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Review Article

On the Possible Involvement of the Endocannabinoid System in the Regulation of Contractile Activity of the Uterus of Pregnant Women and in the Induction of Childbirth (Literature Review)

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Abstract

Endocannabinoids (EC), i.e., anandamide (N-arachidonoylethanolamide, or AEA) and 2-arachidonoylglycerol (2-AG), were discovered in 1992. They form an endocannabinoid (EC-) system, which includes cannabionide receptors (CB1- and CB2-), vanilloid receptors (TRPV1), receptors activated by peroxisome proliferators (PPARalpha, PPARgamma), as well as enzymes synthesizing EC from arachidonic acid, and enzymes degrading EC. 30 years of research have shown that this amazing system plays an important role in the human and animal body, and is probably related to the processes of male and female reproduction. The review is devoted to such little-studied issues as the participation of the EC system in the processes of conception and gestation, regulation of contractile activity of uterine (CAU) and induction of labor in women. Taking into account the ability of EC to inhibit CAU in pregnant women and participate in the induction of childbirth, the interaction of the EC- system with the beta-adrenoreceptor myometrial inhibitory mechanism (beta-ARIM) and the NO-system, which contribute to pregnancy, is discussed.

Keywords: endocannabinoid system (EC- system); anandamide; pregnancy; contractile activity of the uterus (CAU); induction of labor; beta-adrenoreceptor myometrium-inhibitory mechanism (beta-ARIM); NO-system

Summary

1. General understanding of the endocannabinoid (EC) system

1.1. The composition of the business system.

In our review paper "Lipidergic system" [1], published in the textbook "Neurophysiology. The physiology of the central nervous system, part 2" for the first time in the Russian literature, data on the EC system and its components are presented in sufficient detail, including links to review papers by many authors [2-14], which can be found in the PubMed search engine. Here we only briefly report that the components of this system are endogenous cannabinoids (EC), including anandamide (N-arachidonoyl ethanolamide, or AEA) and 2-arachidonoyl glycerol (2-AG), which are formed from arachidonic acid (while the level of 2-AG is many times higher than the level of AEA). They are representatives of N-acylethanolamines (NAE) and monoacylglycerols (MAG), respectively. Their physiological effects occur due to the activation of two cannabinoid receptors (CB1- and CB2-), which belong to the superfamily of G-protein-associated receptors. At the same time, the protein CRIP1a (cannabinoid receptor interacting protein 1a) plays an important role in the realization of the effects of the CB1 receptor, which promotes the transport of the newly synthesized CB1-receptor to the cell surface [13,15]. Some of the physiological effects of EC are due to the activation of vanilloid receptors (TRPV1), as well as receptors activated by peroxisome proliferators (PPARalpha, PPARgamma) and a number of orphan receptors from the family of receptors associated with G-protein (GPR55, GPR110, GPR119). Phospholipase A2 (PLA), phospholipase C (PLC), diacylglycerollipase alpha and beta (DAGL-alpha, DAGL-beta), N-acyltransferase (NAT), NAPE-specific phospholipase D (NAPE-PLD) participate in the synthesis of EC, and degradation of EC occurs under the influence of monoacylglycerollipase (MAGL), amidhydrolase fatty acids (FAAH), cyclooxygenase (COX-1, COX-2), lipoxygenase (LOX) and cytochrome P450. EC transport is carried out by specific transporters. All these factors are included in the EC system. It also includes congeners, i.e., lipids formed in parallel with EC, including N

palmitoylethanolamide (PEA), oleoylethanolamide (OEA), stearoyl ethanolamide (SEA) and others. The EC system functions both in the central nervous system and on the periphery. The EC system is characterized by the synthesis of EC according to "need", rapid hydrolysis of EC and a high rate of desensitization of CB1 and CB2 receptors.

