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Role of antioxidant defense destabilization and lipid peroxidation in the pathogenesis of hypoxia in preterm neonates

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Abstract

This literature review describes current views on problems with the preventive diagnosis of hypoxia in preterm neonates. This is currently an important direction for neonatology as, according to World Health Organization data, the number of premature births in the world is growing annually. Children born earlier than 37 weeks of gestation are at the highest risk of death and disability. Of particular importance among the damaging factors are conditions related to lack of oxygenation in different tissues and organs of a preterm neonate. This paper deals with antioxidant defense destabilization and lipid peroxidation and their influence on the course of hypoxia. Special attention is paid to cytokine regulation of metabolic processes in pregnant women and in infants. The role of cytokines in hypoxia is emphasized, characteristic changes in cytokine levels are described, and current views on the possibility of using recombinant cytokines as corrective factors are presented. The literature review showed that despite significant progress in research into cytokine control of hemostasis in humans, the role of pro- and anti-inflammatory interleukins in oxidative stress in preterm neonates remains unclear. The authors consider that a joint study on lipid peroxidation and cytokine profiles may extend our knowledge of the pathogenesis of hypoxia, allowing us to predict severe and complicated courses and to develop relevant corrective methods.

Keywords: preterm neonates, hypoxia, cytokine status, lipid peroxidation.

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One of the main causes of morbidity in preterm neonates is severe antenatal and intranatal hypoxia [1]. According to recent statistics, 10%–20% of preterm neonates need primary resuscitation related to impaired oxygenation of various tissues and organs [2]. The high prevalence of pathological conditions associated with hypoxia requires the optimization of existing treatment regimens and the development of new diagnostic and preventive measures aimed at correcting oxidative stress. Various mechanisms mediating hypoxia could be of great importance. One of the mediating complexes that plays a role in the development of various pathological conditions is the cytokine system [3, 4].

The functional ability of monocytes and macrophages to secrete pro-inflammatory cytokines is formed by the end of the first trimester of pregnancy [5], whereas the system allowing the synthesis of anti-inflammatory cytokines by lymphocytes develops throughout pregnancy [6]. Low serum levels of interleukins (IL), specifically IL-10 and IL-4, in preterm neonates are directly related to gestational age [7]. It is important to note that, according to several authors, the relationship between levels of pro- and anti-inflammatory cytokines can contribute to the pathogenesis of a number of clinical conditions [8].

There are data on the involvement of cytokines in metabolic processes in numerous pathological conditions in pregnant women [9], and the effect of cytokines on the regulating systems of the fetus and preterm neonate have not been excluded [5]. A significant increase in levels of IL-1, IL-6, and IL-8 in the amniotic fluid was recorded in 50% of the examined women with preterm delivery. It is possible that preterm delivery was stimulated by the increased number of cytokines provoking the development of oxidative stress, which triggered gestational toxicosis [10]. Assumptions about the influence of IL-1 on the development of metabolic disorders in fetuses and newborn are based on the regulation of gluconeogenesis, glycogenolysis, proteolysis, and lipolysis, the disruption of which can play an important role in initiating or maintaining hypoxia in a preterm neonate [10].

Early postnatal adaptation in newborns with a history of hypoxia may also result in immunological changes. Some authors have proposed that levels of factors such as IL-1β, IL-4, IL-6, IL-8, IL-10, and acute-phase proteins factors could be used as assessment criteria for

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these changes. It was noted that a history of hypoxia influenced the activation of cytokines, promoting pro-inflammatory ones (IL-6, IL-8, and interferon γ) while reducing anti-inflammatory ones (IL-4 and IL-10). These changes are interpreted as an inflammatory transformation of the microcirculation, a reflection of the intensification of a systemic acute-phase response. Long-term maintenance of these changes may underlie the high risk of post-hypoxic complications [11].

