lung near term causes activation and migration of fetal AF macrophages to the maternal uterus, where increased production of IL-1beta activates NF-kappaB, leading to labor. We have revealed a

Eur Respir J. 1994 Feb;7(2):372-91.

The proteins of the surfactant system.

Johansson J, Curstedt T, Robertson B.

Abstract

The structural and functional integrity of pulmonary surfactant depends on several specific proteins. Two of these, SP-A and SP-D, are large and water-soluble, while SP-B and SP-C are small and very hydrophobic. SP-A is an 18-mer of 26 kDa polypeptide chains and contains N-linked oligosaccharides. Structurally, it can be characterized as a collagen/lectin hybrid. Together with SP-B, SP-A is required for conversion of secreted endogenous surfactant to tubular myelin in the alveolar lining. It also regulates surfactant secretion and reuptake of surfactant lipids by type II cells; these functions are probably receptor mediated. SP-D, a 12-mer of 39 kDa polypeptide chains, is a collagenous glycoprotein with structural similarities to C-type lectins. Both SP-A and SP-D stimulate alveolar macrophages. SP-B is a 79-residue polypeptide that contains three intrachain disulphide bridges. It exists mainly as a homodimer, which is strongly positively charged and may selectively remove anionic and unsaturated lipid species from the alveolar surface film, thereby increasing surface pressure. SP-C is a mainly alpha-helical, extraordinarily hydrophobic polypeptide containing 35 amino acid residues and covalently linked palmitoyl groups. Its alpha-helical portion is inserted into surfactant lipid bilayers. SP-C accelerates the adsorption of lipid bilayers to an interfacial monolayer. In babies with respiratory distress syndrome, the clinical response to treatment with surfactant containing SP-B and SP-C is much faster than in babies treated with protein-free synthetic surfactant. We speculate that, in the near future, surfactant preparations based on recombinant hydrophobic proteins will be available for clinical use.

Innate Immun. 2010 Jun;16(3):175-82.

Review: Chemical and structural modifications of pulmonary collectins and their functional consequences.

Atochina-Vasserman EN, Beers MF, Gow AJ.

Abstract

The lung is continuously exposed to inhaled pathogens (toxic pollutants, micro-organisms, environmental antigens, allergens) from the external environment. In the broncho-alveolar space, the critical balance between a measured protective response against harmful pathogens and an inappropriate inflammatory response to harmless particles is discerned by the innate pulmonary immune system. Among its many components, the surfactant proteins and specifically the pulmonary collectins (surfactant proteins A [SP-A] and D [SP-D]) appear to provide important contributions to the modulation of host defense and inflammation in the lung. Many studies have shown that multimerization of SP-A and SP-D are important for efficient local host defense including neutralization and opsonization of influenza A virus, binding Pneumocystis murina and inhibition of LPS-induced inflammatory cell responses. These observations strongly imply that oligomerization of collectins is a critical feature of its function. However, during the inflammatory state, despite normal pool sizes, chemical modification of collectins can result in alteration of their structure and function. Both pulmonary collectins can be altered through proteolytic inactivation, nitration, S-nitrosylation, oxidation and/or crosslinking as a consequence of the inflammatory milieu facilitated by cytokines, nitric oxide, proteases, and other chemical mediators released by inflammatory cells. Thus, this review will summarize recent developments in our understanding of the relationship between post-translational assembly of collectins and their modification by inflammation as an important molecular switch for the regulation of local innate host defense.

