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Review Article

Influence of Exogenous and Endogenous Factors During Pregnancy on The Fetal Brain

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Abstract

Unfavorable effects of stress, infections, bad habits, and some medications can lead to disruption of the nervous system in the child later in life. Some maternal hormones (e.g., glucocorticoids) and immune system cells that can penetrate the placental membrane can also damage the fetal brain. The basic stage of human brain development begins before birth, and largely determines a person's ability to learn and develop throughout life. Areas associated with higher cognitive functions play an important role in human mental health. The effects of damaging factors (including drugs) during the active growth and development of the fetal brain are not fully understood because of ethical issues and difficulties in detecting pathological abnormalities at the cellular and molecular levels. The impact of cytokines on fetal brain development is the most studied. The cytokine response of pregnant women to infection has a direct damaging effect on fetal brain development at all stages of pregnancy. Proceeding from the fact that ischemic lesions occur more often in people suffering from atherosclerosis and hypertension, it is important to study the influence of endothelial dysfunction on the nature of brain damage during cerebral ischemia, as well as to develop corrective measures. For this purpose, it is important to assess the character of morphofunctional changes, which will be further used as a comparison group when studying these changes under the influence of endothelial dysfunction.

Keywords: pregnancy; fetal brain

Introduction

Unfavorable effects of stress, infections, bad habits, and some medications can lead to disruption of the nervous system in the child later in life. Some maternal hormones (e.g., glucocorticoids) and immune system cells that can penetrate the placental membrane can also damage the fetal brain. The basic stage of human brain development begins before birth, and largely determines a person's ability to learn and develop throughout life. Areas associated with higher cognitive functions (e.g., prefrontal cortex, subcortical nuclei, especially the amygdala) play an important role in human mental health. The effects of damaging factors (including drugs) during the active growth and development of the fetal brain are not fully understood because of ethical issues and difficulties in detecting pathological abnormalities at the cellular and molecular levels. The impact of cytokines on fetal brain development is the most studied. The cytokine response of pregnant women to infection has a direct damaging effect on fetal brain development at all stages of pregnancy [1]. Human studies have mainly focused on the role of maternal interleukin-6 (IL-6) levels as a marker of prenatal inflammatory processes. For example, a study by M. Rudolph et al. [2] showed that high levels of maternal IL-6 in the third trimester of pregnancy significantly reduce working memory capacity in children. There is evidence for an increased risk of schizophrenia and autism spectrum disorders in children as a result of maternal bacterial and viral infections in pregnancy [3,4]. Key observations suggest that elevated maternal cytokine levels affect the development of brain morphology and functional connectivity, resulting in delayed sensory and cognitive development after birth [2]. Numerous studies have examined the effects of maternal stressors on fetal brain development. Exposure to high maternal glucocorticoid concentrations has long-term, often sex-dependent effects on brain structure and function. High levels of cortisol in pregnant women have been associated with reduced prefrontal cortex, hippocampal volume, altered amygdala volume, impaired development of neural connections, more frequent development of affective symptoms, and internalizing problems in girls [5]. Exposure to stress in early pregnancy also stimulates the activity of microglial cells, which are macrophages endemic to the central nervous system. Due to their phagocytic phenotype, microglia play an important role in the formation, remodeling and contraction of brain synapses [6]. Indeed, prenatal administration of corticosterone increased the density of microglia in the fetal brain and maintained their phagocytic activity [7].

