Coll. Antropol. **25** (2001) 2: 687–694
UDC 618.39:612.43
Review

Review on Prostaglandin and Oxytocin Activity in Preterm Labor

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A B S T R A C T

The principal difference between term and preterm labor is how they are activated. It has been proposed that term labor results from physiological activation of the common terminal pathway, whereas preterm labor is a pathological condition caused by multiple etiologies that activate one or more of the components of this pathway. Increased uterine contractility at preterm labor results from activation and stimulation of the myometrium. Myometrium is stimulated by increased concentrations of prostaglandins and oxytocin. Increased production of stimulatory prostaglandins by intrauterine tissues is generally considered a central component of the cascade of events leading to preterm parturition. Prostaglandins act to mediate cervical ripening and to stimulate uterine contractions and indirectly to increase fundally dominant myometrial contractility by up regulation of gap junctions, oxytocin and arginine vasopressin receptors and synchronizations of contractions. The authors tried to explain the role and influence of oxytocin in human parturition, as well as the novel therapy in inhibiting the contractions in preterm labor. The selective oxytocin inhibitor was tested in vitro on human myometrium and decidua by the author of this article among the first in the world.

Introduction

Term and preterm labor are considered to be fundamentally similar processes except for the gestational age at which they occur. They share a common terminal pathway consisting of uterine contractility, cervical dilatation and activation of the amniotic membranes. This involves anatomical, biochemical, endocrinological and clinical events that occur in the fetus and /or mother. The principal difference between term and preterm labor is how they are activated. It has been proposed that term labor results from physiological activation of the common terminal pathway, whereas preterm labor is a pathological condition caused by multiple etiologies that activate one or more of the components of this pathway.

Received for publication September 27, 2001.

Clinical and experimental evidence indicate that preterm labor results from four primary pathogenic mechanisms: activation of the maternal or fetal hypothalamic pituitary adrenal (HPA) axis; amniochorionic-decidual or systemic inflammation; decidual hemorrhage; and, pathologic distension of the myometrium. Each of these four pathways has a distinct epidemiological and clinical profile, and unique biochemical and biophysical pathways initiating parturition, but shares a common final biochemical pathway involving myometrial activation and stimulation, and enhanced genital tract protease activity promoting PPROM (preterm premature rupture of membranes) and cervical change.

Increased uterine contractility at term and preterm results from activation and stimulation of the myometrium. Activation of myometrium starts with expression of contraction-associated proteins, including connexin 43 as a key component of gap junctions and synthesis of receptors for prostaglandins and oxytocin. Myometrium is stimulated by increased concentrations of prostaglandins and oxytocin. Activation can be provoked by mechanical stretch of the uterus and by an endocrine pathway resulting from increased activity of the fetal hypothalamic-pituitary-adrenal axis. Cortisol, derived from the fetal adrenal in cases of intrauterine compromise or from the maternal adrenal in response to stress, or generated locally from cortisone in choriodecidual trophoblasts, provides a crucial link to uterine stimulation. Cortisol contributes to the increased production of prostaglandins (PG) by fetal membranes and the decidua through the up regulation of prostaglandin endoperoxidase H synthase (PGHS) and the down regulation of 15-hydroxy prostaglandin dehydrogenase (PGDH)[1].

Increased production of stimulatory prostaglandins by intrauterine tissues is generally considered a central component of the cascade of events leading to preterm/term parturition. During pregnancy the levels of primary prostaglandins (prostaglandin E_2 and prostaglandin F_2) in amniotic fluid and peripheral plasma are quite low. During abortion in second trimester the marked increase of amniotic fluid of PGE2 and PGF_2 levels are sufficient for triggering abortion and are of the same level as at the time of preterm delivery[2]. Despite these finding many authors are still searching for mechanisms and differences in production and metabolism of prostaglandins in preterm labor. In late eighties Đelmiš[3] published the data on significantly increased arachidonic acid (AA) content in the placentas of women with chorioamnionitis and preterm delivery compared to those of women with preterm delivery without chorioamnionitis. At that time already it was correctly supposed that intrauterine infection is the important trigger for increased substrate synthesis for further prostaglandin production within placental tissue. The same other authors have demonstrated increased arachidonic acid levels in decidua, membranes and amniotic fluid in preterm labor complicated with intrauterine infection[4].

