

What does initiate parturition?

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Abstract

Several hormonal and other factors have been proposed to be involved in the initiation of parturition. However, definitive sequential events leading to initiation of parturition are still lacking. Conceptual evolution on the mechanism of initiation of parturition since 1891 has been briefed.

Key words: ER α , PR-A, cytokines, CRH, parturition

Accepted May 04 2009

Introduction

More than a century back, Spiegelberg [1] reported that parturition results from substances produced by the fetus. Later, it is suggested that some portion of the central nervous system and fetal adrenal are important [2]. Experiments of Newton [3] and van Wagenen and Newton [4] have shown that following fetectomy, pregnancy continues and placental delivery occurs at or near to normal term in mice and monkeys. Liggins [5] however, reported that ACTH or cortisol infusion into pregnant lambs induces parturition on the 6th day of infusion. Conversely, Chatterjee *et al.* [6] have documented that the administration of glucocorticoid to pregnant rats close to term delays parturition. Liggins [7] later recorded that human fetuses with adrenal hypoplasia are born at or close to term. Administration of large doses of glucocorticoid to pregnant women [8] or sheep [9] before term also failed to induce premature labor.

Molokwu and Wagner [10] have proposed that an increased level of glucocorticoid at the time of parturition is due to the stress of labor but not a cause of parturition. On the other hand, Talbert *et al.* [11] could not detect any significant difference in cord plasma levels of cortisol in infants born after elective Caesarian section compared to those born after spontaneous onset of labor.

Based on 89 publications, the International Planned Parenthood Federation suggested that at term, fetal ACTH by stimulating fetal adrenal glucocorticoid induces a concomitant decrease in progesterone with a concurrent increase in estrogen. As a result, a spontaneous elevation of fetal and maternal prostaglandins and oxytocin leads to softening of the cervix and a simultaneous uterine

myometrial contraction which consequently results in parturition [12]. Cortisol, a progesterone agonist, has however been shown to exert a direct inhibitory effect on estrogen [13] and prostaglandin [14] synthesis.

Parturition is moreover claimed to be driven by a pulsatile pattern of oxytocin secretion [15], but neither oxytocin antiserum [16] nor its antagonist [17,18] is found to prolong gestation or delay parturition. Circulating oxytocin therefore, does not seem to be essential for the initiation of parturition [19].

Progesterone is known to support pregnancy and prevent parturition by promoting myometrial quiescence [20]. In contrast, estrogen stimulates parturition by augmenting myometrial excitability and contractility [21] with a corresponding stimulation of prostaglandins and ripening of the cervix [22]. Therefore to initiate parturition, transformation of myometrium from a quiescent to a contractile state requires a coordination of progesterone withdrawal and estrogen activation. However, in humans [23] and higher primates [24], maternal progesterone and estrogens levels are found to remain elevated during parturition.

RU 486, a progesterone antagonist and a potent abortifacient agent [18,25], not only increases myometrial estrogen receptor (ER) expression, it does also reduce progesterone concentration in several species including rats [26], monkeys [27] and humans [28]. RU 486 also exerts a profound softening action on the cervix [29].

It is now hypothesized that functional progesterone withdrawal occurs by increased expression of progesterone receptor-A (PR-A) type which suppresses myometrial

progesterone responsiveness [30].

Similarly, functional ER α activation is found to be linked with functional progesterone withdrawal [31]. Progesterone withdrawal consequently stimulates prostaglandin synthesis by human endometrium [32], myometrium and cervix [33] and also by the rat myometrium [34]. Released prostaglandin then induces gap junction formation between myometrial cells [35] which facilitates a synchronized propagated uterine contraction with a corresponding ripening of the cervix [36] and finally results in labor [37]. Sugimoto et al [38] have shown that female mice lacking receptors for prostaglandin F 2α do not deliver fetuses at term.

The expression of prostaglandin in the uterine tissue is increased by cytokines [39]. IL-6 and IL-8 are the cytokines produced by human endometrium, myometrium, chorio-decidea and cervixes [40]. Preterm labor due to uterine or intra-amniotic infection is being found to be associated with an increased synthesis and release of IL-6, IL-8 [41] and prostaglandins [42]. Progesterone and glucocorticoids, the well-established anti-inflammatory agents [43] cause a significant inhibition of IL-6 and IL-8 [44] as well as prostaglandin synthesis [45]. However, intraperitoneal infusion of proinflammatory cytokines does not cause activation of the pregnant rat uterus [46]. The integrated role between the cytokines and prostaglandins in the initiation of labor therefore remains enigmatic.

Corticotrophic-releasing hormone (CRH), a peptide highly expressed in human placenta at the end of gestation has also been implicated in the process of labor [47]. An elevation of maternal serum CRH concentration has been documented as early as 18-week of gestation in patients who have subsequently aborted [48]. Estrogen stimulates CRH through its action on prostaglandin synthesis. On the other hand, CRH is found to increase the synthesis and release of prostaglandins from the cells of amnion, chorion and deciduas [49, 50].

In conclusion, the functional progesterone withdrawal with subsequent estrogen receptor activation possibly mediates the formation of prostaglandin which by interacting with cytokines and CRH may result in the initiation of parturition.

Acknowledgement

Constant encouragement of Professor Dr. Dato' Khalid Yusoff, Dean Faculty of Medicine, Universiti Teknologi MARA is very much appreciated..

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