APPLICATION OF ANTIHYPOXIC DRUGS THAT CORRECT ANТЕNATAL HYPOXIA AND STUDY ITS MORPHOLOGIC AND FUNCTIONAL PECULIARITIES (THE LITERATURE REVIEW)

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(received 04.02.2013, published 14.04.2013)

The problem of hypoxia for many years is very relevant and attracts the attention of physiologists and clinicians in terms of the mechanisms of various pathological conditions. Effects of antenatal hypoxia in the infants depend on the severity of exposure, individual tolerance and the age of fetus. In the literature, there is a large amount of data on the effect of antenatal hypoxia during last trimester of pregnancy on the development of the newborn. There is a reduction of oxygen supply to the parts of the body below required for adequate perfusion. At present researchers think about application of a number of regulatory peptides and their constellation to correct the consequences of shock states, including antenatal hypoxia. Cardioprotective effect is achieved due to sufficient energy supply, which helps to maintain normal cardiac contractility. Research and application of new antioxidant drugs in cardiology practice that can enhance the effectiveness of treatment of patients with myocardial infarction are highly relevant.

Key words: antenatal hypoxia, antihypoxant drugs, cardiomyocytes, peptides, neurotransmitters.
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Even though pregnancy and labor are most natural and physiological aspects of human life, these processes are still influenced by numerous endogenous and exogenous factors. There are various factors, which badly affect gestation course and labor, so it is hardly possible to find one without negative impact on their harmonious course. Hypoxia issues and particularly development of numerous pathological states of the disease have been extremely relevant and attracted attention of physiologists and clinicians for many decades [37, 49]. Antenatal hypoxia is a key damaging factor of the “mother-fetus” system. It is generally accepted, that a modern person is rather sensitive to high stresses, like psychoemotional stresses and toxic effects of environment. So, these factors affect a pregnant woman and it leads to fetus prenatal hypoxia development. Lack of oxygen, in its turn, has badly affected every system and organ of a developing fetus. Children, who have borne prenatal hypoxia due to information from their medical histories, are supposed to have physical development delay, changes of visceral system balance and biogenic amines, morphologic and functional damages of brain, heart and lungs, etc. Studying of the antenatal hypoxia effects on heart and the possible treatment methods has particular interest for both basic and applied sciences due to the widespread cardiovascular pathologies [5, 7, 9, 16].

Heart diseases are considered to be among the pathologies which are caused by the profound effects of hypoxic disorders. It is related to peculiarities of oxygen supply of cardiac myocytes. As it is known, the myocardial cells have the maximal level of energy intensity as they perform the most important functions [9, 24]. However, the general amount of blood circulating in the cardiac muscle is comparatively low; despite this it can release the required amount of oxygen extracting maximally oxygen from oxyhemoglobin. It is not accidental that mitochondria occupy about 30 % of cell space [1].

Along with hypoxia, free radicals of oxygen are stored there damaging polyunsaturated fatty acids of cardiac myocytes membranes. It is also accompanied by disorganization of their bio-electrical activity. Especially superoxide anion has such a damaging character, it disproportionates with superoxide dismutase as oxygen and hydrogen peroxide. Hydrogen peroxide, in its turn, reacts with free ions of iron and cuprum. This process is accompanied with formation of highly toxic hydroxyl radicals [13, 41, 42].

Reduction of creatine phosphate is one of the hypoxia metabolic signs and inappropriate supply of energy in neural tissue and myocardium,
respectively. This compound is not only a reserved recourse of macroergic phosphate compounds, but it also transports them to energy expense [22].

As it is known, resynthesis of ATP in mitochondria is closely connected both to redox reactions and reactions of glycolysis, lipolysis and proteolysis. These processes serve as suppliers of acetyl-CoA for the Krebs cycle. It is pointed out that regulatory enzymes of glycolysis are phosphorylase, hexokinase, phosphor fructokinase and pyruvatekinase. Thus, suppression of enzymes during hypoxia leads to lowering of free energy formation and in most cases it has irreversible character. At the same time phosphor fructokinase acts as a main allosteric enzyme during successive reactions of glycolysis. This enzyme inhibits ATP and citrate, but stimulates AMP and ADP [29].