1.2. Functions of the EC system.

This system, according to the literature [1-14], is involved in the implementation of many body functions. Among them are 1) retrograde modulation (suppression or enhancement) of the release of mediators (GABA, glycine, serotonin, adrenaline, nitric oxide, etc.); 2) modulation of the production of hormones and BAS (prolactin, growth hormone, oxytocin, vasopressin, ACTH, cortisol); 3) regulation of neurogenesis and maturation of the nervous system in the antenatal and postnatal period; 4) neuroprotection and cardioprotection; 5) modulation of the inflammation process; 6) induction of apoptosis, including apoptosis of cancer cells; 7) modulation of free radical production, i.e. manifestation of antioxidant or, conversely, pro-oxidant activity; 8) anti-stress effect; 9) antinociceptive and antiemetic effect; 10) formation of positive emotions with the participation of the brain reward system; 11) modulation of the functioning of the motor systems of the brain, thermoregulation processes, energy formation, eating behavior, sleep and wakefulness; 12) activation of cognitive processes; 13) regulation of reproduction and sexual behavior; 14) involvement in the formation of such types of pathology as anorexia, bulemia, obesity, neurodegenerative diseases, epilepsy, depression, psychosis, as well as the formation of drug addiction. This means that the EC system plays an important role in the human and animal body.

However, despite the fact that the existence of the EC system has been known since 1992 (thanks to the work of Raphael Mechoulam [17], to date there is little information about the participation of the EC system in the processes of regulation of contractile activity of uterine (CAU) and induction of labor activity The purpose of our review is to systematize the available data about the role of EC in these processes.

2. The role of the endocannabinoid (EC) system in the formation of pregnancy.

They believe [2,13,14, 15,18], that the EC system plays a key role in human reproduction. In particular, enzymes involved in the synthesis and degradation of EC normalize the level of anandamide for successful implantation. At the same time, progesterone and estrogens are involved in maintaining low levels of endocannabinoids. Due to an increase in FAAH expression and a decrease in NAPE-PLD expression [14], strict control of the EC system and cytokines is necessary for successful implantation and early pregnancy maintenance; this hormonal-cytokine network is a key element at the mother-fetus interface, and any defect in such a network, for example, excessive EC levels, can lead to fetal loss [2,14,15,18]. It is believed that with the participation of the EC system, the embryo is evaluated for its viability, therefore, with its low viability, the EC system prevents the development of the embryo. This is due to the fact that EC increases the production of nitric oxide (NO), which increases its toxic effect on the embryo. Therefore, EC contribute to the termination of pregnancy in its early stages, especially if a urogenital infection is associated, which increases the risk of septic abortion [14,15,18,19,20, 21]. According to Cella M. et al. [18], anandamide modulates NO levels during pregnancy in two independent ways -either by reducing the activity of NO synthase (due to activation of CB- receptors), or by increasing it (due to activation of TRPV1- receptors).

It is reported [13-15] that EC controls the transport of both the embryo and the implantation process. Thus, it is known that in rats, EC, activating CB1 -receptors, promotes (together with adrenergic effects) relaxation of the smooth muscles of the oviducts and thereby increase the likelihood of embryo transfer to the uterus [15]. It is believed that high concentrations of EC may be one of the causes of ectopic pregnancy in women [15].

It should be noted that CB1- and CB2- receptors, vannilloid TRPV1-receptors and fatty acid amidhydrolase (FAAH) are also expressed in the rat placenta [18], which makes it possible to use the rat placenta to study the role of EC in the maturation and functioning of the placenta.

3. The participation of the endocannabinoid (EC) system in the regulation of contractile activity of uterus (CAU)

3.1. The effects of sex hormones on the components of the EC system.

Anticipating the review of the literature data on the effect of the EC system on CAU and labor induction, let us briefly consider the data on the effect of progesterone and estrogens on the components of the EC system, since it is known that these hormones significantly affect the physiological properties of the human and animal myometrium [25].

It has been shown that sex hormones affect the expression of EC system components in various tissues [26,27,28]. Thus, it was found [26], that the content of EC, including anandamide, in the anterior lobe of the pituitary gland and in the hypothalamus in female rats during all phases of the estrous cycle is higher than in males; at the same time, in females, the maximum content of anandamide in the pituitary gland was observed with the dominance of estrogens, i.e., in the estrus phase. It was shown [27] that in mice, a decrease in the expression and activity of fatty acid amidhydrolase (FAAH) in the uterine epithelium during pregnancy occurs under the influence of progesterone and estrogens. It was found [28] those physiological concentrations of progesterone increase FAAH activity in the lymphocytes of pregnant women, and insufficient stimulation of this activity increases the risk of spontaneous abortion.

In turn, endocannabinoids can affect the production of sex hormones. Thus, it was noted [21] that anandamide, by activating CB1-receptors, inhibits the aromatase activity of endometrial stromal cells and thereby reduces the production of estradiol by these cells, reduces the effectiveness of activation of estradiol receptors and, for this reason, worsens decidualization. It was found that abnormal fluctuations in serum progesterone and estradiol levels occur in mice when CB1- receptors are knocked out [29].

