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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Placenta: an organ with high energy requirements

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Abstract. Placenta is a unique organ, without which the very phenomenon of human pregnancy is impossible. Semi-allogeneous nature, localization of the placenta, complex and heterogeneous cellular composition determines its complex and multifaceted role in the course of physiological pregnancy, indicates the importance of studying this organ in a number of reproductive pathologies. The purpose of this review was to analyze the literature sources illustrating the importance of energy-dependent processes in placental metabolism and to determine the molecular basis of placental energy conversion. Publications of foreign and Russian authors from PubMed database and scientific electronic library eLIBRARY.ru were used when writing the review. The review highlights the main functions of the placenta: transport and synthetic functions in terms of their place in the structure of energy expenditure of the organ. The systems by which the transport of ions and gases from maternal blood through the placental barrier is performed, are considered. The role of the placenta in the synthesis of steroid hormones and glucocorticoids is detailed. The main bioenergetic systems are also considered: placental glucose metabolism, the functional activity of mitochondria and the creatine kinase system of the placenta. These data allow us to put the placenta on a par with other organs with high energy requirements (brain, transverse striated skeletal muscles, heart, kidneys, liver), which are most susceptible to metabolic disorders. Maintaining a balance between expenditure and synthesis of macroergic compounds in the placenta is critical for an adequate course of physiological pregnancy, and imbalances can lead to such pathologies as fetal retardation syndrome or preeclampsia. Further study of placental energy supply systems seems important for understanding the mechanisms of intrauterine development disorders and developing their pathogenetic treatment.

Key words: placenta, mitochondria, creatine kinase, mitochondrial dysfunction, pacental steroidogenesis

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Introduction

The placenta is a provisory organ which connects the mother and the fetus. It performs transport, secretory and synthetic functions, which require a lot of energy and without which a successful pregnancy is impossible. This peculiarity of the placenta's metabolism unites it with tissues with high energy requirements, which traditionally include the nervous, transverse striated muscle, as well as liver and kidney tissues.

The aim of this review is to summarize the data on the structure of energy expenditure and the main systems of energy generation in the placenta.

Energy-dependent functions of the placenta

Transport function of the placenta

The placenta is a provisory organ that links the mother and the fetus, ensuring the growth and development of the latter.

The placenta reaches functional maturity by the end of the first trimester of pregnancy. At this stage it consists of germinal and maternal parts. The germinal part of the placenta is divided into a villous (facing the myometrium at the implantation site) and a smooth (facing the uterine cavity) chorion. Chorion villi are branched connective tissue outgrowths containing fetal vessels, and covered with a specific type of epithelium — trophoblast. The maternal part of the placenta is represented by a modified endometrium — decidual sheath, which forms septa (septa) and depressions (lacunas). The latter are filled with oxygenated maternal blood, washing the chorionic villi [1].

As the placenta matures, the cells of its epithelium, the cytotrophoblast (CTB), fuse into a continuous syncytium, the syncytiotrophoblast (STB). As a result, throughout most of pregnancy, the fetomaternal barrier is formed by:

a) The apical surface of the STB in contact with maternal blood lacunae,

b) The cytoplasm and basolateral surface of the STB surrounding the fetal capillary tree branches.

Molecules that move in and out of the mother-fetus direction cross the STB and the fetal capillary endothelium. The latter limits the diffusion of large molecules, but is permeable to low molecular weight compounds [2].

Transport through the placenta occurs by the following mechanisms [3]:

(1) passive diffusion;

(2) para/transcellular transport;

(3) protein-mediated transport;

(4) endo/exocytosis.