Thus, during hypoxia and in case if phosphorylation increases, there takes place activation of key glycolysis enzyme – phosphofructokinase and capability of anaerobic glycolysis increases respectively. At the same time there is rough reduction of macroergs amount in the heart, so products of glycolytic reaction are deposited. These products are lactic and pyruvic acids [6, 7, 8, 35]. Activation of phosphofructokinase slightly improves energy supply of tissues during the initial phases of ischemic and hypoxic cell damage. An addition, acidosis intensifies leading to phosphofructokinase suppression at a peak of its intensiveness and subsequent complete blockade of cell energy supply. Development of metabolic acidosis is also complicated by insufficient redox reactions of fatty acids, amino acids and an excess of acid products of metabolism (of the mentioned compounds) during hypoxia [17, 35].

When utilization of glucose is abnormal, so catabolism of proteins enhances and at the same time amino-groups of amino acids are non-attached and converted into α-ketonic acids. The last are involved into the Krebs cycle with formation of CO2 and water only if there is normal oxygenation of tissues. It is essential that development of metabolic acidosis is also complicated by excess accumulation of amino and α-ketonic acids in the tissues during hypoxia and disturbance of redox reactions at the Krebs cycle [17, 20].

Talking about the dynamic of metabolic acidosis, which develops in a regular manner even with various hypoxia geneses, there is a chain of consequent nonspecific metabolic and functional disorders. They are represented by dynamic transformation of the adaptation reactions into the disadaptation. As it is known, the typical reaction for mast cells and thrombocytes on hypoxia course and acidosis is the degranulation with excessive realise of high active compounds (such as histamine, serotonin, thrombocyte activation factor, leukotrienes and interleukins) [18, 25].

In its turn, excess accumulation of hydrogen ions and other biologically active compounds lead to sharp increase of biologic membranes permeability due to their structural bonds of proteins and lipids and penetration processes after the activation of free-radical oxidation [11, 26].

Thus, the most harmful mechanisms, which cause biological membranes disorders during hypoxia of different geneses, are: metabolic acidosis development, releasing of vasoactive compounds by mast cells, activation of lipid and peroxidation processes, releasing of lysosomal hydrolases during lysosomal membranes disorganization, and their further metabolic shifts complication.

It is obvious that hypoxic necrobiosis development is connected much to disorganization of certain membranes, such as: cytoplasmic, lysosomal, mitochondrial and other biological intracellular membranes, which form particular functional and structural compartments. Besides, the earliest disorders occur in the gradient-formatting and contractile cellular systems [24].

As we know, one of the most energyrich enzymes is Na, K-ATPphase. It provides transmembrane transportation of ions along concentration gradient and keeps the potential level of cell calmness and its excitability [6]. At first partial depolarization occurs, when hypoxic state develops, macroergs deficiency, passive permeability increasing of cytoplasmic membranes of cells if they are disorganized during hypoxia. Later full depolarization of cells develops, these cells cannot be repolarized and consequently the action potential formation and suppression of functional cell activity are absent. One of the consequences of the Na,K-ATPphase suppression and structural components disorganization of cytoplasmic membranes, proteins and lipids is excessive penetration of Na+ and H2O into cytoplasm with further hyperhydration, edema developing and “albuminous swelling” of a cell. Intracellular hyperhydration is one of the typical characteristics of the early reversible phase of cell necrobiosis during hypoxia [2, 5, 11, 43].
Calcium ions are the most damaging factor for the cells during hypoxia [6, 50]. As it is known, intracellular concentration of calcium level is on the average $10^{-7}$ M at rest, this is by 100,000 times lower than in the intercellular fluid. Calcium penetrates from outcellular media into a cell through voltage-dependent calcium channels during the excitation period. Moreover, Phospholipase C activation happens and intracellular lipid intermediaries of diacylglycerol and inozynphosphamin are formed. Cytoplasmic Calcium interacts with calmodulin, the intracellular receptor, then calmodulin-dependent protein kinase activates and certain intracellular reactions take place [19].

There are not enough inactivation mechanisms of cytoplasmic calcium and its taking out of the cells due to action suppressions of ATP-dependent calcium-bump and Natrium-Calcium metabolism, and also destabilizations of mitochondrial and endoplasmic reticulum membranes during hypoxia and energy supply deficiency. These mechanisms act significant roles to keep in balance the level of intracellular calcium in normal conditions. If the level of calcium is excessive, so the process of mitochondria swelling is worse, deficiency of ATP is higher and all the energy-dependent reactions at cells are suppressed [3, 16]. Excessive calcium activates nucleus endonuclease, which fragments DNA, and induces apoptosis. If the level of intracellular calcium is high, so neutral protease activates, so called calcipaines, breaking a cell cytoskeleton and lysing the receptors and protein kinase C [13, 20, 39].