3.2. The historical aspect of the development of the question of the role of the EC system in the regulation of contractile activity of uterine (CAU)

The first review on this issue was published by Melissa Kozakievich and co-authors in 2021 [13]. It argues that the EC system is most likely related to the regulation of CAU and induction of labor, and provides single information about the relaxing effect of EC on contractions of the isolated myometrium of pregnant women. The review examines in detail the role of EC as precursors of prostaglandins and prostamides, which are necessary for the induction of labor activity. At the same time, the authors do not touch on other components of the **CAU** -regulation system, including the role of beta$_2$-adrenoreceptors (AR) in inhibiting of **CAU** during pregnancy and childbirth. Therefore, below (sections 4 and 5) we put forward a number of assumptions regarding the role of the EC system in the processes of regulation of **CAU** and induction of labor, based on the idea of the key role of the so-called beta-adrenoreceptor inhibiting mechanism (beta-ARIM), with the participation of which the optimal **CAU** for fetal gestation is formed [25, 31]. In the review paper by Pařízek A et al. [14] also reported on the ability of anandamide to

suppress oxytocin-induced contractions of the myometrium of women and, in general, inhibit **CAU** and thereby promote fetal gestation. However, the relationship of EC and beta-ARIM is also not discussed in this work [14] and, at the same time, the authors note that the question of the role of EC in the induction of childbirth remains open.

3.3 Brief description of the mechanisms of regulation of CAU in women.

According to our data [25, 30], the isolated myometrium of non-pregnant women has spontaneous contractile activity **(SCA)**. It expresses alpha-adrenoreceptors (AR), the activation of which increases SCA, and in vivo it increases CAU The expression of $beta_2$-AR, the activation of which reduces the SCA of uterine myocytes, is low during in this period. The myometrium of non-pregnant women also contains oxytocin receptors (OR) and M-cholinergic receptors (M-ChR), with the participation of which oxytocin and acetylcholine respectively increase SCA. During pregnancy, the expression of alpha-AR, OR and M-XP decreases in the myometrium, but the expression of beta2-AR increases significantly, when activated (under the influence of noradrenaline of adrenergic terminals or adrenal noradrenaline and adrenalin), spontaneous or induced myometrial CA is inhibited, and in vivo **CAU** is inhibited. Along with nitric oxide (NO), the activation of $beta_2$-AR allows during pregnancy to partially inhibit the SCA of uterine myocytes, thereby forming an optimal for fetal gestation **CAU**. Back in 1987, we proposed calling this important component of the inhibitory mechanism of **CAU** as beta-adrenoreceptor myometrium-inhibitory mechanism (beta-ARIM), believing that its presence is an important factor in pregnancy, and a decrease in its effect on the myometrium is the cause of premature or urgent childbirth [25, 30].

In our opinion, the induction of childbirth is a complex of changes in the mother's body, in which the expression of $beta_2$-AR in the myometrium decreases, i.e., the effectiveness of beta-ARIM decreases, but at the same time the expression of alpha-AR, OR, as well as prostaglandin receptors, histamine, serotonin and other uterostimulants increases. [25, 30].

3.4. Classical ideas about the mechanisms of labor induction.

As is known, the induction of labor activity, according to modern and generally accepted concepts, which are reflected in a number of review papers [13,31,32,33], is based on such processes as: 1) activation of "aseptic" inflammation of the myometrium and fetal membranes, which is induced by prostaglandins PGE_2 and $PGF_{2alpha,}$ which attracts neutrophils and other types of leukocytes to the myometrium; 2) an increase in the content of proinflammatory cytokines in the myometrium; 3) block the expression of nuclear progesterone receptors type B (nPR-B) and increase the expression of nuclear progesterone receptors type A (nPR-A). It is the interaction of progesterone with type B receptors (nPR-B) that increases and supports the expression of $beta_2$-AR in the myometrium and inhibition of the expression of OR, M-XP and other receptors activated by uterostimulants throughout pregnancy in women. In the process of induction of urgent or premature labor in women, despite maintaining a high level of progesterone production by the placenta, this hormone loses its ability to increase the expression of $beta_2$-AR and inhibit the expression of OR and receptors of other uterostimulators, since the expression of progesterone receptors of the nPR-B type stops, and it is replaced by the expression of nuclear nPR-A receptors, when activation of which progesterone retains its ability to repair the myometrium if it is damaged during childbirth.