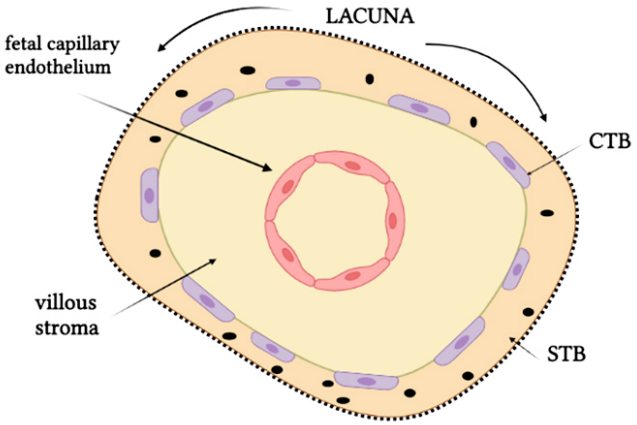

Fig. 1. Schematic image of cross section of a single chorionic villus. STB — syncytiotrophoblast, CTB — cytotrophoblast. The cellular composition of villous stroma is not drawn for simplicity purposes. Endothelial and trophoblast cells are not shown to scale

By passive diffusion, small hydrophobic molecules (such as respiratory gases) are transported. They are well soluble in the cytoplasmic membrane, and therefore their diffusion occurs over the entire surface of the fetal part of the placenta. The intensity of transport of such molecules depends on the rate of their delivery and their distance from the exchange surface (i.e. on the parameters of the fetoplacental and uteroplacental blood flow) [3].

The transplacental transfer of hydrophilic molecules through the STB and the fetal capillary endothelium occurs via the transcellular and paracellular pathways. Local deposits of fibrinoid fibrin type that fill microdamages of STB and serve as a matrix for its reepithelialization by CTC cells are considered as a possible morphological basis for paracellular transport [3].

ABC and SLC proteins located on the surface of the fetal NTBs and fetal vascular endothelium perform active (ATP-dependent) transport in the placenta, as well as facilitated diffusion of xenobiotics and substrates of synthetic reactions. This group includes transporters of glucose, fatty acids, and amino acids [2]. The expression of placental transporter proteins varies depending on the gestational age [4].

In addition, there is evidence that large molecules such as immunoglobulins can move through the STB and the fetal vascular endothelium by endocytosis, but this transport mechanism in the placenta is the least studied [3].

Sodium-coupled transfort systems, such as amino acid transporters, taurine and Na+/H+-pump, are high on the apical surface. In addition, some Na+ returns to the maternal bloodstream through sodium channels and through paracellular transport. This relationship between Na+ entry and exit from the placenta promotes the transport of sodium ions toward the fetus while creating a gradient for substrate transport on the maternal side [5].

The transport of calcium ions through the placenta ensures the maintenance of a higher concentration of Ca2+ in fetal blood compared with maternal plasma and consists of two components: bilateral paracellular diffusion and active transcellular transport through the fetal surface of the STB [6]. In this context, it is interesting to note that in placental tissue in preeclampsia, pronounced abnormalities of calcium homeostasis are found [7].

The transport capacity of the placenta is limited by its surface area. At the same time, the limitation of fetal growth under the influence of a number of pathological factors leads to an increase in placental efficiency (estimated as the ratio of fetal weight to placental weight). Consequently, we can talk about the ability of placental transport systems to adapt to suboptimal conditions of intrauterine development [8].

Synthetic and secretory function of the placenta

In the structure of placental energy expenditure, synthetic processes that ensure its endo- and paracrine function occupy a significant place. Placenta is a source of a wide range of biologically active substances of different chemical nature. They cause changes in the maternal body, characteristic of pregnancy, control fetal morphogenesis and development of the placenta itself.

Among the products of the placenta are found [9]:

– steroid hormones;

– peptide hormones and hormone-like substances: placental lactogen, placental growth hormone, kisspeptin, adipokines (leptin, adipkinin, resistin), growth factors;

– glycoprotein hormones: chorionic gonadotropin, inhibin A and activin A;

– tachykinins, C-reactive protein [10].

Endoplasmic reticulum stress in trophoblast cells, caused by chemical exposure or chronic hypoxia, leads to impaired protein synthesis, slowed proliferative processes in the placenta itself, inhibited its transport and endocrine function and, as a consequence, the development of intrauterine fetal delay [11].

Placental steroidogenesis

Progesterone synthesis

The process of steroid hormone synthesis is multistep, and its individual steps are localized in different compartments of the cell, including the Golgi complex and mitochondria [12]. The first stages of the synthesis of a number of steroid hormones are carried out on the inner membrane of the mitochondria of the placenta.