Activation of the membrane phospholipase, influenced by calcium, leads to further disintegration of the cell membranes, activations of cyclooxygenase and lipoxygenanese. Later prostaglandins, leukotines and free radicals with pronounced cytotoxic action are formed [20, 29].

The role of mitochondrial membranes in the process of disintegration is extremely important in the mechanisms of hypoxic necrobiosis of the cells [10]. Perhaps, the ions $H^+$ are leaking through the membranes during disruption of the mitochondrial membranes structure in case of hypoxia. On the one hand, there is a possibility of active oxygen formation, but on the other hand, ATP resynthesizes insignificantly during the leakage process. Thus, the permeability of mitochondrial membranes increase sharply if there is excessive amount of calcium ions and lipid peroxidation processes activate during hypoxia of various geneses. It also leads to mitochondria swelling, vertigo disorientation of the enzymatic systems transporting electrons and ATP synthesis. As a result, oxidative phosphoration and respiration are separated and all the energy-dependent cellular systems are suppressed, respectively. They are protein synthesis, transmembranic ion transportation, coupling of the excitation and contraction processes at the muscular structures and etc. [29].

A complex of metabolic and functional shifts is formed along with local and systemic metabolic shifts at tissues, which are caused by hypoxia, acidosis and lipid peroxidation processes activation during hypoxia of various geneses. The metabolic and functional shifts are caused by releasing of adaptive hormones, like catacholamines and corticosteroids. Adaptive reactions turn into inadaptive processes rapidly if the sympathoadrenal system is extremely active [14]. Firstly, an angiospasm of peripheral organs and tissues happens if the process of noradrenaline releasing activates, the circulatory hypoxia complicates. The activation of the certain processes (such as: glycolysis, glycogenolisis and lypolisis) may take place against the sympathoadrenal system activation with involved postsynaptic $\beta$-andrenoreceptors. This factor certainly complicates development of acidicotic shifts, which are typical during hypoxia [14]. Strengthening of the adnergetic influence goes along with the lipid peroxide processes activation. This contributes much to the development mechanisms of hypoxic necrobiose of the organs cells and tissues, which are sensitive to ischemia.

The effects of antenatal hypoxia on a newborn’s organism depend on severity, individual tolerance and prenatal development term at the moment of hypoxia influence. References provide much information about the effect of antenatal hypoxia on a newborn’s development during the last trimester of pregnancy. However, questions concerning the hypoxia effect on an embryo during the progestation period and further organism development during the postnatal posthypoxic period are hardly discussed. The progestation period includes the first cell divisions, blastolation, embole growth and formation of organs and systems [7, 39].

Besides, antenatal hypoxia causes significant imbalance of biogenic amine both during the early and late posthypoxic periods. The papers of L. D. White and E. E. Lawson (2007) showed that
the level of zymogenic synthesis of catecholamine system of the rats had been changed by chronic antenatal hypoxia during the late embryonic growth period [40]. So, decreasing of the tyrosine hydroxylase (it catalyzes formation of dopa) and N-methyltransferase (it catalyzes formation of adrenalin) levels in the dorsal part of medulla was registered during the first week of postnatal development. However, increasing of the levels was registered in the ventral part of medulla. The low level of N-methyltransferase in the dorsal part of medulla was preserved during the second week of prenatal/antenatal development [2, 11].

It was shown that antenatal hypoxia, preserving heart failure and heart rate disturbance, could worse congenital heart disease cause [32]. The research of P. V. Balan (1999) showed that young rats had pronounced arrhythmias, including bradycardia, and certain changes in the electrocardiogram during the hypoxia modeling. Complicated heart rate disturbances (like sinoatrial arrhythmics, bradycardia and bigeminy) were fixed during hypoxic shock. At the same time on the certain areas (in a polytopic manner) were pointed extrasystology [4].

The animal rats, which had covered from antenatal hypoxia on their 1–2 days of postnatal development, had heart rate disturbance, particularly tachycardia, and disorders of atrioventricular releasing and repolarization processes. The monkeys’ embryos had heart rate contraction shortening and heart rhythm variability due to acute hypoxia. The authors concluded that the effects of antenatal hypoxia on embryo’s heart state were of parasympathetic manner. Thus, the effects of hypoxia were diminished when antipine had been applied. Reducing in heart rate as a consequence of antenatal hypoxia, which was caused by uterine blood flow reducing, was identified for the sheep’s embryo: heart rate reduction was connected to oxygen saturation reduction and arterial tension lowness [14, 34, 38].