In one third of spontaneous preterm labours there is inflammatory infiltration of the placenta, fetal membranes and /or decidua with increased levels of the products of the lipoxygenase and cyclooxygenase pathways[3]. Bacterial organisms themselves secrete phospholipases resulting in increased release of arachidonic acid (AA) from intrauterine tissues and increased PG production. Alternatively, bacterial endotoxin, such as lipopolisaccharide (LPS) can act on amniotic or macrophage membranes causing PG release, or further release of cytokines. There are also increased levels of cytokines interleukin-1 and interleukin-8 including interleukin-1 , interleukin-6,

and tumor necrosis factor in the amniotic fluid of women with infection. Studies on cytokines such as IL-1 and to a lesser extent, TNF decrease 15-hydroxy prostaglandin dehydrogenase (PGDH) mRNA activity in placental and trophoblast cells, and increase PG production. It is also possible that cytokines cause release of other uterotonins, including oxytocin (OT) but only in acute infections and corticotrophin releasing hormone (CRH) in: decidua, myometrium and/or placenta.

Cytokines and eicosanoids appear to be synergistic, and the net effect may be to overwhelm the normal parturition cascade, resulting in preterm labor. Prostaglandins act to mediate cervical ripening and to stimulate uterine contractions and indirectly to increase fundally dominant myometrial contractility by up regulation of gap junctions[5], oxytocin and arginine vasopressin receptors and synchronizations of contractions. Production and metabolism of prostaglandins in human labor is compartmentalized and differs significantly in preterm labor compared to term labor.

Prostaglandin Synthesis and Metabolism within Fetal Membranes, Decidua and Uterus

Primary prostaglandins, including PGE_2 and PGF_2 are formed from obligate precursor arachidonic acid (AA), which is liberated from membrane phospholipids, such as phosphatydil ethanolamine and phosphatidyl inositol, through the actions of one or more isozymes of phospholipase C (PLC) or phospholipase A_2 (PLA_2). PLA_2 isozymes may include a larger-molecular weight (85–110 kD) cytosolic form ($cPLA_2$) as well as the secretory types ($sPLA_2$), II, III extracellular 14-kD forms and I. Millimolar concentrations of calcium are required for activation of $sPLA_2$, whereas micromolar calcium concentrations are required for $cPLA_2$ activity. The cytosolic PLA_2 preferentially hydrolyzes phospholipids with AA at the sn-2 position; conversely, secretory PLA_2 do not display any selectivity among fatty acids at the sn-2 position.

The $cPLA_2$ activity is highest in the fetal membranes obtained either at term or preterm in absence of labor[6]. Positive diffuse cytosolic phospholipase A_2 immunostaining was found in amnion epithelial cells, in fibroblasts below the amnion epithelial layer, and in chorion cytotrophoblast. Skannal et al.[7] found that $cPLA_2$ activity in fetal membranes increase during pregnancy and is highest in anticipation of labor, becoming depleted after labor.

Net PG output in preterm labor depends on increased activity of prostaglandin endoperoxidase H synthase type 2 (PGHS-2) mainly in chorion and altered expression of chorionic 15-hydroxy-prostaglandin dehydrogenase (PGDH). In patients with idiopathic preterm labor, in the absence of intrauterine infection, decreased immunoreactive ir-PGDH protein in chorion trophoblast cells was found what correlated with decrease in PGDH enzyme activity in the same group of patients. In addition, a decrease in ir-PGDH and PGDH mRNA expression was found in chorion collected from preterm deliveries associated with severe infection in which there is a loss of trophoblast cells. The possible explanation for this finding was that in some patients in preterm labor, without infection, a deficiency in chorion PGDH would allow passage of PGs, generated in amnion and/or chorion, across the membranes, and could be causal to the initiation of preterm labor. In all these studies, changes in PGDH activity in the chorion correlated with changes in levels of PGDH mRNA in the tissue. Thus, control of the enzyme appears to be exerted in part at the level of transcription. Further

these changes in PGDH in chorion occurred in the absence of any such change in placental tissue form the same patients. PGDH activity and expression appeared to be tissue specific.

