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Review

Contemporary notions on the role of 5'-nucleotidase in pregnancy

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Abstract: The review aimed at pooling together available information on 5'-nucleotidase – an enzyme hydrolyzing ribo- and deoxyribonucleoside-5'-monophosphates. The most important product of 5'-nucleotidase activity is adenosine. This enzyme is, in fact, involved in most aspects of normal physiology, along with numerous pathological processes. The article discusses the role of the enzyme in pregnancy, its involvement in early post-implantation development, proliferation, migration/invasion, trophoblast differentiation, decidualization, angiogenesis, vasculogenesis, modulation of cell growth during embryonic development, regulation of hemodynamics, and control of myometrial contractions. A large section of this review is dedicated to the contribution of 5'-nucleotidase to the development of gestational complications, such as preeclampsia. We conducted our study via searching through various databases until October 30, 2021, using the following keywords: 5'-nucleotidase, adenosine, pregnancy, and the combinations of those. All reviewed articles were published in English.

Keywords: 5'-nucleotidase, adenosine, pregnancy.

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Introduction

Geoffrey Burnstock developed the concept of purinergic signaling linking cellular metabolism to many other processes, including proliferation, differentiation, and cell death [1]. The purinergic system components include nucleotides and nucleosides, along with receptors, transporters, and associated enzymes [2]. The latter include nucleoside triphosphate diphosphohydrolases and nucleotide pyrophosphatases/phosphodiesterases, 5'-nucleotidase, alkaline phosphatase, adenosine deaminase, and purine nucleoside phosphorylase. These enzymes were described long before intercellular signaling was discovered [3]. Initially, their functional role was not fully understood, and it was often assumed that clinically overt ectonucleotidase activity was the result of cell damage and access of substrates to cytosolic nucleotidase. In domestic medical science, measuring the activity of such enzymes constitutes a method for diagnosing the pathological condition of organs and systems.

The key component of the purinergic system, discussed in this review, is 5'-nucleotidase. Basically, it catalyzes the last stage of extracellular ATP metabolism with the formation of adenosine, a ligand of a large family of purinergic receptors. The enzyme plays an important role in maintaining a balanced pool of nucleotides involved in various cellular processes [4, 5]. Discovered by J.L. Reiss in 1934, 5'-nucleotidase enzyme was originally defined as a lymphocyte differentiation antigen (CD73) just before its DNA was cloned in 1990 [3, 6]. The name *'CD73'* is most commonly used in recent publications (over the last 10-15 years): it coincided with a shift in emphasis on the immune functions. However, 5'-nucleotidase is ubiquitously expressed in the human body and is involved in nearly all aspects of normal physiology and in many disease-related processes [5, 6].

Various functional roles of this enzyme were reviewed in a number of published sources revealing an involvement of CD73 into various processes in the cardiovascular, respiratory and nervous systems, liver and kidney, endothelial transport and barrier functions, leukocyte transport, as well as into adaptation to hypoxia and ischemia, immunity and inflammation, inhibition of nociception, acute pancreatitis, chronic obstructive pulmonary disease, microbial infection, immune control of the tumor process and metastasis, cardiac hypertrophy, arterial calcification, control of coronary vasodilation, neointima formation, arteriogenesis, atherogenesis, cardioprotection, and vasculopathy of the cardiac allograft [7-14].

Role of 5'-nucleotidase in pregnancy

During pregnancy, an activity/expression of 5'-nucleotidase intensifies. Simultaneous detection of the blood plasma level increase of adenosine in pregnant women allowed concluding that it derived from an increase in CD73 activity in the course of gestation period [15-17]. This circumstance allowed a number of studies expressing an opinion that 5'-nucleotidase played an important role in the reproductive system.

The functional importance of this enzyme is virtually always determined by the role of substances, the metabolism and content of which depends on 5'-nucleotidase activity. In this regard, the functional impact of CD73 is directly related to the effects of adenosine. Extracellular ATP and adenosine, the concentrations of

which are controlled by nucleotidases, play an important role in embryogenesis, organogenesis, and postnatal development in vertebrates, including humans [18]. The earliest studies of their importance in reproduction were discussed in terms of their intracellular functioning, as well as their role as an exergy source. However, it is currently accepted that they have a powerful extracellular effect mediated by the activation of specific membrane receptors. For example, ATP is required to initiate and maintain myometrial contractions, as well as to control Cl^- secretion and Na^+ absorption in the endometrium [19]. Besides, it regulates the decidualization of stromal cells, mediates an interaction between the blastocyst and endometrium; stimulates the activity of placental 11β-hydroxysteroid dehydrogenase type 2, which is believed to play a key role in fetal development; and regulates the vascular bed in the human fetoplacental system [20-22].