Having analyzed the antenatal hypoxia effect on hearts of newborns during postnatal period, it was pointed that the tension index and amplitude of heart rate mode increased. The ECG showed bradycardia, extensions of atrial, atrioventricular and intra-gastric conductions, and, moreover, the life threatening arrhythmias. These changes were caused by severe metabolic and also electrolytic disorders [9]. The obtained data confirms that more pronounced activation of the sympathetic nervous system has newborns with bare antenatal hypoxia. One of the harmful factors to cause cardiopathy is the imbalance in sympathetic and parasympathetic activities of the heart. This imbalance was preserved during the first months of life. However, as for the research, the most severely ill newborns have significantly lower index of the tension. This index may be used as the criteria of the newborn’s severity state with the bared antenatal hypoxia [15].

The data, which were derived using the light microscopy, has proved that there were significant changes at the heart vessels of different caliber [26]. Thus, the study of antenatal hypoxia effects on sheep showed the diameters of capillaries enlarging and the thickness and length of capillaries reducing at the right ventricle comparing to the left one. Besides, antenatal hypoxia may cause the development delay of myocardium. The references about the hypoxic disorders of the heart during antenatal hypoxia say that the most sensitive to unsupplied oxygen are the contractive cardiac myocytes of the subendocardial layer and papillary muscles [9]. There are cardiac histiocyte at this layer, which are related to the peripheral area of cardiac conduction pathways [9].

Moreover, antenatal hypoxia changes the rheological properties of blood, so blood becomes more viscous and less fluidic. The main factor of the rheological properties of blood worsening is the changes of erythrocyte properties. This may be a basic reason of the blood clot formation and cause hypoxic hypoplasia and hypertension of lungs/lungs hypertension [24].

In any case, the progressive changes of the myocardium are complicating are a result of hypoxia, these changes cause the majority of symptoms. These effects are evident as the significant disorders of heart chronotopy (at first tachycardia and later bradycardia develop), worsening of the heart sonority tones (at first the tones are louder and then hollowness begins), developing of arrhythmias of various geneses. In such cases, the application of antihypoxic and antioxidant drugs is accompanied by the reducing of destructive effect of reactive oxygen species. The clinical evidence of these drugs application is heart rate stabilization and limiting of a risk of arrhythmias development [1, 30].

The clinic application of antihypoxic drugs is determined not only by the general views about the effect of drugs, but also their accessibility for the doctors. This accessibility is formed by scientific research and industrial production of these drugs. One should pay particular attention to the
classification of drugs: substrate antihypoxic drugs, regulative antihypoxic drugs and plastic regulators of metabolic processes against hypoxia [28, 31].

The substrate antihypoxic drugs keep the leading role in urgency effect on severe tissue hypoxia. Among this type of drugs, amino acids are distinguished, such as glutamic, asparaginic, cysteine and their salts. The mechanism of amino acid protective function during hypoxia is not clarified. Some studies prove that amino acids activate the processes of oxidative phosphorylation. It is extremely important for treatment of the patients, whose organic hypoxia/hypoxia of organs determines at certain degree the level of endogenous intoxication development. The experiments and clinical application of glutamic acid in the before-ischemic period (20 mg/kg of body weight) during cardiac surgeries helped to prove that better level of the myocardium contraction could be reached under these conditions during the early postoperative period [25]. Perhaps, as glutamic acid restores the substrate fond of the Krebs cycle forming α-ketoglutaric and oxalic acids, this leads to NAD-dependent restoration/renewing of fumarate. At the same time, the wide application of these drugs into the emergency treatment programs of hypoxic state may be glutamic and cysteic acids [45].

The substances, which are mainly used to activate the anaerobic derivatives of energy-rich ergs (if there is deficiency of oxygen), should keep the leading role among other antihypoxic drugs [31]. These are the common substrates of glycolysis, such as: glucose and phosphorylated derivatives of hexose (like 6-glucose phosphate and 1.6-fructose diphosphate). A possible antihypoxic effect of glycolysis substrates is, firstly, connected to preserving of the own energy-rich cells, which are used for primary phosphorylation of the hexoses [33].