Several authors have demonstrated the dynamics of changes in ILs in newborns with a history of hypoxic damage to the central nervous system (CNS). In particular, a >10-fold increase in levels of IL-1α appeared to be a differential and diagnostic criterion for hypoxic damage to the CNS due to infectious or non-infectious causes. It was also noted that an increase in IL-1α levels in the cerebrospinal fluid was more common in preterm neonates than in full-term infants. The authors recommended further study of these indicators as a potential method of assessing reserve capabilities of a child with hypoxic lesions of the CNS [12].

In other sources, the concept of searching for markers of severity for immune homeostasis disorders was formulated more clearly. It was suggested that cytokine status and severity of immune dysfunction at the third week of life directly depended on the severity of the hypoxia and the timeliness and duration of resuscitation given at delivery [3].

In preterm neonates, derivatives of monocyte–macrophage cells such as matrix metalloproteinases can play the role of biochemical markers for CNS lesions. Disruption of the synthesis of natural inhibitors of metalloproteinases occurred during hypoxia, which led to an increase in metalloproteinases levels and development of pathological effects [13–16]. Hypoxic–ischemic-induced antioxidant deficiency triggered the release of pro-inflammatory cytokines, leading in turn to the synthesis of matrix metalloproteinases. Remneva et al. analyzed 288 mother-and-newborn pairs and identified that a high level of matrix metalloproteinase-9 in umbilical cord blood was associated with severe cerebral ischemia, intraventricular hemorrhages, and pneumonia in the newborn [17]. This was attributed to the damage and degradation of collagen IV in the wall of cerebral vessels [17].

In several studies, proteolytic enzymes, in particular dipeptidyl peptidase-4, were found to have an important role in the initiation and course of the hypoxic process [18]. It was noted that the level of dipeptidyl peptidase-4 in full-term newborns served as a differential and diagnostic criterion for various forms of cerebral ischemia. The studies also established the need to identify drugs to inhibit these reactions and prevent severe consequences of cerebral ischemia [19].

Recent studies have assigned high priority to the role of markers of CNS damage in the genesis of perinatal hypoxia. Golosnaya et al. identified that in severe asphyxia in newborns, the levels of destructive factors (e.g., S-100, DR5, and ALCAM genes) increased, whereas the levels of stimulating factors (e.g., brain-derived neurotrophic factor and vascular endothelial growth factor) decreased, indicating a disruption in the balance of adaptive and protective mechanisms in hypoxia [20].

Currently, there are opportunities to use cytokines as a means of correcting various pathological conditions. Promising areas for recombinant cytokine use are the activation of body defenses and the blocking of pathological effects of endogenous cytokines. Colony-stimulating factors, interferons, erythropoietin, and individual ILs have also found applications in medical practice. One of the effects of these drugs was the regulation of regenerative processes for damaged tissues. This does not exclude their influence on hypoxia and in preterm neonates, which is confirmed by the neuroprotective effect of erythropoietin in neonatal practice. Thus, the use of recombinant cytokines is a promising direction among modern high-technology approaches to therapy, as demonstrated in a Russian health care service [21].

An important pathogenetic mechanism for the development of hypoxia is the activation of lipid peroxidation (LPO) processes. A large database of markers for LPO processes already exists. Hypoxia and hyperoxia have a stressor effect on the body. Stress activates LPO processes, which lead to the disruption of membrane structure and lipid metabolism, with a toxic effect on tissues [22, 23]. The products of LPO processes damage the structural and functional integrity of cell membranes and increase vascular and tissue permeability [24].

In ischemia, oxidation of the substrates of the Krebs cycle in the mitochondria is inhibited. As a result of this, levels of reduced nicotinamide adenine dinucleotide phosphate and reduced nicotinamide adenine dinucleotide should increase, which may increase the one-electron reduction of oxygen. Thus, in ischemia, a paradoxical situation arises as the decrease in oxygen concentration leads to an

increase in the number of oxygen radicals and other active forms of oxygen [24].