There was found also a regional distribution of PGDH activity in human fetal membranes (Figure 1).

Because of increased synthesis in chorion and amnion, and decreased metabolism of PGs in chorion, the elevated PGE_2 content is measured in amniotic fluid[2], amnion, chorion, decidua and myometrium, and PGF_2 concentration increases in decidua and myometrium. PGF_2 enters amniotic fluid because of decreased PGDH activity in amniochorionic membrane (Figure 1).

Oxytocin and Preterm Labor

Some of the controversial aspects of the role of oxytocin in parturition may be rationalized by recent research demonstrating expression of the oxytocin gene in peripheral tissues, which suggests a paracrine or autocrine role rather than, or in addition to, an endocrine role for oxytocin in parturition. If the principal actions of the oxytocin are in a paracrine system, important changes may occur without reflection in the maternal circulation. This fact may modify conclusions regarding the role of oxytocin in parturition that were made on the basis of assessment of oxytocin solely as an endocrine factor.

The first suggestion that oxytocin synthesis occurs in peripheral tissues was made after measurement of high OT concentrations in ovine corpus luteal tissues, and Chibbar et al. (1993)[8] demonstrated mRNA encoding oxytocin in human intrauterine tissues in late gestation, principally in decidua but also in chorion and amnion. The anatomical proximity of these tissues to the presumed target tissues – the endometrium and myometrium lends strong support to the hypothesis of an intrauterine paracrine system that regulates the timing of parturition.

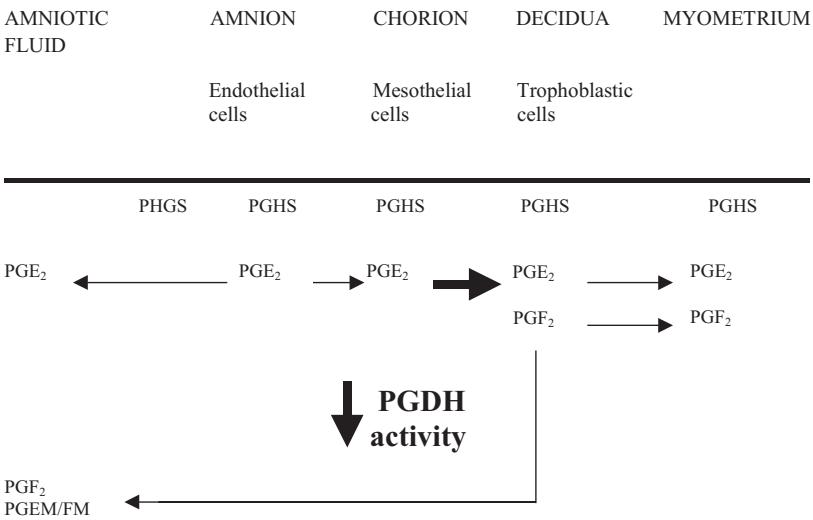

Fig. 1. PG synthesis and metabolism within fetal membranes, decidua and myometrium at preterm labor. Arrows in bold show the key processes in initiation of preterm labor. PGEM/FM are metabolites of PGE_2 and PGF_2 .