The key issue regarding the induction of labor in women is to identify the factors that trigger a decrease in the expression of PR-B receptors. One hypothesis suggests that such factors are pro-inflammatory stimuli, of which the leading ones are prostaglandins PGE_2 and $PGF_{2alpha,}$ which induce "aseptic" inflammation of the myometrium [31]. However, recently, including in connection with the development of the concept of the physiological role of the EC0 system, a hypothesis has been proposed about the leading role of endocannabinoids in this process [13]. In particular, it is postulated that on the eve of an urgent delivery, there is a significant increase in the production of anandamide and an increase in its concentration in the blood. Under the influence of the enzyme cyclooxygenase 2 (COX-2), anandamide is converted into prostamide E2, i.e., prostaglandin E2 ethanolamide, which causes apoptosis of decidual uterine cells; this triggers the rest of the cascade of labor induction [13]. Let us consider in more detail the role and contribution of individual components of the EC -system in the regulation of women's **CAU** and the induction of childbirth, which, in essence, is the purpose of our review.

3.5. Anandamide levels in non-pregnant and pregnant women.

In non-pregnant women, the level of anandamide in the follicular phase is higher (1.68 nM) than in the luteal phase (0.87 nM). [34]. This means that in non-pregnant women, the level of anandamide increases with the dominance of estrogens. It was shown [34] that in the first trimester of a normal pregnancy the level of anandamide is low (0.89 nM), i.e., the same as in the luteal phase of the cycle, and in the second and third trimesters its level is even lower (0.44nM and 0.42nM, respectively), but on the eve of childbirth it increases in 3.7 times, i.e., up to 2.5nM. This is explained by an increase in the synthesis of anandamide and its release from endotheliocytes under the influence of estradiol, which increases the activity of phospholipase D, which participates in the synthesis of anandamide, and increases the activity of the anandamide transporter, but inhibits fatty acid amidhydrolase (FAAH) [13,35]. It is believed that a low level of anandamide is required for successful implantation and progression of pregnancy, and a significant prenatal increase in its level indicates that it plays an important role in the induction of urgent labor. [34]. It was shown [36] that during induction of labor at the end of full-term pregnancy, the level of anandamide increases in 1.5 times (from 1.20 nM to 1.82 nM); at the same time, it was found that induced labor proceeds faster the higher the increase in the level of anandamide. These data also indicate the involvement of anandamide in the induction of spontaneous labor [36]. In preterm labor at 24-34 weeks, as shown by a study of 217 pregnant women [37], the level of anandamide increases, as does the level of congeners – oleoylethanolamide (OEA) and palmitoylethanolamide (PEA). According to the authors [37], the concentration of anandamide exceeding 1,095 nM predicts the termination of pregnancy by premature birth and the period at which they will occur, and the concentration of palmitoylethanolamide (PEA) exceeding 17.50 nM predicts only premature birth. Both of these markers are more reliable and accurate than such well-known markers of premature birth as the length of the cervix, determined by ultrasound measurement, and the level of cervicovaginal fibronectin [37].

3.6. Effects of prenatal increase of anandamide levels.

It is believed that prenatal elevation of anandamide levels causes a number of important effects, including 1) increased expression of oxytocin receptors in the placenta [13, 38] and possibly in the myometrium [13, 38, 39, 40]; 2) apoptosis of decidual cells (due to activation of CB1- receptors and ERK kinase), which increases the production of prostaglandin PGE_2 and prostamide PGE_2 by the fetal membranes (due to increased expression of cyclooxygenase -2 (COX-2) in the amnion and chorion; this is a key point in the induction of aseptic inflammation of the myometrium and fetal membranes and in the induction of labor [13,39]; 3) modulation of the expression of the vanilloid receptor type 1 (TRPV1) and receptors activated

by the proliferator peroxisome (PPARalpha and PPARgamma), although the physiological role of this modulation remains unclear [13].

3.7. Classical ideas about the role of prostaglandins in the induction of labor and new ideas about the role of anandamide in this process.