The steroid hormone synthesis system in STB is an electron-transport chain that carries out electron transfer from NADPH to cytochrome P450scc via the protein adrenodoxin through the enzyme adrenodoxin reductase. The aforementioned proteins are localized on the inner mitochondrial membrane as part of specialized contact sites where they synthesize pregnenolone, a precursor hormone of other steroids, from cholesterol. Further conversion of pregnenolone to progesterone is catalyzed by another enzyme located on the inner mitochondrial membrane, 3β-hydroxysteroid dehydrogenase type 1 [13]. In addition, the steroidogenic electron-transport chain depends on the products of Krebs cycle reactions (such as malate and α-ketoglutarate), which are used to produce reduced equivalents of NADPH.

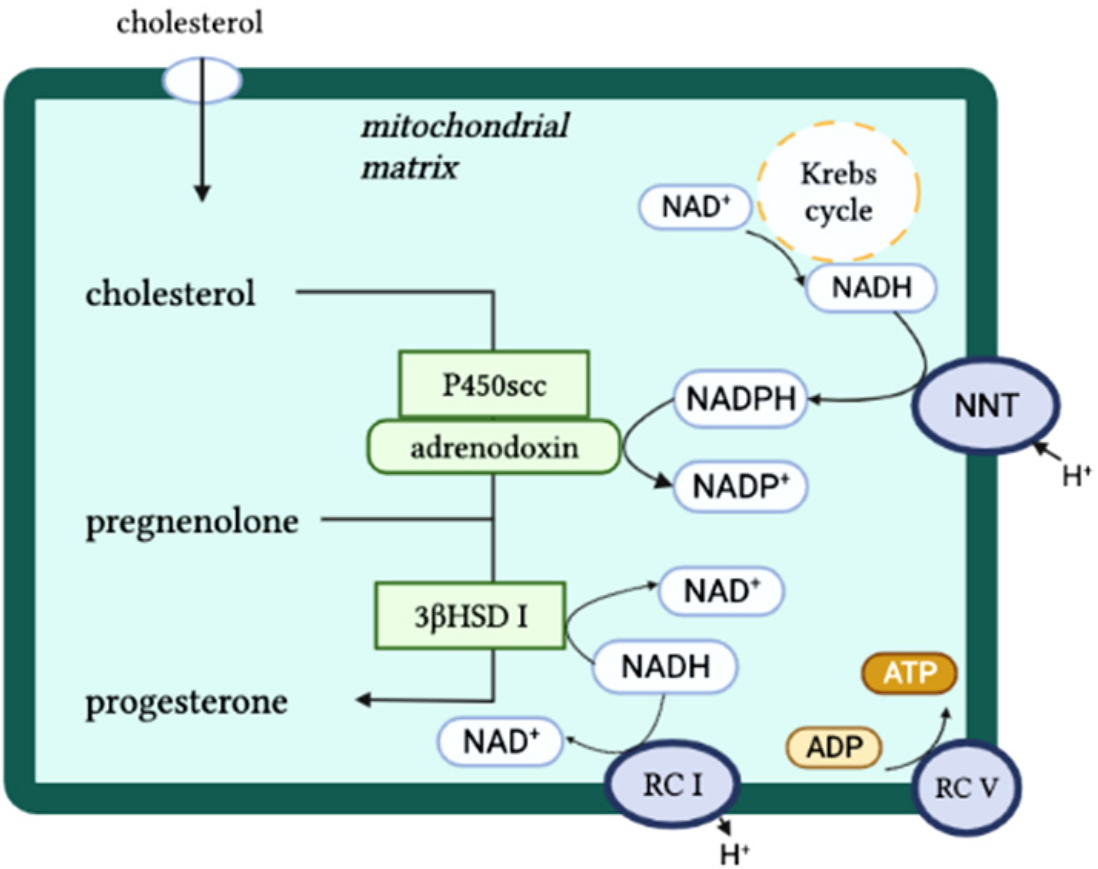

Fig. 2. Steroidogenesis within mitochondrial matrix. P450scc - cholesterol side-chain cleavage enzyme cytochrome P450; 3βHSD I — 3β-hydroxysteroid dehydrogenase type 1; NNT — nicotinamide nucleotide transhydrogenase; RC I — respiratory chain complex I (NADH-CoQ oxidoreductase); RC V — respiratory chain complex V (ATP synthase)

On the other hand, since the conversion reaction of NADH to NADPH is energy-dependent, it requires the mitochondrial respiratory chain to be functionally active as well [14].