A neonatal study showed that stress increased the total number of glial cells in the hippocampus, mainly in girls [8]. Increased activity and number of microglial cells negatively affects neurogenesis. Interesting data were published by E.Davisetal. [9]. It was shown that moderately elevated levels of maternal cortisol in late pregnancy increase the thickness of the cerebral cortex (especially in the frontal lobes) and improve the cognitive functions of the child. These results suggest that prenatal stress (glucocorticoid release) causes sex- and region-specific changes in neurogenic processes that are also dependent on gestational age. In addition to data on the effects of maternal damaging factors on neurogenesis, synaptogenesis, and axon growth, studies have been published on the effects on fundamental processes of fetal brain development, particularly on neurotransmitter levels and bioavailability. The main excitatory substance in the central nervous system is glutamate, which acts through different types of receptors (mGluR). For example, prenatal stress has been shown to decrease mGluR receptor expression in the hippocampus and increase in the amygdala body of the brain, which is a predictor of anxiety disorders in adulthood [9]. The cholinergic system plays an important role in the regulation of brain functions (including learning and short-term memory processes), and its development is strongly influenced by unfavorable maternal factors during pregnancy. In particular, the increased acetylcholine content in the hippocampus of rats undergoing prenatal stress, detected by some authors, is directly related to hormonal disorders and behavioral abnormalities in adulthood [10]. Studies in recent decades have shown that the GABAergic system not only affects virtually all stages of neurogenesis, such as proliferation of neural precursors, migration and differentiation of neurons, but also plays an important role in the development of the central nervous system. The following is an overview of the results of the study. Cells of the developing nervous system respond to GABA from the earliest stages of fetal neurogenesis, even before the onset of synaptogenesis; although quite early expression of GABA receptors and corresponding GABAergic responses have been detected, initially nonsynaptic transmission of endogenous GABA still dominates [11]. Various in vitro and in vivo studies have also reported that GABA acts as a chemoattractant and is an important determinant of neuronal migration [12]. Intrauterine exposure to ethanol, which is thought to activate GABA receptors [13], also results in decreased proliferation and migration of cortical neurons. Ethanol consumption during pregnancy, especially at the beginning of synaptogenesis in the fetal cerebral cortex, has been shown to dramatically reduce the activity and migration rate of neurons, causing apoptotic neurodegeneration, leading to significant structural brain abnormalities and various long-term behavioral, cognitive, and neuropsychiatric disorders [13]. In addition to affecting developing neurons, ethanol causes apoptosis of glial cells and suppression of astrocyte differentiation and migration, which also underlies the neurotoxicity of ethanol [14]. The development of spontaneous neuronal activity and its influence on various neurogenic events is also supported by clinical studies demonstrating that changes in immature neuronal activity can lead to various diseases of the nervous system. Most anesthetic agents are known to act as glutamate receptor antagonists (N-methyld-aspartate receptors), GABA mimetics, or high-density gap junction blockers in the brain and inhibit neuronal activity. In some animal studies, these drugs have been shown to cause severe neurodegeneration in the immature brain [15]. The anticonvulsant drugs vigabatrin, valproate, and lamotrigine have been shown to cause severe cortical malformations when exposed to the fetus, probably due to inhibition of neuronal migration and differentiation [16]. These studies and our understanding of the influence of early neuronal activity on the development of structure and function require a very cautious approach to the use of pharmacologic agents that affect these processes early in human development and throughout gestation. Prenatal hypoxic and ischemic conditions and intrauterine infection also affect fetal cortical development. Various studies have shown that in the immature brain, hypoxia and inflammatory processes cause long-term changes in spontaneous neuronal activity, impair neuronal survival, and promote acute and chronic neuronal dysfunction [17]. More recently, the term "neuroplacentology" has appeared in foreign publications, postulating possible placental programming of neuropsychiatric disorders and emphasizing the role of the placenta in the formation of the fetal brain [17, 19]. Several studies have shown an association between placental dysfunction and fetal brain disorders, not only due to impaired gas exchange and trophics, inflammatory cytokine secretion and damage to the placental barrier, but, more importantly, due to impairment or loss of placental neuroendocrine regulatory function. Understanding how specific placental factors affect fetal brain development and increase the risk of later psychiatric and neurological disorders will allow the development of new treatment strategies to maintain physiologic development and protect the fetal brain from further damage, especially during the critical period when brain neurogenesis is most intense. Conclusion Recent studies of prenatal endogenous and exogenous damaging factors have shown that they affect the structural and functional development of the fetal brain to varying degrees, making it very difficult to predict their effects.