Kozakiewicz M. et al. [13] share the idea that the induction of the labor process is carried out by increasing the level of estrogens and increasing uterine distension under the influence of a growing fetus, as well as due to aseptic inflammation of the myometrium, placenta and fetal membranes (under the influence of proinflammatory cytokines), thereby increasing the expression of cycloxygenase 2 (COX-2), which provides synthesis of PG_{F2alfa} and PGE_2 from arachidonic acid in the amnion and chorion, which contributes to the "maturation" of the cervix, changes in the structure of the membranes and their rupture, and contraction of the myometrium, separation of the placenta and uterine involution. This point of view is reflected in earlier [21, 31] and later [32, 33] works. But in addition, Kozakiewicz M. et al. [13] proposed a new version of the concept of labor induction. According to this variant, the "culprit" of the induction of urgent and premature labor is the prenatal increase in the production of anandamide and its transformation into prostamide E_2, which is a powerful inducer of apoptosis of the decidual membrane. As is known, it is apoptosis of decidual cells, which are formed during pregnancy from fibroblast-like stromal decidual cells, that induces an increase in the synthesis of prostaglandins PGF_{2alpha} and PGE_2 in the amnion and chorion. [13, 21]. According to M. Kozakiewicz et al. [13] anandamide, stimulating phosphorylation of mitogen-activated protein kinase P38, activates the transcription factor NF-kB; this factor increases the expression of COX-2, due to which prostamide E2 (prostaglandin ethanolamide E_2) is formed from anandamide. It causes apoptosis of these cells, which is regarded as a key moment in the induction of labor [13, 21]. Recall that anandamide, under the influence of fatty acid amidhydrolase (FAAH), which, as is known [41], is expressed in human placenta and decidual cells, undergoes hydrolysis to form arachidonic acid, which is a substrate for COX-2 [13]. When anandamide is oxidized under the influence of COX-2, prostaglandin H2-ethanolamide (PGH2-EA) is formed. Prostaglandin-ethanolamides are formed from it. They are called "prostamides" and are similar in function to prostaglandins [42]. In addition to inducing apoptosis of decidual cells due to prostamide E2, anandamide, activating CB1-receptors, increases the expression of COX-2 in aminone and chorion, and thereby increases the production of PGE_2 and $PG_{F2alpha}$ in these structures [21].

The central issue of the discussion about anandamide as a key inducer of childbirth is the question – is prostamide E2 formed from anadamide in decidual cells? The complexity of solving this issue is explained by the fact that it is impossible to distinguish prostaglandins and prostamides using biochemical methods based on the use of antibodies, but this can be done if liquid chromatography-mass spectrometry methods are used, which have been used for these purposes relatively recently [13, 43]. Therefore, it is proposed to review the results of studies that link labor induction with prostaglandins, since, according to the concept of M. Kozakiewicz et al. [13], the key role in the induction of spontaneous (urgent) childbirth in humans is played not by prostaglandins, but by prostamides formed from anandamide. Note that a variant of the concept by M. Kozakiewicz et al. [13] is not shared by all authors [14,15]

3.8. CB1- and CB2- receptors in the myometrium of women and the effect of endocannabinoids on CAU.

Returning again to the question of the effect of **endocannabinoids** on the CA of the myometrium of women, we note that the myometrium of non-pregnant women contains CB1- and CB2 -receptors [44]. The myometriia of pregnant women also express CB1- and CB2- receptors [13, 22, 39,45], due to which EC reduces the SCA of myometrium and, most likely, reduces **CAU.** But in childbirth the expression of CB1- and CB2--receptors decreases ([13, 46], which indirectly indicates a decrease in the inhibitory effect of EC on SCA and **CAU.** Thus, in experiments with isolated myometrium of pregnant women obtained during planned cesarean section, it was shown [45] that anandamide and delta 9 tetrahydrocannabinol (Δ9 THC) in concentrations from 1 nM to 100 microns, activating CB1-receptors, dose-dependently inhibit the myometrial SCA.There is no information in the literature on the effect of endocannabinoids on the myometrium of women in labor and maternity.

3.9. CB1 and CB2 receptors in rat myometrium and the effects of activation of these receptors.

It has been shown that the myometrium of non-pregnant rats contains CB1- and CB2- receptors, the activation of which is accompanied by a decrease in the myometrial SCA, especially in the metestrus phase [47]. This information may be of interest for the development of new tocolytic agents. It should be recalled that earlier rodent myometrium was widely used in the search for tocolytics among $beta_2$-adrenergic receptor agonists [25].