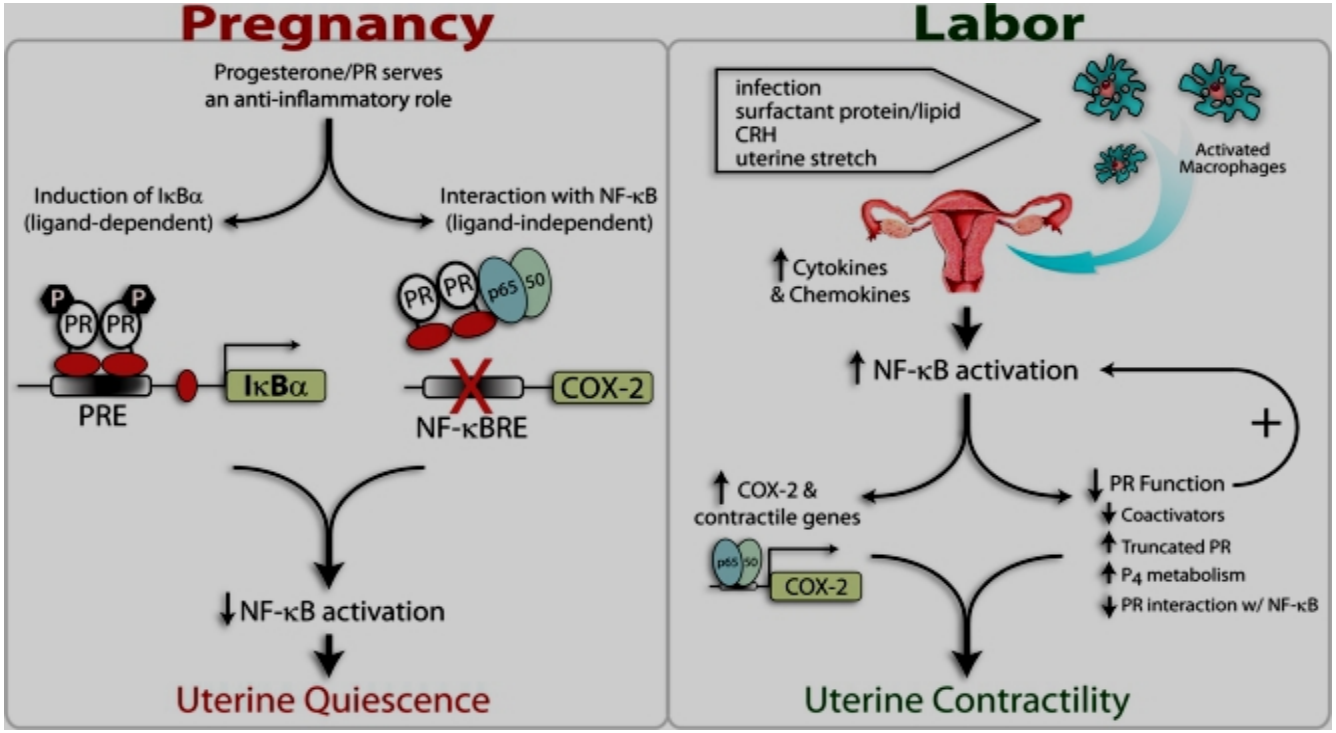
Mol Endocrinol. 2009 Jul;23(7):947-54.

Minireview: fetal-maternal hormonal signaling in pregnancy and labor.

Mendelson CR

Abstract

Mechanisms underlying the initiation of parturition remain unclear. Throughout most of pregnancy, uterine quiescence is maintained by elevated progesterone acting through progesterone receptor (PR). Although in most mammals, parturition is associated with a marked decline in maternal progesterone, in humans, circulating progesterone and uterine PR remain elevated throughout pregnancy, suggesting a critical role for functional PR inactivation in the initiation of labor. Both term and preterm labor in humans and rodents are associated with an inflammatory response. In preterm labor, intraamniotic infection likely provides the stimulus for increased amniotic fluid interleukins and migration of inflammatory cells into the uterus and cervix. However, at term, the stimulus for this inflammatory response is unknown. Increasing evidence suggests that the developing fetus may produce physical and hormonal signals that stimulate macrophage migration to the uterus, with release of cytokines and activation of inflammatory transcription factors, such as nuclear factor kappaB (NF-kappaB) and activator protein 1 (AP-1), which also is activated by myometrial stretch. We postulate that the increased inflammatory response and NF-kappaB activation promote uterine contractility via 1) direct activation of contractile genes (e.g. COX-2, oxytocin receptor, and connexin 43) and 2) impairment of the capacity of PR to mediate uterine quiescence. PR function near term may be compromised by direct interaction with NF-kappaB, altered expression of PR coregulators, increased metabolism of progesterone