Fetal hypoxia and newborn asphyxia are accompanied by an accumulation of LPO products; a deficiency of retinol, tocopherol, and riboflavin; and a decrease in the activity of glutathione peroxidase, glutathione reductase, and superoxide dismutase in both the mother and the newborn [25].

One of the main substrates for free radical reactions is lipids, primarily polyunsaturated fatty acid molecules, and the lipid components of low- and very low-density lipoproteins [26]. The oxidation of fatty acids produces hydroperoxides, which are then metabolized into secondary (malondialdehyde) and tertiary (Schiff bases) LPO products [27]. LPO processes occur in all cells, but leukocytes, platelets, and hepatocytes are the most powerful free radical generators [28]. Other compounds formed in LPO processes include alcohols, ketones, aldehydes, dialdehydes, and epoxides. The formation and accumulation of these compounds contributed to a significant change and even disruption in the function of biological membranes [29, 30]. The most important of these compounds are the aldehydes and dialdehydes due to their high biological activity. Malondialdehyde is of particular interest as its identification by a color reaction with thiobarbituric acid serves as one of the leading and most accessible methods of studying the intensity of LPO processes in pathological processes, including hypoxia [31].

LPO products become inactive after interaction with protein enzymes (e.g., lactate dehydrogenase, cytochrome oxidase, and trypsin). Some authors have identified a significant inhibition of LPO processes at birth in healthy newborns, which they believed to be an adaptive mechanism necessary to overcome the stress of birth. In children with mixed hypoxia, a marked increase in membrane metabolism was noted, whereas in children with chronic hypoxia, there were signs of both increased metabolic processes and inhibition of LPO [32].

In intact cells and tissues, an intensification of LPO processes is countered by a powerful antiradical (antioxidant) defense system. Enzymatic antioxidant mechanisms and nonenzymatic endogenous and exogenous antioxidants function to break the reaction chain of free radical peroxide oxidation or to directly destroy peroxide molecules and create a more compact membrane structure that reduces the access of oxygen to lipids [29].

However, powerful and prolonged stress leads to depletion of protective systems and antioxidant potential and to significant oxidative destruction of internal organs [29]. Compensatory activation of antioxidant protection occurs in response to the intensified LPO processes under various pathological conditions, including those in newborns [25]. Some authors believe that significant activation of free radical oxidation processes is accompanied by a decrease in the activity of key antioxidant enzymes [29].

Despite having a higher oxygen consumption than adults, the toxic effect of reactive oxygen is effectively controlled in healthy newborns by protective antioxidant mechanisms. In severely ill children, the energy supply for these processes is low, and initial stocks of products are depleted due to a prolonged increase in peroxidation and associated destructive processes in cells and subcellular structures [33]. A number of authors have suggested that a peroxynitrite level in umbilical cord plasma is a marker of oxidative stress in newborns and a prognostic criterion for the severity of CNS damage [34].

The regulatory effect of a vegetative nervous system on LPO processes is known. In experiments performed on rats with a history of stress, the stimulating role of epinephrine on peroxidation processes was proven, whereas acetylcholine contributed to longer-lasting but less pronounced changes in the LPO system. In the same experiment, the effective antioxidant action of a combination of L-tryptophan and nicotinic acid was demonstrated. Activation time of LPO processes and antioxidant system was dependent on the age of the rats, with earlier activation characteristic of older individuals due to depletion of the nonenzymatic antioxidant system [35, 36].

Thus, the data presented in this literature review highlight the relationship between LPO and cytokine status and changes in hypoxia. It can be assumed that levels of individual ILs are a trigger mechanism for oxidative stress, which leads to destabilization of LPO and antioxidative activity, aggravating the severity of hypoxia. In our opinion, the study of individual pro- and anti-inflammatory cytokines levels will enable the formulation of a more precise explanation of the pathogenesis of hypoxia and identification of the predictors of a severe or complicated course. This is especially important for predicting and diagnosing hypoxic conditions in preterm neonates.

The authors declare no conflict of interest on the article submitted.

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