According to the literature, trophoblast differentiation is accompanied by a significant change in mitochondrial morphology, namely, the transformation of large round mitochondria with lamellar cristae into small mitochondria with a dense matrix and tubular-vesicular cristae of STB mitochondria. Simultaneously with the growth of the area/volume ratio of mitochondria, increases the efficiency of cholesterol transport to the inner mitochondrial membrane to cytochrome P450scc localized there increases; this process is a rate-limiting step of placental steroidogenesis [13]. It has been shown that CTB contains only 20 % of the total amount of P450scc found in the human placenta homogenate: presumably, cytochrome P450scc expression is activated during CTB syncytization [13].

The placenta, unlike the adrenal glands, is not able to synthesize de novo cholesterol in sufficient amounts. It is assumed that STB can use a small amount of synthesized cholesterol to maintain the morphology of its own cytoplasmic membranes. Also, STB mitochondria contain the enzyme ATP-diphosphohydrolase, which supplies cholesterol transport with energy: the ADP formed during the hydrolytic reaction is used to synthesize ATP in the respiratory chain. To prevent energy dissipation, the activity of ATP-diphosphorylase and the V respiratory complex of the mitochondrial chain are closely coordinated [13].

The placenta receives cholesterol for progesterone synthesis from maternal low-density lipoproteins, which enter the STB by endocytosis [13]. Nonmetabolized maternal cholesterol enters the fetal bloodstream through the fetal vascular endothelium, on which the corresponding ATP-dependent transfer proteins ABCA1 and ABCG1 are expressed [15].

The placenta is a source and target of estrogens

The placenta is a source of estrogens: estrone (E 1), estradiol (E 2) and estriol (E 3). At the same time, the placenta tissue does not contain steroid-17-hydroxylase (CYP17) and therefore cannot convert progesterone to androgens — dehydroepiandrosterone, dehydroepiandrosterone-sulfate — necessary for de novo estrogen synthesis; these substrates come from the fetal adrenal glands. The absence of CYP17 makes the formation of progesterone and estrogens in the placenta possible without progesterone being consumed for androgen synthesis [16].

It is important to consider that throughout pregnancy, the placenta serves not only as a source, but also as a target for estrogens. Thus, all cell types present in the placenta, as well as amniocytes, contain some or other estrogen receptors (ERα, ERβ, GPER-1). During syncytization of the trophoblast, its receptor profile also changes. In accordance with this, estrogens induce different responses in the trophoblast at different stages of differentiation and can also directly affect it [17]. In addition, the membrane receptor to estrogen associated G-protein (GPER-1) is involved in trophoblast invasion and its content in the placenta is significantly reduced in fetal growth retardation syndrome [18].

In the context of this review, it is important to note that in studies on isolated mitochondria E 2 and progesterone act as stimulators of oxidative phosphorylation, while increasing the coupling of oxidation and phosphorylation in the respiratory chain and reducing free radical synthesis [19]. Under conditions of ischemic and toxic damage in vitro, pretreatment of cells with E 2 has a protective effect with respect to ATP synthesis, oxidative phosphorylation processes and maintenance of mitochondrial membrane potential [20]. E 2 increases the level of nuclear transcription factor TFAM, which is necessary for mitochondrial DNA replication (mtDNA), and increases the expression of respiratory complexes subunits encoded by the nucleus [21]. ERα and ERβ are present in mitochondria, and the E 2 receptor complex has been shown to translocate into the mitochondrial matrix [22]. Moreover, the mtDNA contains an E 2-sensitive sequence, apparently allowing estrogen to have a direct effect on mitochondrial genome function [22]. Mitochondrial estrogen receptors are of great interest, but their role in the placenta is currently poorly understood.

