MOLECULAR PATHWAYS IN THE ENDOCRINOLOGY OF PARTURITION

F.A. Anca*

“Carol Davila” University of Medicine and Pharmacy, Obstetrics and Gynecology Dept., University Emergency Hospital, Bucharest, Romania

Abstract

The entire complex process of labor is the central concern of obstetrics and premature labor poses a threat to the mother and fetus and represents a core medical and social issue. In this respect, understanding the mechanism of uterine contractions at a molecular level helps shed some light on possible future prevention and treatment. New research has emphasized the role of endocannabinoids by two metabolic pathways with final products that act as antagonists: prostaglandins and prostamides (prostaglandin-ethanolamides), but with competition on substrates and enzymes. Thus, the dominant pathway will be selected on account of cellular and tissue environment.

Key words: prostaglandins, prostamide, endocannabinoid, inflammation, contractility, premature labor.

INTRODUCTION

Understanding the mechanism of uterine contractility still represents a challenge of modern obstetrics. Inflammation occupies a central role in the physiology of premature labor. However, more often, inflammation constitutes the decisive factor of the myometrial cell contractility in premature or at term labor. The core factor of this process, as known, is represented by prostaglandins (1). However, there is another category of substances involved: endocannabinoids. To date, we have good knowledge about the existence of a definite network, including eCBs, hormones, prostaglandins, and cytokines that warrant a successful pregnancy in animals and humans (2).

The endocannabinoid system and labor

Endocannabinoids and their receptors are practically found in every tissue, including the ovaries, uterus, amnion epithelium, chorion and placenta; the cellular response to these molecules varies according to local intra and extracellular environment (3). Being a component of the maternal-fetal interface,

endocannabinoids and their receptors play an important role in pregnancy and delivery and there is a large amount of evidence which has demonstrated that endocannabinoid signaling *via* cannabinoid receptors is an important player in various female reproductive events, including sperm-egg fusion as fertilization, preimplantation development of embryos and their timely transport from the oviduct into the uterus, attainment of uterine receptivity, embryo-uterine crosstalk during implantation and decidualization, trophoblast differentiation and placental development, and initiation of parturition (2).

Thus, we consider of being of utmost importance the detailed study of these substances and their implication in preterm labor. Contraction is induced by the presence of prostaglandins, which are synthesized from arachidonic acid (AA). The same substrate, AA, and part of the same enzymatic system are used in the formation of prostamides (prostaglandin-ethanolamides). Prostamides are derivatives of the endocannabinoid system, from anandamide. Thus, prostamides might be considered as important as prostaglandins in the context of myometrial contractility (1).

The synthesis of prostaglandins begins with the release of arachidonic acid from the cellular membrane phospholipids, catalyzed by phospholipase A2 (PLA2), phospholipase C or diacyl and monoacylglycerol lipase. Cyclooxygenase 1 or 2 (COX1, COX2) will convert AA into prostaglandin H2, which will further create other prostaglandins (D2, E2, F2 α , I2) and thromboxane A2 (TXA2). The activity of COX 1 and 2 varies according to cellular environment and tissue specificity. COX1 is the constitutive prostaglandin synthase and COX2 is variable (inducible). COX2 activity is modulated by cellular environment and is specific to each tissue (4). The most studied endocannabinoids are anandamide and 2-arachidonoylglycerol (2AG), which are derived from the membrane phospholipids and are endogen agonists of the cannabinoid receptors CB1 and CB2. As before

*Correspondence to: Alexandru Florin Anca MD PhD, “Carol Davila” University of Medicine and Pharmacy, Dept. of Obstetrics and Gynecology, University Emergency Hospital, Bucharest, Romania, E-mail: alfanca@yahoo.com

mentioned, the synthesis of endocannabinoids uses the same enzymes as in the synthesis of eicosanoids. The substrate to produce anandamide is N-arachidonoyl phosphatidyl ethanolamine, a component of the cellular membrane. The activation of the cell will stimulate the activity of phospholipase D, which will catalyze the detachment of the anandamide. Anandamide will be converted by a specific inducible enzyme, fatty acid amide hydrolase (FAAH) into arachidonic acid and ethanolamide. AA will continue its physiologic pathway with the formation of prostaglandins. On the other hand, in the presence of COX2, anandamide will convert into prostamides, which are known as prostaglandin-ethanolamides and will have opposite cellular response to prostaglandins (1).