Mechanisms for progesterone/PR regulation of uterine quiescence during pregnancy and induction of uterine contractility in preterm and term labor. During most of pregnancy, the uterus is maintained in a quiescent state by the PR, which acts in a ligand-dependent and -independent manner to block activation of the inflammatory transcription factors (*e.g*. NF-κB). PR acts in a ligand-dependent manner to up-regulate expression of the NF-κB inhibitor IκBα in myometrial cells. Alternatively, PR acts in a dominant ligand-independent manner (likely via direct protein-protein interaction) to block NF-κB activation, DNA binding, and transactivation of contractile genes within the uterus. Labor can be initiated preterm as a result of bacterial infection, resulting in enhanced migration of macrophages to the maternal uterus with release of cytokines/chemokines and activation of NF-κB. However, at term, enhanced macrophage activation and migration and increased uterine NF-κB activity are likely induced by signals produced by the maturing fetus. These include increased secretion of surfactant proteins and lipids by the fetal lung into amniotic fluid, augmented production of CRH by the placenta, and enhanced uterine stretch caused by the growing conceptus. Within the uterus, the activated NF-κB directly acts to increase expression of contractile genes and causes an impairment of PR function by effecting 1) down-regulation of PR coactivators, 2) increased

Mol Endocrinol. 2012 Nov;26(11):1857-67.

The microRNA (miR)-199a/214 cluster mediates opposing effects of progesterone and estrogen on uterine contractility during pregnancy and labor.

Williams KC et al.

Abstract

Progesterone (P(4)) and estradiol-17β (E(2)) play critical and opposing roles in regulating myometrial quiescence and contractility during pregnancy and labor. Although these contrasting hormonal effects are likely mediated via differential regulation of inflammatory and contractile genes, the underlying mechanisms remain incompletely understood. Recently we discovered that targets of the microRNA (miR)-200 family, transcription factors zinc finger E-box binding homeobox (ZEB)-1 and ZEB2, serve as P(4)/progesterone receptor-mediated regulators of uterine quiescence during pregnancy. In the present study, we found that levels of the clustered miRNAs, miR-199a-3p and miR-214, were significantly decreased in laboring myometrium of pregnant mice and humans and in an inflammatory mouse model of preterm labor, whereas the miR-199a-3p/miR-214 target, cyclooxygenase-2, a critical enzyme in synthesis of proinflammatory prostaglandins, was coordinately increased. Overexpression of miR-199a-3p and miR-214 in cultured human myometrial cells inhibited cyclooxygenase-2 protein and blocked TNF-α-induced myometrial cell contractility, suggesting their physiological relevance. Notably, E(2) treatment of ovariectomized mice suppressed, whereas P(4) enhanced uterine miR-199a-3p/214 expression. Intriguingly, these opposing hormonal effects were mediated by ZEB1, which is induced by P(4), inhibited by E(2) and activates miR199a/214 transcription. Together, these findings identify miR-199a-3p/miR-214 as important regulators of myometrial contractility and provide new insight into strategies to prevent preterm birth.

Nat Rev Endocrinol. 2013 Jul;9(7):391-401.
MicroRNAs--mediators of myometrial contractility during pregnancy and labour.

Renthal NE, Williams KC, Mendelson CR.

Abstract
The maintenance of myometrial quiescence and initiation of contractility, which lead to parturition at term and preterm, involve a shifting equilibrium between anti-inflammatory and proinflammatory signalling pathways. Progesterone (P4), acting through the progesterone receptor (PR), has an essential and multifaceted role in the maintenance of myometrial quiescence. This effect of P4-PR signalling is mediated, in part, by its anti-inflammatory actions and capacity to repress the expression of genes that encode proinflammatory cytokines, such as IL-1 and IL-6, and contraction-associated proteins, such as OXTR, GJA1 and PTGS2. By contrast, increased expression of genes that ultimately lead to parturition is mediated by enhanced inflammatory and estradiol-17β (E2) and estrogen receptor α signalling, which reduce PR function, thus further intensifying the inflammatory response. To obtain a more complete understanding of the molecular events that underlie the transition of the pregnant myometrium from a refractory to a contractile state, the roles of microRNAs, their targets, and their transcriptional and hormonal regulation have been investigated. This article reviews the actions of the miR-200 family and their P4-regulated targets-the transcription factors ZEB1, ZEB2 and STAT5B-in the pregnant myometrium, as well as the role of miR-199a-3p and miR-214 and their mutual target PTGS2. The central role of ZEB1 as the mediator of the opposing actions of P4 and E2 on myometrial contractility will be highlighted.