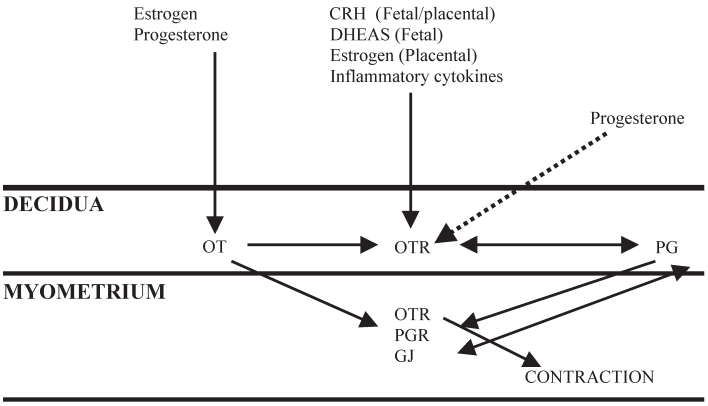

Fig. 2. The hypothesized positive feedback loop between OTR and PG in decidua and myometrium that are under stimulative influence of estrogens, CRH, DHEAS and proinflammatory cytokines. The decidual response is to produce OT that stimulates OTR in decidua, and decidual response is to produce PG in decidua, which, in turn, will increase synthesis of OTR in myometrium, and decidua. Estrogen, CRH and DHEAS from placental tissue induce synthesis of PGR (prostaglandin receptor) and GJ in myometrium. Progesterone strongly inhibits the production of OTR.

One of the most consistent findings in the study of parturition in human is the increase of OT receptors before the onset of preterm and term labor[9,10]. OT receptors are located in the cell membranes of the uterine smooth muscle, and their stimulation initiates myometrial contraction. The number of OT receptors increases dramatically in late gestation[11,12], and this process is likely the result of stimulated gene expression, as there is a large increase in detectable OT receptor mRNA towards term. The trigger for this increased gene expression is unknown, but may be related to increased estrogen levels in late gestation. The same proliferation of OT receptors occurs in myometrium also in preterm labor[13].

In addition to the myometrial receptors, OT receptors have been also found in decidua, as well as in almost all other reproductive tissues[9,12–15]. Their number also increases with gestation. Decidual OT receptors when activated with OT produce prostaglandins in particular PGF_2 (Figure 2).

The locally produced PG may produce de novo uterine contractions, through actions on prostanoid receptors on myometrial cells. In addition, they increase myometrial sensitivity to OT by further upregulating OT receptor production. They also increase formation of myometrial gap junctions, further enhancing uterine contractile ability. Oxytocin has recently been shown to up-regulate PGHS-2 (COX-2) and PGF_2 synthesis in endometrial cells[16]. Estrogens from placenta induce synthesis of oxytocin (OT) and arginine vasopressin (AVP) receptors in myometrium and decidua[11], and binding of these neuropeptides to their receptors activates the inositol triphosphate pathway. Progesterone appears to have a positive effect on OT but a strongly negative effect on OT receptors, whereas estrogen appears to upregulate both (Figure 2).

Myometrial OT receptors belong to a family of G protein-mediated receptors, and are very similar to V1 and V2 vasopressin receptors. V1 receptor for argini-

ne vasopressin is also present in human myometrium[11]. They stimulate uterine contractions by causing an increase in intracellular calcium. This is achieved by two mechanisms: rapid mobilization of calcium from sarcoplasmatic reticulum (SR), and a slower, more sustained entry of extracellular calcium through receptor-operated membrane channels.

The mechanisms for opening of receptor-operated membrane channels are not well understood, but seem to be mediated through G proteins. OT receptor is a classical membrane receptor with seven transmembrane domains linked through a G protein complex to a phospholipase C–protein kinase C signal transduction system. The coupling proteins include q and 11 subunits. Within seconds of OT stimulation, there are markedly higher intracellular concentration of inositol triphosphate and Ca^{2+}. The higher Ca^{2+} and calmodulin increase myosin light chain kinase, which catalyses the contraction response through activation of contraction-associated protein (CAP) expression[17]. CAP expression is dependent on degree of the stretch of human myometrium and the increased stretch leads to increased number of gap junctions and increased levels of mRNA encoding connexin 43 (gap junction protein) as well as OT and PGF receptors in myometrium.

This rapid response mechanism, together with a swift influx of extracellular calcium, is also believed to be responsible for the generation of prostaglandins in uterine tissues, stemming mainly from the calcium-dependent activation of phospholipase A_2 and the provision of the prostaglandin precursor arachidonic acid[18].