Extracellular adenosine, formed as a result of CD73 action, coordinates early post-implantation events [15, 19]. Adenosine could be the factor involved in proliferation, migration/invasion, and differentiation of trophoblasts [23]. The exact mechanisms underlying adenosine signaling during pregnancy have not been identified yet. The regulation of the matrix metalloproteinase activity is among the proposed possible options [24].

The level of adenosine substantially increases during cell differentiation into specialized secretory decidual cells [22] and coincides in time with the morphological changes observed during decidualization. The data obtained in the study of the mechanism of decidualization implied that successful and effective process requires a balance and interaction between ATP as a proinflammatory molecule and adenosine as an anti-inflammatory factor [22].

Adenosine, in all likelihood, plays a major role in placenta, as evidenced by various facts. First, the localization of 5'-nucleotidase was found on the outer surface of the plasma membrane microvilli in syncytiotrophoblast [25, 26], which was considered evidence of CD73 involvement in the regulation of microcirculation in human placenta. Second, the placental trophoblast expresses nearly entire spectrum of purinergic receptors [22]. Also, the participation of placenta in regulating the function associated with adenosine was observed in many experiments [20, 27, 28]. Hence, this nucleoside potentially controls metabolic signals via acting on purinergic receptors at the interface between the placenta and the decidua. The study of the transport and metabolism of adenosine in the human placenta demonstrated that it occurred both intra- and extracellularly [27]. Adenosine regulates the transport of nutrients and the tone of the vascular bed in the human fetoplacental complex [29, 30]. Notably, the nucleoside can cause vasodilatation or vasoconstriction, depending on the specific site of action in the placenta [31], as well as oxygen tension [32].

Adenosine may also be important in angiogenesis and vasculogenesis of the placenta and fetus. Numerous studies conducted on various cells established that the nucleoside substantially stimulated the production of proangiogenic factors, such as vascular endothelial growth factor (VEGF), membrane-bound soluble fms-like tyrosine kinase-1 (sFlt-1), interleukin (IL)-6, IL-8 and basic fibroblast growth factor (bFGF) [23, 33-35]. Despite the fact that the role of this nucleoside in the formation of blood vessels in pregnancy was little studied, it may be involved in the control of these processes.

A number of reports mention adenosine as one of the endogenous effectors that could selectively modulate cell growth during embryonic development [36]. Extracellular adenosine plays a signaling role in the control of early morphogenesis after implantation [37, 38]. An importance of adenosine was characterized particularly well in the morphogenetic development of vertebrate limb buds [39] and the nervous system [40]. The role of CD73 in the structural and functional brain remodeling, as well as during synaptogenesis, is quite important [41]. As the terminal member of the enzyme cascade breaking down extracellular ATP, CD73 primary role is thought to be the production of adenosine. However, some data indicate that the functions of CD73 go beyond the activity of the adenosine-producing enzyme. CD73 carries epitopes involved in cell-cell and cell-matrix interactions, binds to extracellular matrix components, and is capable of mediating cell adhesion. Accordingly, the enzyme is of great importance for intercellular adhesion, signaling, and cell migration during the development of the brain, and possibly other organs and systems [7, 26, 41]. It is assumed that adenosine, in addition to its participation in development, participates in the regulation of fetal metabolism [42].

It is also believed that adenosine may play a role in hemodynamic changes in pregnancy, since it is involved in the regulation of a vascular tone. Adenosine can cause vasodilating and vasoconstrictive effects through different mechanisms [29, 31, 35, 43].

Besides, adenosine controls the myometrial contractions. In the course of some experiments, the suppression of contractile activity in uterine muscles was revealed [44], whereas other researchers discovered that adenosine caused an increase in contractions of the uterine smooth muscles [45]. It was suggested that there were two types of adenosine receptors in the myometrium: one mediating excitatory responses and the other mediating inhibitory effects [20].