J Biol Chem. 2015 Sep 11;290(37):22409-22.

The miR-200 family and its targets regulate type II cell differentiation in human fetal lung.

Benlhabib H et al.

Abstract

Type II cell differentiation and expression of the major surfactant protein, SP-A, in mid-gestation human fetal lung (HFL) are induced by cAMP and inhibited by TGF-β. cAMP induction of SP-A promoter activity is mediated by increased phosphorylation and DNA binding of thyroid transcription factor-1 (TTF-1/Nkx2.1), a master regulator of lung development. To further define mechanisms for developmental induction of surfactant synthesis in HFL, herein, we investigated the potential roles of microRNAs (miRNAs, miRs). To identify and characterize differentially regulated miRNAs in mid-gestation HFL explants during type II pneumocyte differentiation in culture, we performed miRNA microarray of RNA from epithelial cells isolated from mid-gestation HFL explants before and after culture with or without Bt2cAMP. Interestingly, the miR-200 family was significantly up-regulated during type II cell differentiation; miR-200 induction was inversely correlated with expression of known targets, transcription factors ZEB1/2 and TGF-β2. miR-200 antagonists inhibited TTF-1 and surfactant proteins and up-regulated TGF-β2 and ZEB1 expression in type II cells. Overexpression of ZEB1 in type II cells decreased DNA binding of endogenous TTF-1, blocked cAMP stimulation of surfactant proteins, and inhibited miR-200 expression, whereas cAMP markedly inhibited ZEB1/2 and TGF-β. Importantly, overexpression of ZEB1 or miR-200 antagonists in HFL type II cells also inhibited LPCAT1 and ABCA3, enzymes involved in surfactant phospholipid synthesis and trafficking, and blocked lamellar body biogenesis. Our findings suggest

http://www.origo.hu/egeszseg/terhesseg

Kiderült, milyen folyamat indítja be a koraszülést

Illyés András

Igen összetett kölcsönhatások zajlanak két gén, illetve a mikroRNS-ként ismert apró, egyszálú nukleinsav-molekulák között.

A szülés megindulásának idejét egy bonyolult, kétszeres negatív visszacsatoláson alapuló molekuláris szabályozó mechanizmus befolyásolja.

Két olyan génről van szó (ZEB1 és ZEB2), amelyek a progeszteron nevű hormonra érzékenyek. A progeszteron alapvető szerepet tölt be a szülés megindításában, mind az egereknél, mind az embereknél. Fontos különbség azonban, hogy az egerek esetében a hormonszint csökkenése indítja meg a szülést, míg a szülő nőkben elsőként nem a hormonszint változik meg, hanem a hormonreceptorok érzékenysége csökken. Ennek következtében azonban végül ugyanúgy lecsökken a vérben keringő progeszteron szintje, majd megindulnak a méhösszehúzódások.

Az egerek méhfalában vett mintákban azt tapasztalták a kutatók, hogy a progeszteronszint csökkenését követően - vagyis a szülés megindulása előtt - csökken a ZEB1 gén aktivitása, vagyis kevesebb fehérje íródik át a génről. Ennek hatására fokozódik a már említett mikro-RNS molekulák egyik típusának, az miR-200 molekuláknak a termelődése. Ez visszahat a ZEB1 és a ZEB2 gének aktivitására, csökkentve az aktivitásukat, aminek következtében még több mikro-RNS kezd termelődni – ez az egyik negatív visszacsatolási kör.

A ZEB1 és a ZEB2 által termelt fehérjékről emellett az is kiderült, hogy képesek elnyomni két olyan gén működését, amelyek a méhösszehúzódások megindításáért felelős fehérjéket termelnek. Ezek közé tartozik az oxitocin nevű hormon receptora és a connexin-43 nevű fehérje. Ha csökken a ZEB1 és a ZEB2 szintje, az emiatt egy másik hatással is jár: megnő az oxitocinreceptort és a connexin-43-at kódoló gének aktivitása, és megindul a szülés. Ez a másik negatív visszacsatolási kör.