Recent evidence, however, indicates that oxytocin may also activate, in a calcium-independent fashion, alternate signaling pathways involving mitogen-activated protein kinase (MAPK) in myometrial cells. Such a signal transduction mechanism has been shown to mediate a variety of cellular events, leading to the expression of various genes and the synthesis of new proteins. The MAPK cascade has been implicated in the induction of cyclooxygenase-2 (COX-2) in macrophages, in response to stimulation with inflammatory lipopolysaccharide[19].

Pharmacological Tools in Preterm Uterine Contraction Inhibition

Available tocolytic drugs such as -mimetics[20], calcium channel blockers, magnesium sulphate[20] and PG synthase inhibitors, have multiple side effects that are major drawbacks for the management of preterm labor.

Today it is readily apparent that there are distinct receptors for OT and arginine vasopressin (AVP) in the pregnant and parturient uterus as was previously assumed in binding sites. Only a limited number of binding studies support the notion that human preterm labor could be associated with premature OT-receptor gene expression during pregnancy.

The use of an OT antagonist is a novel strategy for the management of preterm labor, with fewer potential side effects due to bioselective nature. Atosiban (1-deamino-2-D-Tyr-(OET)-4-Thr-8-Orn-oxytocin), a peptidic OT-receptor antagonist was in vitro tested first in 1987 by Akerlund[21]. During (1988) and Ivanišević (1989) performed studies with this compound and Fuchs[14] and it was found that it is a highly selective and specific OT antagonist in preterm myometrium and decidua for OT binding sites. At that time was already clear that main result of this inhibition of OT binding sites on membranes of preterm myometrium might be inhibitions of uterine contractions in vivo. In decidua atosiban inhibition of OT to bind to its specific binding sites might result in inhibition of phosphoinositol metabolism in the cell membrane and de-

crease the influx of PGF_2 into the myometrium.

In vivo, when atosiban is infused intravenously at 300 cg/min, a steady state concentration is reached after one hour, with an elimination half-life of 18 3 min. Until today a number of randomized, placebo-controlled trials with atosiban were reported. Atosiban infused intravenously was shown to have clinical advantages over current tocolytic agents. When -agonists are administered, they usually start at low concentration and increase the dose if the contractions remain whereas the opposite applies with atosiban, where the infusion starts with a bolus dose and then 300 cg/min infusion followed by 100 cg/min, so actually one gives progressively less atosiban with time for same effectiveness. Although atosiban was comparable to -agonists in delaying delivery[22,23], safety outcomes for mother and fetus were substantially improved with atosiban, and neonatal outcomes were similar. Hence, atosiban shows promise as a selective tocolytic agent for prevention of preterm birth at least in those where the etiology of preterm labor is not primarily infection.

The development of OT antagonists, as well as of other pharmacological agents that could influence this paracrine network, affords an opportunity to develop new strategies to treat or prevent preterm labor and its potentially expensive and tragic consequences.