During pregnancy, the expression of CB1- and CB2- receptors in the rat myometrium is preserved, as well as the ability of EC to inhibit the myometrial SCA [48]. Regarding changes in the expression of CB1- and CB2-receptors in the myometrium of rodents on the eve of childbirth, the literature data are ambiguous [13,48, 49,50]. According to some data, there is a prenatal decrease in the expression of CB1 -receptors [49], and according to other data, on the contrary, on the eve of childbirth, the content of CB1-receptors in the myometrium increases and the effectiveness of their activation increases [48-50].

4. Assumptions about the possible effects of the endocannabinoid system during pregnancy

The literature data presented above, due to their small number, do not allow us to give a definitive answer to the question of the participation of the EC-system in the regulation of CAU and in the induction of labor activity. At the same time, there is important information in the literature that allows us to make a number of assumptions about the role of the EC -system in the formation of optimal CAU for bearing a fetus. Below we discuss six such assumptions.

4.1. The EC- system increases the efficiency of beta-ARIM functioning.

As noted above, norepinephrine (NA) as a mediator of the terminals of the sympathetic nerves of the uterus, as well as adrenaline and NA as adrenal hormones inhibit the SCA of uterine myocytes in pregnant women and thereby inhibit CAU [25, 30]. We assume that EC increases the efficiency of beta-ARIM functioning, since anandamide, firstly, by itself, as noted above, is able to suppress the SCA of the myometrium of pregnant women [45]), and secondly, EC during pregnancy can increase the secretion of NA from the adrenergic terminals of the uterus and thereby increase the effectiveness activation of $beta_2$-AR. This is indicated by data on the ability of EC, including anandamide, to increase the secretion of adrenergic endings in the central nervous system [51] or from sympathetic endings of visceral organs [52]. In addition, EC is known to increase the effectiveness of $beta_2$-AR agonists [51,53], including due to the ability of EC to have an antioxidant effect on brain neurons [54]. According to our data [55], ascorbic acid, tryptophan, histidine, tyrosine and other antioxidants restore the activation efficiency of $beta_2$-AR erythrocytes, reduced under the influence of ROS.

4.2. EC during pregnancy increases the production of nitric oxide (NO), which contributes to the inhibition of CAU.

As is known [1, 25, 56], NO inhibits **CAU** in pregnant women and improves uterine blood flow. Literature data indirectly indicate that EC can increase the intensity of NO production in the myometrium and in endotheliocytes of uterine vessels, which, in particular, has been established in relation to uterine arterioles of pregnant women [57] and decidual cells [20, 21].

4.3. EC during pregnancy increases the immunological tolerance of the mother to the fetus, which contributes to pregnancy.

Indeed, it has been noted in the literature that EC reduce the activity of immunocompetent cells, including neutrophils [58] and T- cells [58], which is due to the inhibition of nitric oxide production in these cells [59] and production of ROS [58].

4.4. EC during pregnancy can block the process of inflammation and thereby prevent the induction of premature birth.

Thus, it is known that EC, by activating CB1- and CB2- receptors, as well as GPR 18/GPR55 receptors, reduce the production of proinflammatory cytokines, i.e., they exhibit an anti-inflammatory effect. This is shown in particular in relation to microglia [59,60].

4.5.EC during pregnancy can reduce platelet activity.

For this reason, endocannabinoids can reduce the risk of platelet aggregation and blood clots formation, since according to the literature [61], anandamide is able to reduce platelet activity.

4.6. EC during pregnancy prevents the production of oxytocin by the hypothalamus and thereby prevents premature birth.

This is evidenced by the data of Luce V. et al. [62], according to which EC, activating CB2- receptors and vanilloid TRPV1 receptors, increase the synthesis of nitric oxide in the hypothalamus and thereby inhibit the production of oxytocin.

5. Assumptions about the role of the EC system in the induction of labor and in the regulation of labor activity.

So, it was noted above that on the eve of spontaneous childbirth, the level of anandamide in the blood increases in 3.7 times, which due to an increase of EC production in endotheliocytes under the influence of estradiol and a growing fetus [13,34,35,37]. This increases due to the formation of prostamide PGE_2 causes apoptosis of the decidaular membrane [13, 39], which indicates an inflammatory process in the myometrium, chorion and amnion due to increased production of prostaglandins PGF_{2alpha} and PGE2; this ultimately increases CAU and dilates of the cervix, i.e., creates a condition for the birth of a fetus and placenta [13, 21, 43]. At the same time, anandamide increases the expression of oxytocin receptors (OR) in the myometrium [13, 38, 40]. Note that the ability of anandamide to cause apoptosis of decidual cells has been confirmed by many authors. At the same time, it is shown that apoptosis occurs due to such processes as 1) an increase in NO production [19, 20, 21,]; 2) increased production of ROS [21]; 3) formation of ceramide and its toxic metabolites [19]; 4) cell cycle arrest, decrease in mitochondrial membrane potential, activation of caspases (-9, -3,-7) and induction of endoplasmic reticulum stress [21]; 5) formation of prostamide E_2 from anandamide, which is the strongest apoptic factor [13, 21].

