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МИНИСТЕРСТВО ВЫСШЕГО И СРЕДНЕГО СПЕЦИАЛЬНОГО
ОБРАЗОВАНИЯ РЕСПУБЛИКИ УЗБЕКИСТАН

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ
УЗБЕКИСТАН

ТАШКЕНТСКАЯ МЕДИЦИНСКАЯ АКАДЕМИЯ

СБОРНИК МАТЕРИАЛОВ МЕЖДУНАРОДНОЙ НАУЧНО-ПРАКТИЧЕСКОЙ КОНФЕРЕНЦИИ МОЛОДЫХ УЧЁНЫХ “ВОПРОСЫ БИОФИЗИКИ В МЕДИЦИНЕ”

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PERINATAL HYPOXIA EFFECTS ON THE ENERGETIC FUNCTION OF BRAIN NEURONAL MITOCHONDRIA

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Abstract*. This article presents the biophysical and molecular mechanisms of the response of brain neurons to hypoxia, describing disturbances in mitochondrial energy functions and ion homeostasis in cells exposed to hypoxia and ischaemia.*

Keywords*: perinatal hypoxia, ischaemia, brain, neuron, cell homeostasis, necrosis, apoptosis.*

Perinatal hypoxia is an important factor in the development of the central nervous system. The more advanced neonatal intensive care technologies improve survival rates, but do not prevent neurological disorders, resulting in increased morbidity in the adult population [1-3].

Perinatal hypoxia is a pathological process associated with oxygen deprivation during pregnancy and the early neonatal period. Perinatal hypoxia decreases or stops the supply of oxygen to the body, and under-oxidised products of metabolism accumulate in the blood. The cerebral ischaemia (decreased cerebral blood flow) is an equally important factor in the development of neuronal abnormalities in the perinatal period. In this condition there is not only oxygen deprivation, but also a reduction in glucose supply to the brain tissue [4]. The majority of neurological abnormalities caused by perinatal hypoxia result from a combination of hypoxia and ischaemia [5]. The placenta dysfunction, prolonged labour, premature delivery and cardio-respiratory disorders of the mother cause perinatal fetal hypoxia [6]. The intrauterine hypoxia and asphyxia of the newborn is a major pathogenetic factor in brain damage. The prenatal hypoxia rate is 1-6 per 1 000 infants and is one of the main causes of perinatal mortality [4]. The high incidence and very severe consequences for the child make research into the neurochemical mechanisms underlying the effects of perinatal hypoxia urgent [2].

The developing brain is very sensitive to hypoxic damage as its oxygen requirements are very high compared to other organs and tissues [7]. Poor oxygen supply (hypoxia) and/or reduced blood flow (ischaemia) activate various cytotoxic agents and cell death pathways leading to brain damage [8]. The neuropathological processes are triggered during the acute phase of hypoxia/ischaemia and continue during reperfusion [9]. There are various pathogenic mechanisms underlying hypoxic

damage, such as accumulation of toxic metabolites including glutamate, impaired Ca^{2+} exchange, release of pro-inflammatory mediators, accumulation of iron, overproduction of free radicals, reduction of energy stores and synthesis of macroergic compounds [10]. The reduction of macroergs and increased levels of intracellular and extracellular damaging factors lead to disruption of cellular homeostasis [9].

The activity and excitability of neurons is directly regulated in response to O_2 reduction by altering membrane channel conduction. Plasma membrane of brain neurons contains a specific type of potassium channels whose subunits form four transmembrane groupings and two transmembrane pores (background K2P channels) [11]. Their function is related to maintaining cell membrane potential at rest, as well as to the regulation of K^+ homeostasis and neuronal excitability. Some hormones and neurotransmitters, anaesthetics as well as physico-chemical factors such as hypoxia and changes in extra- and intracellular pH modulate the effects of background K2P channels. These K2P channels are potential-independent and permanently active. Their blockade causes depolarisation and their activation causes hyperpolarisation of the neuronal membrane. The family K2P channels of mammals are subdivided into 6 subfamilies. TASK-1/TASK-3 types of K2P channels are sensitive to hypoxia and significantly affect neuronal excitability. Hypoxia and acidosis cause TASK-1/TASK-3 channels to be blocked, leading to membrane depolarisation and neuronal activation [11].

Hypoxia-induced brain damage develops through processes that occur during the acute phase of hypoxia-ischaemia and continue into the reperfusion phase. Oxygen and glucose deprivation in the background of hypoxia-ischaemia or immediately afterwards causes primary energy deficiency [12]. The reduction in oxygen availability leads to impaired electron transport in the mitochondrial respiratory enzyme chain, with the result that the associated process of oxidative phosphorylation suffers, which reduces the synthesis of macroergic compounds such as ATP. There is an energy deficit in the cells. Glucose metabolism is then switched mainly to the anaerobic pathway, leading to the accumulation of lactate and the development of acidosis. Lactate accumulation plays a positive role in adapting to O_2 deficiency, but with increasing levels lactate has a damaging effect [11].

Additionally, disruption of ATP synthesis leads to impairment of energy-dependent homeostatic functions, such as maintenance of cell membrane potential. The ATP-dependent Na^+/K^+ pump is disrupted, leading to intracellular accumulation

of Na^+, Ca^{2+} ions and water, and cytotoxic oedema develops. As a result, cell death occurs along the necrotic pathway [13]. The depolarisation of the membranes of neurons induces the release of glutamate, leading to further cellular excitation and excessive Ca^{2+} input into the cytoplasm. High Ca^{2+} concentration leads to NO-synthase activation (increased NO content), formation of free radicals, activation of phospholipase (membrane lipid degradation), proteases (protein degradation) and nucleases (DNA degradation). The effect of intracellular Ca^{2+} current on the endothelium of capillaries and arterioles contributes to vasoconstriction and worsens ischaemia. The subsequent reperfusion aggravates the metabolic abnormalities in the brain. Especially, tissue re-oxygenation after an ischaemic episode increases the amount of free oxygen in the cells, which is predominantly used through the oxygenase pathway, being converted into reactive oxygen species (the so-called oxygen paradox). In this period, the damage to cell structure and function is often more severe than in ischaemia [11].

Nonetheless, the development of neuronal damage is not limited to the period of hypoxia/reperfusion. The animal experiments showed significant recovery of cellular metabolism after the end of neonatal hypoxic exposure, followed by a secondary energy deficit [14]. Generally, 6-48 hours after acute hypoxia, cellular energy metabolism is again impaired due to an accumulation of mitochondrial damage, leading to the release of cytotoxic enzymes and pro-apoptotic proteins from the mitochondria [15]. Consequently, some of the neurons that survived the initial energy deficiency die after hours or days mainly through the apoptotic pathway [16].

In summary, despite numerous studies, the long-term effects of perinatal hypoxia and their underlying mechanisms are poorly understood to date. The study of the consequences of perinatal hypoxia and the search for safe and effective methods of their treatment remain the most important task of modern medicine and neuroscience.

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