REFERENCES

1. CHALLIS, J. R., S. K. SMITH, Biology of the Neonate, 79 (2001) 163. — 2. IVANIŠEVIĆ, M., J. ĐELMIŠ, Intern. J. Gynaecol. Obstet., 31 (1990) 355. — 3. ĐELMIŠ, J., J. Perinat. Med., 17 (1989) 417. — 4. ROMERO, R., M. MAZOR, K. Y. WU, M. SIRTORI, E. OYARZUM, M. D. MICHELL, J. C. HOBBINS, Semin. Perinatol., 12 (1988) 262. — 5. GARFIELD, R. E., E. L. HERTZBERG, Prog. Clin. Biol. Res., 327 (1990) 673. — 6. XUE, S., D. E. BROCKMAN, D. M. SLATER, L. MYATT, Prostaglandins, 49 (1995) 351. — 7. SKANNAL, D. G., D. E. BROCKMAN, A. L. W. EIS, S. XUE, A. TARIQ, L. MYATT, Am. J. Obstet. Gynecol., 177 (1997) 179. — 8. CHIBBAR, R., F. D. MILLER, B. F. MITCHELL, J. Clin. Invest., 91 (1993) 185. — 9. FUCHS, A. R., O. BEHRENS, H. HELMER, A. VANGSTED, M. IVANIŠEVIĆ, J. GRIFO, C. BARROS, M. FIELDS, Am. J. Obstet. Gynecol., 163 (1990) 1961. — 10. FUCHS, A. R., O. BEHRENS, H. C. LIU, Am. J. Obstet. Gynecol., 167 (1992) 1559. — 11. IVANIŠEVIĆ, M, O. BEHRENS, H. HELMER, K. DEMAREST, A. R. FUCHS, Am. J. Obstet. Gynecol., 161 (1989) 1637. — 12. ZINGG, H. H., F. ROZEN, K. CHU, A. LARCHER, A. ARSLAN, S. RICHARD, D. LEFEBVRE, Rec. Prog. Hor. Res., 50 (1995) 255. — 13. FUCHS, A. R., F. FUCHS, P. HUSSLEIN, M. S. SOLOFF, Am. J. Obstet. Gynecol., 150 (1984) 780. — 14. FUCHS, A. R., A. VANGSTED, M. IVANIŠEVIĆ, K. DEMAREST, Am. J. Perinatol., 6 (1989) 205. — 15. IVANIŠEVIĆ, M., J. ĐELMIŠ, D. BUKOVIĆ, M. MAJEROVIĆ, Coll. Antropol., 19 (1995) 525. — 16. ASSELIN, E., P. DORLET, M. A. FORTIER, Endocrinology, 138 (1997) 4798. — 17. JENKIN, G., J. Reprod. Fertil., 45 (1992) 97. — 18. IVELL, R., J. RUSSELL: Oxytocin. (Plenum Press, New York, 1995). — 19. HWANG, D., B. C. JANG, G. YU, M. BOUDREAU, Biochem. Pharmacol., 54 (1997) 87. — 20. ĐELMIŠ, J., D. BUKOVIĆ, M. IVANIŠEVIĆ, M. MAJEROVIĆ, Coll. Antropol., 19 (1995) 215. — 21. AKERLUND, M., P. STRÖMBERG, A. HAUKSSON, L. F. ANDERSEN, J. LYNDRUP, J. TROJNAR, Br. J. Obstet. Gynaecol., 94 (1987) 1040. — 22. MOUTQUIN, J. M., D. SHERMAN, H. COHEN, P. T. MOHIDE, D. HOCHNER-CELNIKIER, M. FEJGIN, Am. J. Obstet. Gynecol., 182 (2000) 1191. — 23. FUCHS, A. R, F. FUCHS, P. STUBBLEFIELD: Preterm birth: Causes, prevention, and management. (McGraw-Hill, New York, 1993).

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ULOGA PROSTAGLANDINA I OKSITOCINA U PRIJEVREMENOM PORODU

S A Ž E T A K

Porod u terminu rezultat je fizioloških promjena koje su neophodne za njegovu aktivaciju i progresiju, dok je prijevremeni porod patološko stanje izazvano brojnim etiološkim faktorima koji sudjeluju u aktivaciji jedne ili više komponenti kaskade poroda. Pojačana kontraktilnost uterusa rezultat je upravo aktivnosti i stimuliranosti miometrija. Miometrij je stimuliran zbog povećane endokrine i lokalne koncentracije prostaglandina i oksitocina u reprodukcijskim tkivima a upravo autokrina i parakrina funkcija ovih hormona je ključna za nastanak prijevremenog poroda. Prostaglandini posreduju u sazrijevanju cerviksa, stimulaciji kontrakcija uterusa, indirektno pojačavaju kontrakcije maternice koje nastaju u fundusu uterusa povećavajući stvaranje međustaničnih spojnica, nadalje potiču nastanak receptora za oksitocin i vazopresin u miometriju i decidui te sinhroniziraju kontrakcije uterusa. Autori ovog rada prikazali su ulogu i utjecaj oksitocina u porodu, te po prvi puta u hrvatskoj literaturi progovorili o selektivnom inhibitoru oksitocina čija svojstva vezivanja za oksitocinski receptor u miometriju i decidui su među prvima u svijetu i sami testirali in vitro.