Glucocorticoid synthesis

The placenta expresses 11β-hydroxysteroid dehydrogenases type 1 and 2 (11β-HSD 1, 11β-HSD 2), which catalyze the forward and reverse conversion reactions between cortisone and cortisol, respectively. 11β-HSD 2 is localized in the STB and, through inactivation of maternal cortisol, represents the main barrier to its entry into the fetal bloodstream. In addition, the ATP-dependent pump ABCB 1, located on the apical surface of the STB, removes the unmetabolized cortisol fraction. As a result of 11β-HSD 2 and ABCB 1 activity, maternal cortisol, which can inhibit fetal growth, is reduced in fetal tissues and the placenta. Interestingly, low 11β-HSD 2 activity in placental tissue is associated with such pathological conditions as preeclampsia, intrauterine developmental delay, and preterm delivery [23].

Thus, the processes of placental biosynthesis, among which hormone production occupies a special place, require maintaining the energy supply of this organ at a high level.

Placental energy sources

Placental glucose metabolism

Glucose metabolism in the fetoplacental region has been studied in detail in animals [24]; however, the results of these studies cannot be unequivocally extrapolated to humans because of significant morphological and physiological differences between placentas of different biological species. It is known that the human placenta at the early stages of its formation is characterized by high activity of pyruvate kinase, one of the key enzymes of glycolysis, which decreases with the gestational age [25].

Experiments on cells demonstrate that the CTB is characterized by a combination of glycolytic and oxidative mechanisms of energy production, while aerobic metabolism predominates after symplast formation [26]. On the other hand, under conditions of experimental hypoxia in STB, a decrease in O2 concentration to at least 3 % is accompanied by compensatory activation of anaerobic glycolysis, which allows maintaining protein biosynthesis at an optimal level [27]. At the same time, there are indications in the literature of inhibition of placental glycolysis in fetal growth retardation syndrome (in particular, reduced activity of the rate-limiting enzyme phosphofructokinase) [27].

During pregnancy, the placenta contains enzymes required for gluconeogenesis and high levels of pentose phosphate shunt enzymes; the latter is a source of NADPH, which is used, among other things, during the synthesis of steroid hormones [25].

Placental mitochondria

According to the literature, there are two subpopulations of mitochondria: a heavy one (presumably, from the CTB cells) and a light one (located in the STB) [28]. The latter is characterized by its smaller size, irregular shape, atypical cristal morphology, low oxygen metabolism and specialization to steroidogenesis (high cytochrome P450sc activity) [28]. At the same time, during pregnancy, STB as the final stage of trophoblast differentiation begins to surpass CTB in volume, which should be taken into account when trying to assess the differential contribution of the mentioned mitochondrial fractions to the overall metabolic activity of the placenta [29]. Nevertheless, recent studies show that the intensity of glycolysis and oxidative phosphorylation in CTB cells isolated from late gestational placenta is higher than that of STB. The intensity of mitochondrial respiration in other types of placental cells (stroma, endotheliocytes) is significantly lower than in trophoblast [30].

There is also an increased content of *β*-oxidation enzymes of long-chain fatty acids in STB mitochondria; the latter are used by the placenta as an energy source for many transport and synthetic processes [31]. It is worth noting that the activity of placental enzymes of *β*-oxidation of fatty acids is higher compared with those in the liver [32]. Oxidative stress induced by H2O2 exposure to placental tissue leads to a dose-dependent decrease in the intensity of *β*-oxidation, without changing the expression of its key enzymes [33]. Similarly, *β*-oxidation is reduced in the placentas of women with PE [34].

