Journal of Steroid Biochemistry & Molecular Biology 170 (2017) 19–27

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Fetal-to-maternal signaling in the timing of birth

Carole R. Mendelson[a,b,*], Alina P. Montalbano[a], Lu Gao[a,1]

[a] Departments of Biochemistry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, USA
[b] Obstetrics & Gynecology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form 5 July 2016
Accepted 10 September 2016
Available online 11 September 2016

Keywords:
Pregnancy
Parturition
Progesterone
NF-κB
Fetal lung
Surfactant protein A
Platelet-activating factor

ABSTRACT

Preterm birth remains the major cause of neonatal morbidity and mortality throughout the world. This is due, in part, to our incomplete understanding of the mechanisms that underlie the maintenance of pregnancy and the initiation of parturition at term. In this article, we review our current knowledge of the complex, interrelated and concerted mechanisms whereby progesterone maintains myometrial quiescence throughout most of pregnancy, as well as those that mediate the upregulation of the inflammatory response and decline in progesterone receptor function leading to parturition. Herein, we review findings that demonstrate a role of the fetus in the timing of birth. Specifically, we focus on our own studies indicating that maturation of the fetal lung and enhanced secretion of the surfactant components, surfactant protein A (SP-A) and the potent inflammatory glycerophospholipid, platelet-activating factor (PAF), initiate a signaling cascade culminating in parturition. Our studies suggest an essential role of steroid receptor coactivators, SRC-1 and SRC-2, which activate expression of genes encoding SP-A and LPCAT1. LPCAT1 is a key enzyme in the synthesis of PAF, as well as DPPC, a highly surface-active glycerophospholipid component of surfactant. Thus, we describe a novel pathway through which the fetus contributes to the initiation of labor by signaling the mother when its lungs have achieved sufficient maturity for survival in an aerobic environment.

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1. Introduction

Preterm birth (<37 weeks gestation) is the leading cause of infant mortality during the first four weeks of life throughout the world [1]. The highest rates of preterm birth are found in parts of Africa and in North America. In the United States, the incidence of preterm birth has increased steadily over the past several decades and has recently plateaued at ~11.5% of all live births. Moreover, there remain significant and persistent racial disparities in preterm

* Corresponding author at: Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9038, USA.
E-mail address: carole.mendelson@utsouthwestern.edu (C.R. Mendelson).
[1] Present address: Department of Physiology, Second Military Medical University, 800 Xiangyin Rd., Shanghai, China.

http://dx.doi.org/10.1016/j.jsbmb.2016.09.006
0960-0760/

birth rates. While the prematurity rate among white infants is ~11%, close to 18.0% of births among black infants are preterm. The underlying factors contributing to this racial disparity remain unclear [2]. Whereas, infection with associated inflammation of the fetal membranes likely provides an important stimulus for preterm labor [3,4], signaling molecules that promote the inflammatory response leading to labor at term are less certain. There is increasing evidence to suggest that the fetus generates signals that contribute to the initiation of labor. In this mini-review, we will consider evidence to suggest that the fetus produces signals leading to labor at term. We first will consider the fetal tissues and signaling molecules proposed to serve a role in the initiation of parturition at term and then focus on our own studies which strongly suggest that these signaling molecules arise from the fetal lung.

2. Progesterone (P_4) acting through nuclear progesterone receptor (PR) maintains myometrial quiescence throughout most of pregnancy

Myometrial quiescence throughout most of pregnancy is mediated by increased circulating levels of P_4, produced by placenta and/or the ovarian corpus luteum, depending upon the species. Progesterone blocks myometrial contractility through its binding to two nuclear receptor isoforms, PR-A (94 kDa) and PR-B (114 kDa), which are the products of a single gene [5,6]. As shown in Fig. 1 (left panel), the mechanisms whereby P_4/PR maintains uterine quiescence are multiple and overlapping. For example, P_4/PR can exert a pronounced anti-inflammatory effect, by inhibiting activation/DNA binding of the pro-inflammatory transcription factors, nuclear factor κB (NF-κB) [7] and activating protein 1 (AP-1) [8]. P_4/PR also can block induction of the proinflammatory response by upregulating expression of the NF-κB inhibitor, IκBα [7], and the mitogen-activated protein kinase (MAPK) inhibitor, MAPK phosphatase-1/dual specificity phosphatase 1 (MKP-1/DUSP1) [9]. Moreover, P_4/PR also maintains myometrial quiescence by increasing expression of the transcriptional inhibitor, ZEB1, which binds to the promoters of the contractile genes, gap junction protein connexin-43 (*CX43/GJA1*) and oxytocin receptor (*OXTR*), to suppress their expression throughout most of pregnancy [10,11].