A koraszülés-kutatás „szent grálja”

a vizsgált mikro-RNS család nem mutat jelentős különbségeket az egérben és az emberben.

Olyan egerekben, amelyeknél mesterséges úton indították meg a koraszülést, a génkifejeződési mintázatok megegyeztek azzal, amit az előző két esetben tapasztaltak, így feltételezhető, hogy a koraszülés során valóban ezek a folyamatok zajlanak le.

„ … ezek a visszacsatolási körök a fontosak a koraszülésben. A kutatók nem figyeltek erre, mert valami sokkal nyilvánvalóbb dolgot kerestek - nem tűnt valószínűnek, hogy épp itt van a kulcs”.

A jövőben új szereket lehet majd kifejleszteni a koraszülés hatékony megelőzésére: ilyenből jelenleg nem sok van, így egy általánosan alkalmazható gyógyszer kidolgozása akár a koraszülés-kutatás „szent gráljának” is nevezhető.

Nat Commun. 2014 Jun 17;5:4108.

Diminished hERG K+ channel activity facilitates strong human labour contractions but is dysregulated in obese women.

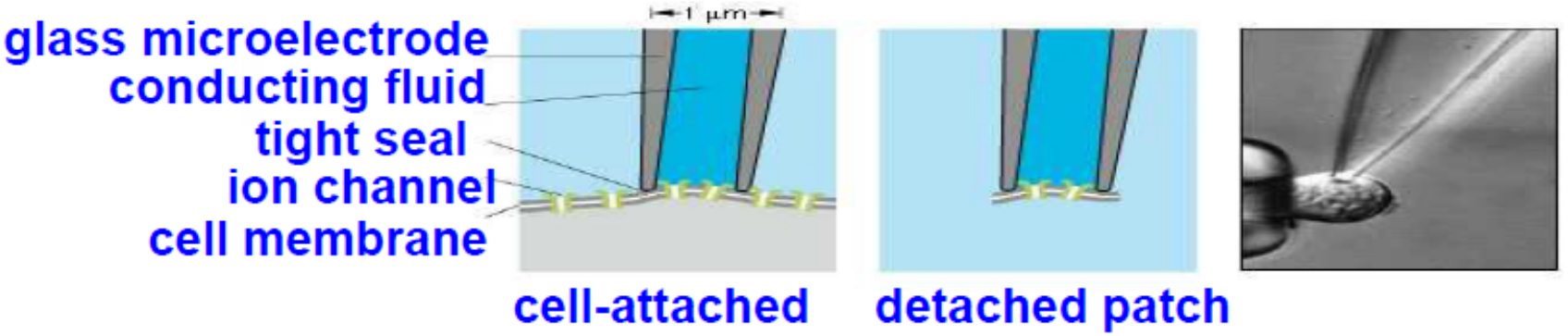
Parkington et al.