Endothelial dysfunction and its impact on brain development

As is known, the endothelium of blood vessels is a single-layer layer of squamous cells of mesenchymal origin lining their inner surface. It is involved in the synthesis and metabolism of biologically active substances, providing in conditions of normal activity trophic organs and protective functions, synthesizes anticoagulants. The endothelium of blood vessels is a dynamic and plastic biological system that can quickly change its physiological characteristics depending on regulatory or pathogenic influences. In a broad sense, DE is understood as a short-term or persistent, potentially reversible disorder of the whole spectrum of phenotypic properties of endotheliocytes or a complex of various disorders of its functioning without obvious signs of morphological damage [28]. In the narrow sense of the word, DE is understood as the occurrence of NO synthase deficiency of vascular endothelium (NO-dependent DE), which is manifested by vasoconstriction. In DE, the balance between the production of vasodilating (NO, prostacyclin, hyperpolarizing endothelial factor, platelet-activating factor), angioprotective, antiproliferative factors, on the one hand, and vasoconstrictor (endothelin, thromboxane A, prostaglandins, endoperoxides, angiotensin II), prothrombotic, proliferative factors, on the other hand, is disturbed. Currently, the determining role of endothelial dysfunction (ED) in the occurrence of various somatic pathologies, primarily cardiovascular diseases [29] has been established, but this issue is not sufficiently developed in the occurrence of obstetric pathology. There are only sporadic data on the role of DE in blood circulation disorders in the mother-fetus system. The endothelium takes an active part in the regulation of vascular tone, and, consequently, in the regulation of blood circulation, including placental circulation. Histamine, bradykinin, prostacyclin and NO provide vascular dilatation, while endothelin-1 (ET-I, thromboxane, angiotensin II and serotonin have a vasoconstrictor effect [30,31,32]. Structural damage to the endothelium and impairment of its functional properties may play an important role in impaired antenatal fetal development due to impaired O2 and nutrient delivery. It is obvious that inhibition of vasodilatory properties of the endothelium of blood vessels can be the cause of impaired uteroplacental circulation and intrauterine development of the offspring. Disruption of the integrity of the endothelial lining of microvessels, in turn, can initiate adhesion, platelet aggregation and thrombogenesis. In the production of endothelial factors in the physiologic course of pregnancy, general regularities have been established. Changes in the production of endothelial factors begin early in pregnancy, which may be due to the influence of factors of the implanting fetal egg and is aimed at maintaining the forming blood supply in the mother-chorion-embryo system. In the first trimester of pregnancy there is a stimulation of endothelial functions of the forming fetoplacental complex, which is manifested by an increase in the concentration of factors (nitric oxide and prostacyclin) permanently formed in the endothelium. Starting from the II trimester of pregnancy, activation of endothelial function in the system "mother-fetus" is noted, manifested by an increase in the production of von Willebrand factor, thromboxane and endothelin. Starting from the period of the second wave of trophoblast invasion (16-18 weeks), the content of thrombomodulin and fibronectin

increases in the blood serum of pregnant women, which suggests the formation of endothelial dysfunction syndrome in the fetoplacental complex even in physiologic pregnancy [33,34,35]. Endothelial dysfunction during pregnancy is the basis of many complications of the gestational process (gestosis, fetoplacental insufficiency, immunoconflicted pregnancy) [36]. It is characterized by a change in the level of endothelial factor production in the fetoplacental complex, compared with physiologically occurring pregnancy. Disruption of endothelial function may be the cause of low birth weight [37], and insufficient NO production plays a role in hypertension of pregnant women [38], the occurrence of preeclampsia [39].

Methods of modeling experimental preeclampsia

Mice and rats are most often used for modeling experimental preeclampsia, less often rabbits, sheep, and cows. There are several ways of modeling PE. Most of them are based on:

1. Drug exposure leading to impaired NO metabolism [53].
2. Reduction of blood flow in uterine arteries by their embolization or ligation [54].
3. using in the experiment animal lines with a number of genes switched off (knock-out animals) or transgenic animals [55].
4. limitation of nutrient supply to the fetus [56].

Disruption of NO metabolism is modeled by administration of non-selective NO synthase inhibitor - L-NAME. The literature describes different ways of drug administration - subcutaneous, intraperitoneal, intramuscular, and oral. The doses used depend on the route of administration and vary widely (from 10 to 250 mg/kg). When administering ADMA-like agent - L-NAME to pregnant females, the development of pathology corresponding to the criteria of clinical manifestations of gestosis was observed. There was a statistically significant increase in systolic and diastolic BP, a significant decrease in microcirculation in the placenta, and a moderately pronounced increase in proteinuria. The study of nitric oxide production by vascular endothelium showed that L-NAME administration leads to a dramatic decrease in eNOS expression and nitrite ion content [57]. Reduction of uterine arterial blood flow was modeled by hypoperfusion of one or both uterine horns (by applying silver clips to the abdominal aorta above the bifurcation, to the ovarian arteries) on the 14th day of pregnancy. In the experiment, the application of clips led to a significant increase in BP, increased proteinuria, decreased microcirculation and pronounced changes of ischemic genesis in the placenta of both uterine horns [57]. There are ways to model pre-eclampsia by replacing drinking water with 1.8% sodium chloride solution from day 1 to 21 of gestation. The data of researchers indicate the development of neurological deficit in offspring born to females with EP, manifested by a decrease in learning ability and impaired short-term memory. In addition, the data obtained indicate a negative effect of EP caused by the replacement of drinking water with hypertonic sodium chloride solution not only on the cognitive functions of the offspring, but also on lipid and carbohydrate metabolism and urinary system in postnatal ontogenesis [58].

Effect of L-NAME on the brain and the body as a whole

As a result of oxidative stress, the endothelium is damaged rather quickly. Not only structural changes in the cerebral vascular bed, but also disturbances in the functional properties of the vascular wall are important in the genesis of vascular diseases of the GM. Currently, the vascular endothelium has become an important object of attention of researchers.