3. Inflammatory signaling and the initiation of term and preterm labor

Labor, both term and preterm, is accompanied by an inflammatory response. Increased levels of proinflammatory cytokines are found in amniotic fluid [12] and the myometrium, cervix, and fetal membranes are infiltrated by immune cells [13–15], which secrete proinflammatory cytokines and chemokines [3] (Fig. 1, right panel). This promotes an inflammatory signaling cascade that results in activation of NF-κB and other proinflammatory transcription factors (*e.g.* AP-1) in myometrium [14,16], cervix and fetal membranes [17–19]. Activated NF-κB and AP-1 increase expression of genes that promote myometrial contractility, including the prostaglandin $F_{2\alpha}$ receptor [20], *CX43* [21], *OXTR* [22] and cyclooxygenase-2 (*PGHS2*, COX-2) [23], which catalyzes the production of contractile prostaglandins [24–26]. In preterm labor, intra-amniotic infection associated with chorioamnionitis may provide the stimulus for increased amniotic fluid interleukins and inflammatory cell migration [27]. On the other hand, the inflammatory response leading to labor at term is triggered by increased mechanical stretch [28,29] imposed by the growing conceptus, as well as by fetal signaling molecules produced in increasing amounts toward term [14,30–35] (Fig. 1), which are described in *Section* 4.

The increased inflammatory response that occurs toward term also is caused by a relative increase in E_2/ERα signaling and decline in P_4/PR function (Fig. 1, right panel). The increase in circulating estradiol-17β (E_2) [36,37] and/or increased estrogen receptor α (ERα) activity [38,39] induce immune cell migration into the uterus and antagonize the anti-inflammatory actions of P_4/PR

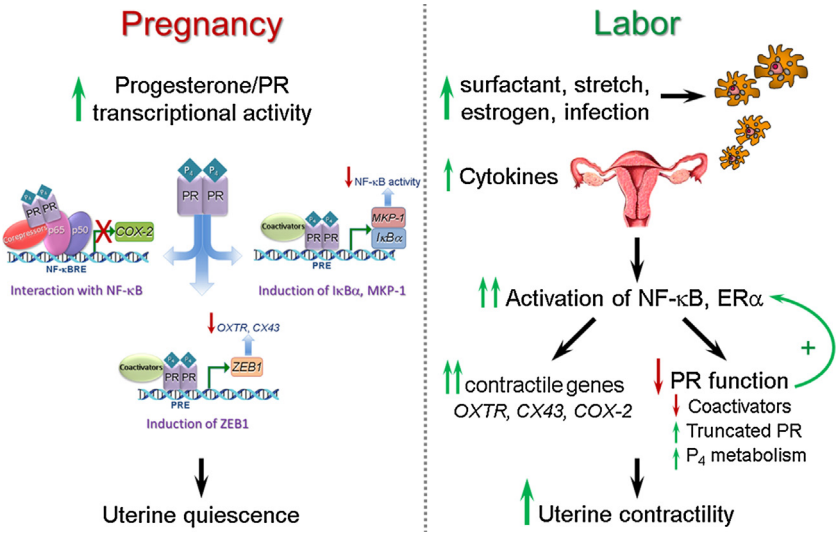

Fig. 1. Mechanisms for P_4/PR maintenance of myometrial quiescence throughout most of pregnancy (left panel) and for the initiation of term and preterm parturition (right panel). During pregnancy, increased P_4 acting through PR can maintain myometrial quiescence *via* several mechanisms, including: interaction with NF-κB p65 and recruitment of co-repressors to block p65 transcriptional activation; transcriptional induction of the NF-κB inhibitor, IκBα, and/or the MAPK inhibitor, MKP-1/DUSP1, and; transcriptional induction of ZEB1, which suppresses transcription of myometrial contractile genes. The initiation of labor at term (by increased secretion of surfactant components from the fetal lung, increased uterine stretch and increased circulating E_2) and preterm (by infection with chorioamnionitis) is accompanied by activation of macrophages that may be of fetal origin, their migration to the maternal uterus and release of proinflammatory cytokines. This results in an increase in myometrial NF-κB and ERα transcriptional activity and upregulation of contractile and proinflammatory genes, as well as a decline in PR function, which further accelerates the inflammatory process leading to labor.