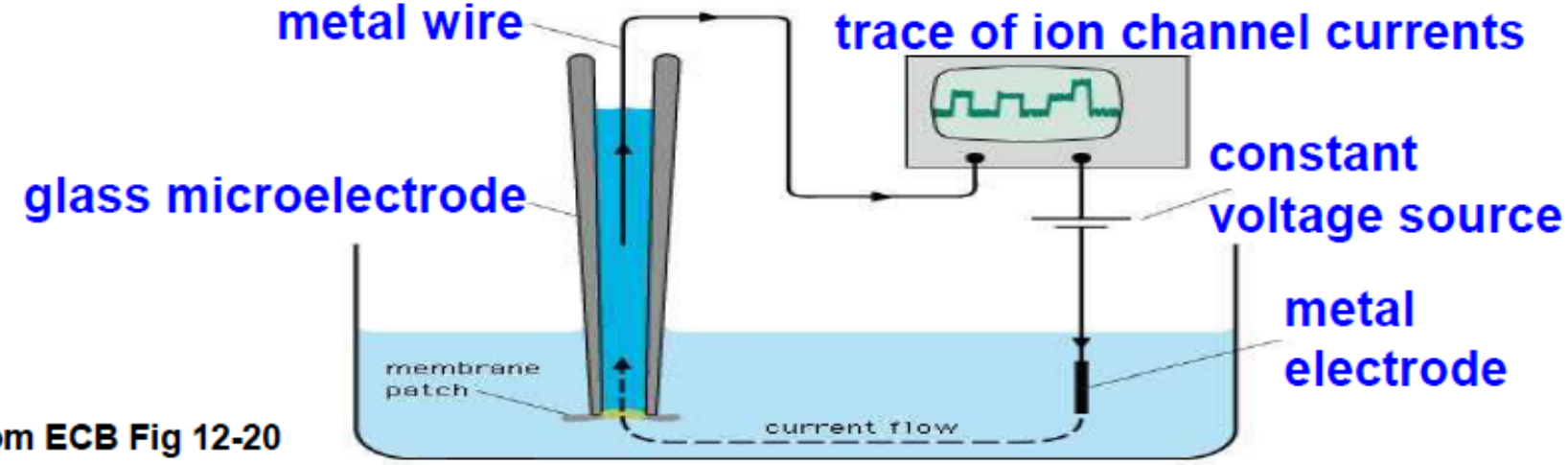
Abstract

Human ether-a-go-go-related gene (hERG) potassium channels determine cardiac action potential and contraction duration. Human uterine contractions are underpinned by an action potential that also possesses an initial spike followed by prolonged depolarization. Here we show that hERG channel proteins (α-conducting and β-inhibitory subunits) and hERG currents exist in isolated patch-clamped human myometrial cells. We show that hERG channel activity suppresses contraction amplitude and duration before labour, thereby facilitating quiescence. During established labour, expression of β-inhibitory protein is markedly enhanced, resulting in reduced hERG activity that is associated with an increased duration of uterine action potentials and contractions. Thus, changes in hERG channel activity contribute to electrophysiological mechanisms that produce contractions during labour. We also demonstrate that this system fails in women with elevated BMI, who have enhanced hERG activity as a result of low β-inhibitory protein expression, which likely contributes to the weak contractions and poor labour outcomes observed in many obese women necessitating caesarean delivery.

Ion channel recording

- Ion movements across membrane can be detected by electrical measurements
- Technical advances now permit measurement of electrical current through single channel molecule - patch clamp recording





Adapted from ECB Fig 12-20

THE BEHAVIOR OF FOUR NEUROLOGICAL MUTANTS OF DROSOPHILA*

WILLIAM D. KAPLAN AND WILLIAM E. TROUT III

Department of Biology, City of Hope Medical Center, Duarte, California, 91010

Received August 26, 1968

SINGLE gene changes offer an efficient and attractive way to study the genetic control of behavior. Drosophila, with its numerous technical advantages, would seem to provide a fruitful approach in working out the complexities of neurological control. The four neurological mutants discovered serendipitously and described in this report present just such an opportunity.

The phenotype common to all four is a rapid shaking of the legs following etherization. Because the mutants appeared, among the progeny of four different males of the original thirty treated, they represent four independent mutational events. Subsequent study has disclosed that three separate gene loci are involved, all on the *X*-chromosome.

Genetics **61:** 399-409 February 1969.

TABLE 1

Localization of mutant genes on X-chromosome

Genotype	Number of offspring counted	Number of crossovers between:		Recombinational fraction between mutant and closer of two markers	Position on *X*-chromosome
Hyperkinetic^{1P}	2431	*ct* and *Hk*^{1P}	262	2.1	30.9 ± 0.6*
		Hk^{1P} and *v*	51		
Hyperkinetic^{2T}	2027	*cv* and *Hk*^{2T}	333	2.6	30.4 ± 0.7*
		Hk^{2T} and *v*	52		
Shaker^{5}	1770	*f* and *Sh*^{5}	24	1.4	58.2 ± 0.6*
		Sh^{5} and *car*	69		
Ether à go-go	2479	*g* and *Eag*	139	5.6	50.0 ± 1.0*
		Eag and *f*	179		

* Limits of recombinational fraction corresponding to level of significance of one in twenty. Based upon method of STEVENS (1942).