The degree of activation of FAAH plays a central role in the metabolic pathway that becomes dominant. In the placenta, studies have demonstrated that FAAH expression is higher in the third trimester. If FAAH is intensely activated, anandamide will convert to arachidonic acid and complete the formation of prostaglandins, the effectors of myometrial contraction. At the other end, if FAAH activity is low, the concentration of anandamide will increase and it will convert to prostaglandin H2 ethanolamide which will synthesize prostamides. Thus, the myometrial contractility will be indirectly suppressed by the non-formation of prostaglandins. Studies have concluded that FAAH regulates anandamide signaling through CB receptors. A high concentration of prostamides is correlated with the activation of COX2 and the accumulation of anandamide. In a low COX2 concentration environment, anandamide will in turn activate the cannabinoid receptors and have different cellular effects depending on their cellular expression and context (adaptor proteins). The inhibition of COX2 will increase the concentration of anandamide which will activate the cannabinoid receptors. In the placenta, there is a high level of CB1 receptors and their interaction with anandamide might lead to the synthesis of prostaglandins or prostamides delivering a proinflammatory (uterine contractions) or anti-inflammatory (uterine quiescence) effect (5). In labor, the level of anandamide increases to greater concentrations, thus its role in the physiology of parturition. 2AG, catalyzed by COX2 will form prostaglandin-glycerol esters, compounds that act as competitors for prostaglandin (4).

In a study performed on mouse uteri (6) it was observed that by inducing contractions after injections with lipopolysaccharides selected from *Escherichia*

Coli serotype 055:B5, showed that FAAH activity in the uteri did not increase significantly, but the expression of CB1 was higher than the expression of CB2. As a conclusion, in this model of induced labor there appears to be an increase of prostaglandins via the endocannabinoid system through the activation of CB1 receptors. Evidence has emerged that the alterations in CB1 receptor expression affect the pregnancy outcome.

In 2016, Xiaofei *et al.* (7) showed that in mice, by administering a long acting anandamide that activated CB1 receptors induced preterm labor by induced senescence of the decidua, but the action of an antagonist on these receptors managed to prolong pregnancy. Exposed to inflammation process through multiple factors, the endocannabinoid-eicosanoid system is altered and the increase in anandamide levels will provoke senescence and induce preterm labor.

For example, in women, the chronic use of marijuana is often associated with fetal abnormalities and early pregnancy termination. Plasma anandamide levels have been shown to be associated with onset of labor. Plasma anandamide levels are significantly increased in laboring term than those in nonlaboring term. A significantly higher expression of CB1 has been observed in placental villous from nonlaboring compared to laboring women. This finding indicates that the higher anandamide level and lower placental CB1 expression are essential for the timely onset of labor (2).

As mentioned before, the cellular response of endocannabinoids is variable and has tissue specificity depending on the cellular milieu; therefore, every ligand will induce a local different response depending on the adaptor proteins present at that moment. 2AG will use the same enzymes used for the synthesis of prostaglandins but with different final metabolites: prostaglandin-glycerol (esters of prostaglandins with glycerol). In this manner, 2AG is a competitor for the prostaglandins. Its role is under current investigation. Management of preterm labor means use of proven interventions such as use of a single course of antenatal corticosteroids to accelerate fetal lung maturation (8) and tocolytic drugs to delay delivery and potentiate the effects of antenatal corticosteroids or allow transfer to a higher-level facility before delivery (9). Prostaglandin inhibitors and calcium-channel blockers have the highest probability of improving neonatal outcomes by delaying delivery and have the lowest maternal side-effects. Prostaglandin inhibitor available treatment is made with anti-inflammatory substances that decrease the prostaglandin concentration in the uterus:

indomethacin. However, the use of indomethacin in the third trimester increases the risk of antenatal closure of the ductus arteriosus. Joshua P Vogel published recently an analysis of the WHO Multicountry Survey on Maternal and Newborn Health to assess coverage for these interventions in preterm deliveries (10). From a total of 303,842 women included in our analysis, 17,705 (6%) gave birth. This analysis shows that despite the wealth of trial evidence about the efficacy and indications for antenatal corticosteroids and tocolytic drugs in preterm birth, remarkably little data are available for clinical patterns of their use. Recently, a study of nanomedicine (11) has proposed the use of nanoparticles with nanoliposomes encapsulating indomethacin that transfer the active substance to the placenta, increasing the concentrations of indomethacin at the placental level and reducing its transfer to the fetus.

In conclusion, recent studies of endocannabinoids have emphasized their importance in pregnancy and the mechanism of premature or at term labor. Eicosanoid and endocannabinoid metabolic pathways are competitors for the same substrates and enzymes but with the synthesis of different effector molecules: prostaglandins and prostamides, respectively. Both anandamide and 2AG are ligands for the cannabinoid receptors CB1 and 2; and by binding to these receptors they will induce a cellular response which depends entirely on the cellular context. Through the inducible enzymes, FAAH and COX2, the activation of these metabolisms differs and the myometrial contractions might appear or not. Clinical practice is the main beneficiary from these studies. Treatment for the prolongation of labor by expression of FAAH and COX2 or the specific activation of CB receptors by anandamide will decrease the rate of premature birth, neonatal morbidity and mortality.

Conflict of interest

The author declares that he has no conflict of interest concerning this article.

References

1. Peiris HN, Vaswani K, Almughlliq F, Koh YQ, Mitchell MD. Review: Eicosanoids in preterm labor and delivery: Potential roles of exosomes in eicosanoid functions. *Placenta* 2017; 54:95-103.
2. Rosaria Meccariello, Natalia Battista, Heather B. Bradshaw, and Haibin Wang, "Updates in Reproduction Coming from the Endocannabinoid System", *International Journal of Endocrinology*, vol. 2014, Article ID 412354, 16 pages, 2014.
3. Battista N, Bari M, Maccarrone M. Endocannabinoids and reproductive events in health and disease. *Endocannabinoids* 2015. Springer; 343-358
4. Vannucini S, Bocchi C, Severi FM, Challis JR, Petraglia F. Endocrinology of human parturition. *Ann Endocrinol (Paris)* 2016; 77(2):105-113.
5. Mitchell MD, Rice GE, Vaswani K, Kvaskoff D, Peiris HN. Differential Regulation of Eicosanoid and Endocannabinoid Production by Inflammatory Mediators in Human Choriodecidua. *PLoS ONE* 2016; 11(2): e0148306.
6. Bariani MV, Dominguez Rubio AP, Cella M, Burdet J, Franchi AM, Aisemberg J: Role of the endocannabinoid system involved in the LPS-induced preterm labor. *Reproduction* 2015; 150:463-472.
7. Xiaofei Sun, Wenbo Deng, Yingju Li, Shuang Tang, Emma Leishman, Heather B. Bradshaw, Sudhansu KD. Sustained endocannabinoid signaling compromises decidual function and promotes inflammation induced preterm birth. *J Biol Chem* 2016; 291: 8231-8240.
8. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2017; 3. Art. No.: CD004454.
9. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *BMJ* 2012; 345: e6226.
10. Vogel JP, Souza JP, Gulmezoglu AM, Mori R, Lumbiganon P, Qureshi Z, Carroli G, Laopaiboon M, Fawole B, Ganchimeg T, Zhang J, Torloni MR, Bohren M, Temmerman M. Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health. *Lancet* 2014; 384(9957):1869-1877.
11. Refuerzo JS, Leonard F, Bulayeva N, Gorenstein D, Chiossi G, Ontiveros A, Longo M, Godin B. Uterus-targeting liposomes for preterm labor management: studies in pregnant mice. *Sci. Rep.* 2016; 6, 34710.