It is interesting to note that the mitochondria in smooth chorion STB cells which are not a part of

the fetomaternal border, are morphologically similar to those in villous chorion STB. The presence of a well-developed endoplasmic reticulum and some enzymes characteristic of STBs (alkaline phosphatase, NADPH-diaphorase, NADPH-oxidase Ca2+-ATPase) was also shown for these cells. This allows us to speak about smooth chorionic NTBs as metabolically active cells similar to the vortex symplast. Thus, smooth chorion CTB cells degrade uterotonins — endothelin and prostaglandins — of amniotic fluid, as well as perform synthesis of extracellular matrix [35].

In STB mitochondria, in comparison with CTB, the membrane potential is reduced, as well as the conjugation of oxidative phosphorylation and ATP synthesis; the latter can lead to superoxidanion-radial production [36]. In addition, P450scc contributes to the generation of reactive oxygen species in mitochondria [37]. On the other hand, CTB of the first trimester of pregnancy is characterized by high antioxidant protection in due to the expression of superoxide dismutases and catalase, whereas in STB these enzymes start to be detected only after 16 weeks of pregnancy [38]. Thus, we can conclude that in the first trimester of pregnancy, STB is more vulnerable to oxidative damage than CTB, especially under hypoxic conditions. This fact may be significant for understanding how some placental abnormalities are formed.

Syncytization of the cytotrophoblast requires a fully functional respiratory chain: inhibitors of oxidative phosphorylation complexes in non-lethal doses disrupt human CTB differentiation [28]. Mitochondrial biogenesis also increases during differentiation; eventually, the mature placenta STB contains a large number of small mitochondria. The role of mitochondria in trophoblast differentiation is demonstrated by the studies, according to which impaired mitochondrial respiration prevented syncytization of the STB as well as synthesis of placental hormones [28].

Fluctuations in pO2 throughout pregnancy affect placental mitochondria. Before the 10th week of gestation, pO2 in the placenta is low and is approximately 2.5 %, as the lumen of the spiral uterine arteries is blocked by extravasal trophoblast cells. This period is characterized by a reduced content of mitochondria in the placenta and a high intensity of glycolytic processes compared with later gestational periods when, as a result of the establishment of uteroplacental blood flow, pO2 increases at least 3-fold and is ≈8.5 % [39].

During the formation of a complete uterine-placental circulation, there is also an increase in mitochondrial biogenesis, an increase in oxidative stress and the activity of placental antioxidant systems [39]. Experiments on permeabilized first- and third-trimester placentas demonstrate an increase in the number of placental mitochondria, an increase in their respiratory capacity and cytochrome oxidase activity (IV respiratory complex) by the end of pregnancy [39].

During labor, uterine contractions lead to a sharp restriction of uterine-placental blood flow and placental damage by the mechanism of ischemia/reperfusion. This can probably explain the higher respiratory activity of placental mitochondria during vaginal delivery compared to cesarean section [39].

It is now established that mitochondrial dysfunction occupies an important place in the development of pregnancy complications, such as PE and fetal growth retardation syndrome (more details in reviews: [40, 41]).

Creatine kinase system of the placenta

Creatine kinases (CKs) are a family of enzymes which catalyze the reversible transfer of a phosphate residue from ATP to creatine to form phosphocreatine and ADP. There are cytosolic and mitochondrial isoforms of creatine kinases. On the one hand, mitochondrial creatine kinase (mtCK) is functionally linked to the respiratory chain proteins; on the other hand, both isoforms form a unified system of transport and deposition of macroergic compounds inside the cell.

Two isoforms of creatine kinases, cytosolic creatine kinase B (CKB) and the mitochondrial ubiquitious form, were found in the human placenta, the former being quantitatively predominant in preterm pregnancy [42].

By the third trimester of pregnancy, the CK content in placental tissue increases significantly [43]. To explain the mechanism of this phenomenon, it is important to take into account the presence of E 2-dependent

sequences in the CK genes. It has been shown that the increase in estrogen levels during pregnancy is consistent with the dynamics of mtCK expression, and the addition of E 2 to endometrial cell culture causes a rapid increase in mRNA mtCK content in them [43]. Estrogen receptors are present in the trophoblast cells, as well as in the endometrium [44]. In the uterus, E 2-mediated CKB expression is mediated by ERα [45]; we cannot exclude the existence of a similar mechanism for creatine kinases in the placenta. In addition, the CK genes contain a regulatory sequence for glucocorticoids [46].