In late pregnancy, an increase in placental 5'-nucleotidase activity was observed in humans [46]; hence, it was suggested that this could be due to increased estrogen synthesis and facilitation of uterine contractions during labor [20].

Therefore, 5'-nucleotidase and adenosine generated by it play a significant role in pregnancy. However, too much adenosine could be detrimental [47]. For example, in an animal experiment, it was found that mouse embryos with elevated adenosine levels died in the post-implantation period [35, 48].

Increased adenosine levels in pregnancy

High levels of adenosine are conventionally observed in overweight/obese pregnant women [49], which, according to some researchers, may play an important role in general physiological adaptation during pregnancy, including adaptation of the cardiovascular, nervous and immune systems. The concentration of adenosine in plasma is significantly increased in the vomit of pregnant women (hyperemesis gravidarum) [50]. The authors of that study proposed that high nucleoside content protected against the sickness progression via modulating sympathetic neurotransmission. An increase in the concentration of adenosine was also discovered in low weight fetuses [51], which Y. Yoneyama et al. interpreted in terms of the protective response to a low oxygen content and an acidotic shift in the pH of the mother's blood.

Altered levels of adenosine are found in blood plasma of the umbilical cord vein in gestational diabetes mellitus (GDM). M. Subiabre et al. construed elevated concentrations of adenosine in the fetal blood as a reflection of disturbances in the metabolic state of the human placenta in GDM [52]. In GDM, an adenosine-mediated disturbance in the contractile response of smooth muscles in the chorionic arteries and veins was recorded as well, which indicated a complex change in adenosine signaling in the fetoplacental system [53].

An increase in the level of adenosine in the placenta occurs due to the suppression of its metabolism caused by pharmacologically significant ethanol concentrations. Such situation mediates placental disorders and causes a reduction in blood flow, which may lead to insufficient oxygen transport and/or fetal acidosis. The resulting fetal hypoxia is an etiological component of growth retardation that may contribute to the pathogenesis of fetal alcohol syndrome [54].

In our opinion, data on the pathogenetic role of CD73 and adenosine in the development of preeclampsia are important. It has been repeatedly reported [23, 55-58] that adenosine levels in the maternal and/or fetal circulation were significantly elevated in patients with preeclampsia, compared with women experiencing normal pregnancy, and correlated with the severity of the disease.

Curiously, there is the so-called *adenosine paradox* in preeclampsia, in which elevated levels of adenosine do not stimulate angiogenesis, despite the fact that adenosine is a proangiogenic factor. The mechanism underlying this phenomenon is unclear, suggesting that it may be associated with the ability of adenosine to regulate the expression of its receptors [59].

Currently, there are several alternative explanations of the elevated nucleoside levels in this disease. Since adenosine plays a protective role in hypoxia/reperfusion preconditioning, as well as in inflammation, its increased concentration in women with preeclampsia could be interpreted as a protective or compensatory mechanism [23, 30]. This hypothesis has not been confirmed yet, either experimentally or clinically.

There are various hypotheses about how the nucleoside modulates a variety of processes that may contribute to the development of the disease. The mechanisms include adenosine regulation of the release of proangiogenic and antiangiogenic factors, trophoblast invasion, inhibition of placental development, transformation of spiral arteries, cellular stress, and inflammation associated with potential asymptomatic ischemia and hypoxia in the placenta [23, 30, 48].

Several options have been proposed that interpret the increase of adenosine levels in maternal blood by ATP hydrolysis and/or enhanced platelet activation [60]. The release of adenosine from activated platelets is, by most accounts, a factor leading to an increase in baseline plasma adenosine concentrations. This happens due to an increase in the activity of the corresponding enzymes in platelets. Elevated maternal adenosine concentrations in preeclampsia are presumed the result of oxygen deprivation and ischemia [61], microthrombi formation, or increased secretion of catecholamines. The mechanisms leading to augmented maternal plasma 5'-nucleotidase activity are unknown. The roles of hypoxia, IL-1β, tumor necrosis factor α, and norepinephrine production in this phenomenon were discussed in the published sources [23].