Unfortunately, our hopes for the protective function of the phosphorylated carbons during hypoxia were not proved. We have obtained just average positive changes applying 6-glucose phosphate and 1.6-fructose diphosphate, and their mixture, so called hexose-phosphate. One proved that various phosphorylated carbons are little different from each other due to their antihypoxic activities. It is known that the cell membranes are almost impermeable for any intermediate derivatives/products of glycolysis. This fact reduces the value of these substances as the antihypoxic drugs and explains their nearly equal effectiveness during hypoxia [8, 44].

The wide application of Glucose-Insulin-Potassium was based on the same mechanism. The main idea of the process is the changing of hypoxia-effected myocardium of certain severity degree from uneconomic peroxidation of free fat acids to more energy-wise glucose in case of hypoxia. The hypoxic myocardium is the most appropriate object for this therapeutic influence as only 25–30% of O₂ are used for glucose oxidation even at normal conditions; the rest of O₂ is used for lipids and lactate oxidation. The application of Glucose-Insulin-Potassium for acute myocardium attack can slow down the free fat acids oxidation by 100 times (100%) and increase glucose absorption by the effected heart by 2-3 times [20, 23, 48].

However, attempts to apply widely the drugs based on exogenous ATP were insignificant. For instance, an intravenous injection of ATP-based drugs (Phosphobion) at higher doses showed some contrasting effects during the severe attacks of supraventricular tachycardia. Only when the exogenous phosphocreatine drugs were applied into the clinical practice, the known step forward was done in the treatment of the organ hypoxic damages [31]. Exogenous phosphocreatine, which is contained at the normal cardiac myocytes in high concentration, should be considered as one of the natural factors to stabilize the cell membranes. Disappearance of exogenous phosphocreatine from the cardiac myocytes can be one of the factors to destabilize and disrupt the cell membranes during ischemia. The very grounded and informative experiments pointed that exogenous phosphocreatine injected into blood at high doses, influenced much on energy supply, structural utility of the ischemic cardiac myocytes membranes and their contraction function. Thus, when exogenous phosphocreatine acts, it reduces the physiological manifestations of ischemia of myocardium, arrhytmogenic activity of an ischemic focus and extensive activity of LPO. The trade drug of phosphocreatine, called Neoton (produce by Alfa Schipparelli Wassermann) is used for urgency cardiology. Unfortunately, it may be applied to treat the acute attack of myocardium as soon as a first symptom is pointed at the earliest terms [1, 23].

It is known that succinate stimulates restorative functions at a cell. There was pointed out a phenomenon of the rapid oxidation of succinate at the cell cytoplasm using succinate dehydrogenase. The process is accompanied by restoration of
The biological importance of this phenomenon is that rapid resynthesis of ATP by the cells and increasing of their antioxidant activity take place. High antihypoxic and antioxidant activities of succinates is used for the infusion media, like “1.5 % Reamberyen for infusion”, produced by NTFF “Polysan”. It contains the active substance, such as mixed sodium N-methyl glutamine salt of siccine acid, electrolytes in the optimal proportion for saline blood substitute. Experience of reamberyen application for the patients with severe obstructive jaundice, damaged livers of drug-addicts, for the patients with critical state of various geneses and the acute attack of myocardium allows hope for the widest application of this infusion media as a drug for emergency states [20, 23].

The medications with clear organotropic cytoprotective effect were produced. Trimetazidine is considered to be one of them. Due to certain experimental trails and clinical research trimetazidine prevents from establishing of metabolic disorders induced by an ischemic myocardial syncytium, but at the same time the structure and function of the tissues are preserved. If trimetazidine is applied before ischemic heart disease, so it keeps energy potential of the cardiac muscle on the same level, corrects imbalance of ions, prevents from intracellular acidosis and storing of calcium and natrium ions and reduces harmful influence of the free radicals. These characteristics of trimetazidine allow using it for balloon angioplasty and surgery on the coronary artery [36]. Thus, there is a chance to protect the myocardium of the patients with ischemic heart disease diminishing absolutely the consequences of ischemia if it still develops despite the treatment. However, the positive effect of this drug is insignificant if it is applied after the ischemic damage, when the positive effect of proper antihypoxic drug should be the most effective.