We can supplement the understanding of the role of endocannabinoids in the induction of labor and in the regulation of labor activity by making the following 8 assumptions, which are based on literature data on the physiological effects of endocannabinoids. At the same time, our assumptions are based on the idea that on the eve of childbirth and during labor, the effectiveness of beta-ARIM functioning decreases, and for this, in addition to the prenatal decrease of $beta_2$-AR expression and an increase of alpha-AR expression, other events must occur in which endocannabionoids can play a key role. These possible events are presented below in the form of 8 assumptions.

5.1. Endocannabinoids stop enhancing the release of norepinephrine (NA) from nerve endings.

Thus, ECS reduce the effectiveness of $beta_2$-AR activation, including by increasing the production of ROS.

5.2 Endocannabinoids stop increasing nitric oxide production

In other words, EC reducing an important component of the CAU - inhibition system of pregnant women.

5.3. On the eve of urgent labor and during labor, activation of adrenoreceptors (probably alpha-AR) increases the synthesis of endocannabinoids and expression of CB1 and CB2 receptors.

This assumption is based on data that activation of AR increases the synthesis of EC [63] and the synthesis of CB1- and CB2- receptors [64]

5.4. Endocannabinoids on the eve of urgent labor and during labor increase the release of oxytocin from the neurohypophysis. Indeed.

It is reported in the literature that EC, by activating CB1- receptors, can increase the production of oxytocin in the hypothalamus by increasing the synthesis of nitric oxide by the endothelium of portal vessels [65].

5.5. Endocannabinoids on the eve of urgent labor promote the transition of neutrophils circulating in the blood into the myometrium and fetal membranes, and thereby contributes to the formation of aseptic inflammation of these structures.

Indeed, according to Balenga N. et al. [66], neutrophils, as participants in the induction of childbirth in women, are attracted to the focus of aseptic inflammation, i.e., into the myometrium and into the fetal membranes, due to the presence of chemokines and endocannabinoids (EC) in these foci. By activating orphan receptors GPR55 of neutrophil, EC attract neutrophils to the inflammatory site, and by activating CB2- receptors of neutrophil, EC increase the intensity of their degranulation and increase production of ROS. All this enhances the ability of neutrophils to induce labor, as they contribute to aseptic inflammation of the myometrium and fetal membranes.

5.6. Endocannabinoids increase platelet activity during labor, which reduces the likelihood of blood loss during this period.

Indeed, it has been noted in the literature that anandamide and 2-arachidonoylglycerin, activating CB1- receptors, increase platelet activity by increasing the production of NO and ROS in them [67].

5.7. Endocannabinoids may have an antinociceptive effect during labor.

This assumption is based on data that anandamide, modulating the synthesis of nitric oxide upon activation of CB1- receptors, causes analgesia [68].

5.8. EC during labor prevents fetal brain damage.

Indeed, the literature reports that endocannabinoids, by reducing the production of ROS and proinflammatory cytokines in the brain, reduce the degree of perinatal brain damage, including that occurring during the birth process [69].

6. Conclusion

All the assumptions we have made, of course, require strict evidence and clarification of the type of receptors due to which endocannabinoids realize the above effects, but in general, the literature data indicate the prospects for further study of the role of EC in the regulation of CAU during pregnancy and childbirth, and the participation of endocannabinoids in the induction of labor, as well as the involvement of the EC-system in the formation of a

number of obstetric complications, including preeclampsia [15,24], miscarriage [24] and ectopic pregnancy [15, 24].

In this review, data on the effects of cannabis use could be important for understanding the role of EC since it is known that the main component of cannabis is Δ9-tetrahydrocannabinol, an agonist of CB1 -receptors. But the literature data on this issue are contradictory and there is no information about the positive effect of taking cannabis on the outcome of pregnancy and childbirth [2, 13, 14.].

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Authors declare lack of the conflicts of interests.

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