The influence of ischemic brain injuries on the development of endothelial dysfunction (DE) is currently insufficiently investigated. An important role in the pathogenesis of ischemic brain injuries is played by the disturbance of the vascular-platelet link of the hemostasis system. There are few works in the literature on the complex study of endothelial function in ischemic conditions, as well as on the assessment of interaction between endothelium and hemostasis system in IHM, and determined the goals and objectives of the performed work. Ischemic damage of brain tissue activates the release of tissue thromboplastin into the blood, which triggers the cascade of coagulation hemostasis, leading to hypercoagulation. In the ischemia zone there is a decrease in prostacyclin synthesis in the vascular endothelium and an increase in thromboxane A2 production, which leads to activation of thrombogenic properties of the vascular wall [59]. Proceeding from the fact that ischemic lesions occur more often in people suffering from atherosclerosis and hypertension, it is important to study the influence of endothelial dysfunction on the nature of brain damage during cerebral ischemia, as well as to develop corrective measures. For this purpose, it is important to assess the character of morphofunctional changes, which will be further used as a comparison group when studying these changes under the influence of endothelial dysfunction.

A significant breakthrough in the study of the endothelium was the discovery of the endothelial relaxation factor, nitric oxide (NO).

When detailing the pathogenesis of cerebral ischemia, the question arose about its participation in the pathogenesis of ischemic damage of the GM. It was found that NO is formed with the participation of neuronal and extraneuronal sources forming a "nitrergic system". Snyder S. H. and Bredt D.S. in 1989 identified regions of the GM that produce NO. Because of this, the NO synthase enzyme was isolated in pure form. It turned out that up to 2% of cortical neurons have NO synthase activity, the highest amount was observed in the cerebellar cortex. In the nervous system NO takes part in synaptic connections as a neurotransmitter, ensuring the efficiency of synaptic transmission (synaptic plasticity), plays a role in the regulation of synaptogenesis during the formation of neural and cerebral blood flow systems. Through the activation of various NO synthase isoforms, nitric oxide is involved in the pathogenesis of ischemic GM lesions, but the role of neuronal, macrophage, and endothelial NO synthase in neurodegeneration is not fully understood. It has been suggested that decreased nitric oxide synthase activity may be a consequence of oxidative stress in the cerebellar cortex, cerebellum, and hippocampus, and that low NO levels during brain ischemia are responsible for increased leukocyte adhesion to the endothelium, which increases the depth of damage caused by activated leukocytes [61]. The data on the role of non-selective inhibitor of all isoforms of NO synthase L NAME in the pathogenesis of ischemic brain damage are contradictory. According to some authors, a single application of L NAME caused a protective effect on the model of IHM in rats, manifested in the reduction of the infarction zone [60]. The neuroprotective effect revealed by intraperitoneal (15 hours before modeling of cerebral ischemia) administration of L-NAME (50-100 mg/kg) in rats suggested a key role of NO in the pathogenesis of ischemic strokes [61]. Some studies have shown that mice with genetic deficiency of NO synthase are more resistant to ischemic brain damage. They showed a decrease in the area of the infarct zone after ischemia [59] and a decrease in the content of neurotoxic excitatory amino acids [62]. At the same time, other researchers have established a negative effect of L-NAME in GM ischemia. In particular, L-NAME administration led to a decrease in antihypoxic resistance of experimental animals under hypoxic test conditions, as well as an increase in platelet aggregation, brain edema, brain myeloperoxidase activity and an increase in plasma concentration of lipid peroxidation products. The use of L-NAME is a well-established model for experimental hypertension, cardiovascular, renal disease, ADMA-like preeclampsia, etc. [58]. L-NAME inhibits nitric oxide synthase (NOS), resulting in decreased nitric oxide (NO) production. Rats injected with L-NAME showed a decrease in NO production in late gestation (days 14-20) [64, 58]. This decrease in NO synthesis is associated with a significant increase in maternal blood pressure, loss of vascular refractoriness to vasopressor stimuli, and decreased placental weight as well as offspring weight [63, 60]. In addition, rats treated with L-NAME in late gestation showed decreased perfusion of the uteroplacental bed as well as the placenta [58]. This implies that inhibition of NO synthesis in pregnant rats may serve as a useful model of preeclampsia in humans [62]. Nitric oxide is an important protective molecule in the vascular system, and endothelial NO synthase (eNOS) is responsible for the majority of NO production in blood vessels. Recently, functional endothelial NO synthase (eNOS) has been described in red blood cells (erythrocytes). RBC-eNOS contributes to the intravascular

NO pool and regulates physiologic functions [61]. Functional eNOS oxidizes its substrate L-arginine to L-citrulline and NO [64]. L-arginine, a semi-essential amino acid, is a natural substrate for NOS and is responsible for NO production [61]. Nitric oxide maintains vascular integrity by inhibiting platelet aggregation, leukocyte adhesion to endothelium and vascular smooth muscle.

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