Placental 5'-nucleotidase activity in preeclampsia

As mentioned above, preeclampsia is associated not only with an increased concentration of adenosine in the mother, but also in the fetoplacental system. Compelling explanations for the underlying cause of such increase in placental adenosine concentrations were presented by different authors. It was shown that adenosine production in placental tissues was enhanced by 5'-nucleotidase, localized in syncytiotrophoblast. Because syncytiotrophoblast is the largest source of CD73, an increase in the activity of this placental enzyme is, according to the authors of the mentioned study, a key factor in the formation of adenosine in preeclampsia [62]. Joint experiments by Chinese and Japanese scientists revealed that the genetic deletion of CD73 prevented an increase in the level of adenosine in the placenta and reduced the severity of preeclampsia symptoms [63].

Notably, CD73 is stimulated by hypoxia and inflammation [64], suggesting that inflammation and hypoxia-induced CD73 activity leads to adenosine production. An increase in the level of the latter intensifies the signaling pathways, through which adenosine exerts its action.

Investigation of the molecular basis for the prolonged and enhanced placental adenosine signaling that causes preeclampsia is in progress. More recently, hypoxia-inducible factor-1α (HIF-1α) was hypothesized to play a pivotal role in enhancing placental adenosine signaling. T. Iriyama et al. [65, 66] conducted experiments on modeling preeclampsia and found that a high concentration of adenosine underlay an increased level of placental HIF-1α, which, in turn, induced the expression of 5'-nucleotidase, thereby creating a positive feedback loop. The latter promoted the continuous production of HIF-1α. The result was a chronic adverse cycle of adenosine production mediated by 5'-nucleotidase signaling via a specific receptor. It contributed to a persistent increase in the level of the transcription factor HIF-1α and, consequently, the activation of the gene encoding sFlt-1, which caused the development of preeclampsia symptoms.

An idea was proposed to explain the reduction of blood flow in the fetoplacental region during preeclampsia through an adenosine-mediated NO-dependent mechanism [67, 68]. It was suggested that adenosine, acting via NO and VEGF, could alter placental angiogenesis in preeclampsia. According to the authors of the hypothesis, adenosine, through the activation of specific membrane receptors, increased the level of intracellular cAMP and reduced the binding of the nuclear transcription factor NF-κB to the NOS2A promoter, which led to a decrease in the gene transcriptional activity and a decrease in the expression of inducible nitric oxide synthase. This phenomenon may partially explain the reduction in placental blood flow, which is characteristic of preeclampsia.

In our opinion, the research by A. Huang et al. was promising in terms of establishing a possible mechanism of the negative effect of adenosine in preeclampsia. The authors demonstrated that elevated levels of adenosine in the placenta caused not only the characteristic signs of preeclampsia, but also placental DNA hypomethylation, which was associated with changes in gene expression and the disease development [69].

Interesting results are presented in the publication by C. Escudero et al. [59]. In their opinion, a decrease in adenosine-mediated angiogenesis in preeclampsia may be associated with the future development of hypertension in the offspring.

Conclusion

Since the discovery of 5'-nucleotidase over 80 years ago, its contribution to molecular signaling for a wide class of physiological and pathological processes, including pregnancy, has been established. However, much remains to be investigated. In our opinion, the analysis of 5'-nucleotidase role in pregnancy is just beginning. It is necessary to reveal whether the results regarding the participation of CD73 in various biological processes, obtained in other body systems, could be extrapolated to the fetoplacental complex. The answers to many questions remain uncertain. How CD73 regulates proliferation, invasion, trophoblast differentiation, and stromal cell decidualization? Under what conditions adenosine expands? Under what circumstances it narrows the lumen of blood vessels in the placenta and uterus, and also enhances/suppresses contractions of the myometrium? What are the sequence and molecular regulation of the angiogenic adenosine signaling pathway and the functional implications of adenosine signaling in the human fetoplacental system? And, finally, does CD73 have any other role in gestation other than adenosine production?

To date, multiple associations were established between adenosine concentration and the clinical features of preeclampsia and other diseases, accompanying pregnancy. However, further studies on the mechanism of CD73 action in these complications are needed to fully understand how the adenosine paradox arises, and whether an increase in adenosine levels has a compensatory effect, or else, it is a trigger for the disease development.

Conflict of interest

The authors declare no conflicts of interest.

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