It is also known that the hormone parathyroidin and vitamin D (regulators of calcium metabolism) increase CKB activity in placental tissue explants, presumably in a receptor-mediated way [47]. In this regard, it is interesting to note that preeclampsia is characterized by decreased levels of parathyroidin and vitamin D in the blood [7]. Unfortunately, no data are currently available on the possible effect of these molecules on mtCK function and/or expression.

The human placenta in late gestation is capable both of synthesizing creatine de novo and importing it with the help of the SLC 6A8 carrier from maternal blood [48]. Creatine supplementation increases total creatine content not only in most organs, both maternal and fetal, contributing to the protection of the fetal brain from hypoxia during labor [49].

Creatine is synthesized from the amino acids arginine, glycine, and methionine in two sequential enzymatic reactions involving, respectively, arginine: glycine amidine transferase (AGAT) and guanidine acetate methyltransferase (GAMT) [48]. In the placenta, GAMT and SLC 6A8 are localized in the STB, and AGAT is found in the stroma of villi and the endothelium of fetal capillaries [50]. It has been shown that the expression level of SLC 6A8 and AGAT is inversely proportional to the weight of the newborn and the weight of the placenta [50]. It is also interesting to note that the gene encoding AGAT is imprinted and is expressed in extraembryonic tissues (placenta and yolk sac) only from the allele inherited from the mother, which suggests epigenetic mechanisms of this enzyme regulation [51].

The functioning of the placental creatine kinase system in normal and abnormal pregnancies has been insufficiently studied and requires more research attention.

Conclusion

The information presented in this review demonstrates the role of energy-dependent processes in the placenta's function in ensuring the vital functions of the fetus and maintaining pregnancy. The interest in placental energy metabolism is dictated by the fact that the success of pregnancy directly depends on the adequacy of placental energy supply systems. A detailed study of the functioning of these systems will open up opportunities for creating new approaches to the treatment of pregnancy complications.

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Плацента: орган с высокими энергетическими потребностями

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Аннотация. Плацента — это уникальный орган, без которого невозможен сам феномен беременности человека. Полуаллогенная природа, локализация плаценты, сложный и гетерогенный клеточный состав определяют ее сложную и многогранную роль в протекании физиологической беременности, указывают на важность изучения этого органа при ряде репродуктивных патологий. В рамках данного обзора перед нами стояла цель — провести анализ литературных источников, иллюстрирующих значение энергозависимых процессов в метаболизме плаценты, определить молекулярные основы плацентарной конвертации энергии. При написании обзора были использованы публикации зарубежных и отечественных авторов из базы данных PubMed и научной электронной библиотеки eLIBRARY.ru. В обзоре освещены основные функции плаценты: транспортная и синтетическая функции с точки зрения их места в структуре энергетических

затрат органа. Рассмотрены системы, с помощью которых происходит транспорт ионов и газов из крови матери через плацентарный барьер. Детализирована роль плаценты в синтезе стероидных гормонов и глюкокортикоидов. Также рассматриваются основные биоэнергетические системы: плацентарный метаболизм глюкозы, функциональная активность митохондрий и креатинкиназная система плаценты. Приведенные данные позволяют поставить плаценту в один ряд с другими органами с высоким уровнем энергетических потребностей (головной мозг, поперечнополосатая скелетная мускулатура, сердце, почки, печень), которые наиболее подвержены метаболическим нарушениям. Поддержание баланса между расходом и синтезом макроэргических соединений в плаценте является критическим для адекватного протекания физиологической беременности, а нарушения баланса может привести к таким патологиям, как синдром задержки развития плода или преэклампсия. Дальнейшее изучение плацентарных систем энергообеспечения представляется важным для понимания механизмов нарушений внутриутробного развития и разработки их патогенетического лечения.

Ключевые слова*:* плацента, митохондрии, креатинкиназа, митохондриальная дисфункция, плацентарный стероидогенез

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