REGENCY
whiskyagogo.com
Whisky a Go Go
WED GRAVEYARD BBQ
TIME IS THE ENEMY
KAUSTIK
CHECHNYA
Clark St
NO CRUISING ZONE
DO NOT BLOCK
8901
whiskyagogo.com
BRUCE SPRINGSTEEN
THE SEEGER SESSIONS
MADONNA
DEPECHE MODE
DISTURBED

Mol Cancer. 2010 Jan 27;9:18.

The potassium channel Ether à go-go is a novel prognostic factor with functional relevance in acute myeloid leukemia.

Agarwal JR, Griesinger F, Stühmer W, Pardo LA.

BACKGROUND:

The voltage-gated potassium channel hEag1 (KV10.1) has been related to cancer biology. The physiological expression of the human channel is restricted to the brain but it is frequently and abundantly expressed in many solid tumors, thereby making it a promising target for a specific diagnosis and therapy. Because chronic lymphatic leukemia has been described not to express hEag1, it has been assumed that the channel is not expressed in hematopoietic neoplasms in general.

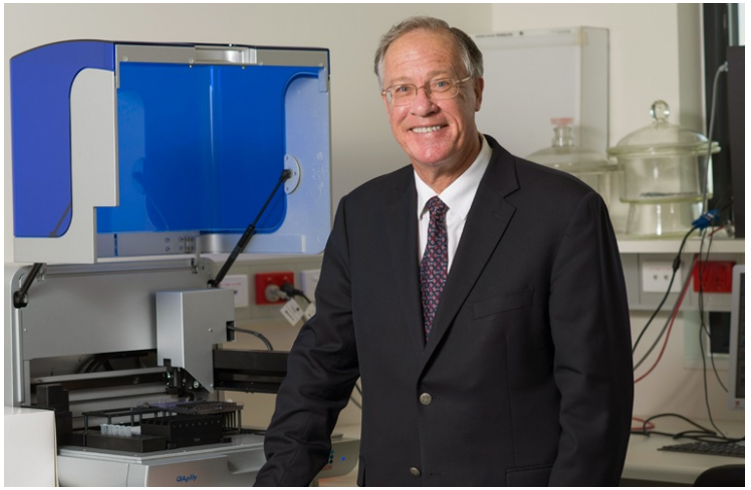
RESULTS:

Here we show that this assumption is not correct, because the channel is up-regulated in myelodysplastic syndromes, chronic myeloid leukemia and almost half of the tested acute myeloid leukemias in a subtype-dependent fashion. Most interestingly, channel expression strongly correlated with increasing age, higher relapse rates and a significantly shorter overall survival. Multivariate Cox regression analysis revealed hEag1 expression levels in AML as an independent predictive factor for reduced disease-free and overall survival; such an association had not been reported before. As a functional correlate, specific hEag1 blockade inhibited the proliferation and migration of several AML cell lines and primary cultured AML cells in vitro.

CONCLUSION:

Our observations implicate hEag1 as novel target for diagnostic, prognostic and/or therapeutic approaches in AML.

Australian researchers unlock key to triggering labour



Researcher Prof Shaun Brennecke from the Women's and the University of Melbourne said the finding significantly advances understanding of how labour progresses.

Published today in Nature Communications, this research represents a major advance in our understanding of how labour progresses, with implications for all women who have complicated labours, according to lead researcher Professor Helena Parkington at Monash University's School of Biomedical Sciences.

What she found was that during pregnancy uterine muscle contraction is prevented by electricity flow and this electricity needs to be switched OFF to allow labour contractions to occur effectively. The switch stays turned ON

in overweight women. "The reason is stays ON is that the "molecular hand" that should turn the switch OFF fails to appear in sufficient quantities in the uterine muscle of overweight women when labour should be occurring", she says. "These women also respond poorly to our current methods of induction".

This is the first time that the switch and the "molecular hand" controlling it have been identified in uterine muscle.

The clinical significance of this discovery is that, having identified the problem responsible for malfunctioning labour

J Clin Invest. 2015 Jul 1;125(7):2808-24.
Steroid receptor coactivators 1 and 2 mediate fetal-to-maternal signaling that initiates parturition.
Gao L et al.

Abstract
The precise mechanisms that lead to parturition are incompletely defined. Surfactant protein-A (SP-A), which is secreted by fetal lungs into amniotic fluid (AF) near term, likely provides a signal for parturition; however, SP-A-deficient mice have only a relatively modest delay (~12 hours) in parturition, suggesting additional factors. Here, we evaluated the contribution of steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2), which upregulate SP-A transcription, to the parturition process. As mice lacking both SRC-1 and SRC-2 die at birth due to respiratory distress, we crossed double-heterozygous males and females. Parturition was severely delayed (~38 hours) in heterozygous dams harboring SRC-1/-2-deficient embryos. These mothers exhibited decreased myometrial NF-κB activation, PGF2α, and expression of contraction-associated genes; impaired luteolysis; and elevated circulating progesterone. These manifestations also occurred in WT females bearing SRC-1/-2 double-deficient embryos, indicating that a fetal-specific defect delayed labor. SP-A, as well as the enzyme lysophosphatidylcholine acyltransferase-1 (LPCAT1), required for synthesis of surfactant dipalmitoylphosphatidylcholine, and the proinflammatory glycerophospholipid platelet-activating factor (PAF) were markedly reduced in SRC-1/-2-deficient fetal lungs near term. Injection of PAF or SP-A into AF at 17.5

Researchers find molecular mechanisms within fetal lungs that initiate labor

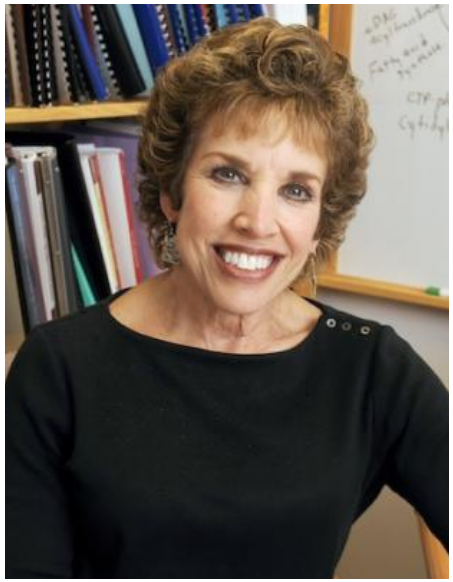
Jun 22, 2015

http://www.utsouthwestern.edu/newsroom/news-releases/year-2015/june/molecular-mech

Previous studies have suggested that signals from the fetus initiate the birth process, but the precise molecular mechanisms that lead to labor remained unclear. UT Southwestern biochemists studying mouse models found that the two proteins − steroid receptor coactivators 1 and 2 (SRC-1 and SRC-2) – control genes for pulmonary surfactant components that promote the initiation of labor. Surfactant is a substance released from the fetus' lungs just prior to birth that is essential for normal breathing outside the womb.

UT Southwestern researchers found that the proteins SRC-1 and SRC-2 activate genes inside the fetus' lungs near full term, resulting in an increased production of surfactant components, surfactant protein A (SP-A), and platelet-activating factor (PAF). Both SP-A and PAF are then secreted by the fetus' lungs into the amniotic fluid, leading to an inflammatory response in the mother's uterus that initiates labor.

"Our study provides compelling evidence that the fetus regulates the timing of its birth, and that this control occurs after these two gene regulatory proteins − SRC-1



“By understanding the factors and pathways that initiate normal-term labor at 40 weeks, we can gain more insight into how to prevent preterm labor,” said Dr. Mendelson, Director of the North Texas March of Dimes Birth Defects Center at UT Southwestern.

The study was conducted with current and former UT Southwestern researchers, including first author Dr. Lu Gao; Dr. Elizabeth Rabbitt; Dr. Jennifer Condon; Dr. Nora Renthal; Dr. John Johnston; Dr. Matthew Mitsche; and researchers from the Institut de Génétique et de Biologie Moléculaire et Cellulaire, France, and Baylor College of Medicine in Houston.