For example, this situation may occur with sodium salt pentamer of dioxy-O-phenelyne tiosulphuric acid that is patented as “Olyfem” in Ukraine. Studying of biochemical nature/characteristics of olyfem activity during the experiment showed that the drug influenced on a respiratory chain of mitochondria as to its high electron-withdrawing properties that are typical for the polyphenolic compound [19, 21]. Olyfen increased effectiveness of tissue respiration, released the tissue from unoxidated derivatives/products, normalized concentration of hydrogen ions and restored functions of mitochondria during experimental hypoxia conditions. One thought that olyfem would accelerate up the renewed equivalents oxidation and normalize respiratory processes at the cells with high metabolic properties due to the byopss in mitochondrial chain of ions transportation. Olyfen was one of the most active antiaggregants of thrombocytes during the clinical trials. These antihypoxic effects could be explained by microcirculation enhancing and mediated positive changes of oxygen supply in the tissues [8, 21].

The other group of antihypoxic drugs contains the drugs, which we previously called plastic regulators of hypoxia affected metabolism. They are inosine, bimethyl and atmezol, etc. Their effects it the changing of metabolic processes influenced by structural proteins and enzymes compounds, which are responsible for the energy supply of cells. The plastic regulators of hypoxia affected metabolism are the most effective if they are applied before hypoxia attack occurs. Inosine, as the derivative of purine and nucleoside, can penetrate into the actively functioned cells (such as myocytes, hepatocytes and renal tubular cells) and increase their balance of energy [15]. There are evidences about inosine properties to speed up activity of certain enzymes of the Krebs cycle, stimulate syntheses of nucleotides influencing positively on the energy-provided processes, and provide restitution of cell damaging. Thus, preoperative prescription of riboxin increases resisting to hypoxia, which requires the operations either on the heart or the liver. It surely leads to the hypoxia of the organ. If inosine is prescribed during the complicated hypoxic state, so it does not affect urgently, it may be delayed for few days. Because of this, application of riboxin during the acute attack of myocardium has more insignificant affect comparing to regulative and substrative antihypoxic drugs.

Application of the peptide compounds is one of the possible ways of either complete elimination or at least relieve of complications of hypoxia. As for the classification of I. P. Ashmarina (1998) it was called “the constellations of regulative peptides”. The regulative peptides are the class of physiologically active compounds of protein nature, which perform the key role in regulation and
realization of various organism functions in both normal and pathological states [26, 27]. The peculiarities of regulative peptides are polyfunctional and with a cascade-manner of influence leading to prolongation of the peptidergic effects. Referring to the conception about the regulative peptides functional continuum by I. P. Ashmarina there should be involved the peptides compounds united by the principle task for adaptive control during the development of such acute states as hypoxia [3, 4].

Depoteinized blood hemolysate of vealers may be considered as the correcting antihypoxic drugs due to its clinical accessibility. This substance contains a wide range of the low-molecular compounds, such as glycolipids, nucleosides and nucleotides, oligopeptides and amino acids [19, 37, 41]. The drugs made of this hemolysate (like Solkoseril, Solco, Aktovegin and Nicomed) are applied at high doses (for example, 2 g per day) to treat the patients with great variety of illnesses, by the way hypoxia is also in their pathogeneses. There were many curious points observed as these drugs were applied: increasing of the glucose supply level to the brain cells during oxygen deficit, lowering of the cerebral edema manifestation, enhancing of cerebral circulation during occlusion of the magistral vessels, rapid decreasing of hyperglycemia manifestation during treating of diabetes, and etc. Perhaps, one still does not know the effective mechanisms for increasing hypoxia tolerance. However, solcoseryl is considered to be one of the possible mechanisms, because there were pointed certain improvements while applying it: blood circulation delay in case of hypoxia, preventing from myocardium deficiency against carbonic oxid and cyanide poisoning, positive results of the standard reactions on aggression in cardiosurgery and having sustained serious mechanical injuries. Due to these characteristics of solcoseryl, it may be considered as one of the choices for treating systemic, myocardial and cerebral hypoxia (for exapme, a cranio-cerebral trauma, apoplectic and ischemic strokes) [6, 19].

The “Erbisol” drug is thought to be the perspective peptide complex. It is a kind of an innovative type of endogenic regenerative biologic immunomodulatory drugs, which was produced at the Research and Production Centre “Erbis”. Pharmacological activity of the drug is determined by containing of the low-molecular biological active peptides. These peptides activate natural, control system of organism formed by the evolution; these systems are responsible for search and treat of the pathological changes [10, 12]. Erbisol makes the immune system to speed up restoration of damaged cells and tissues and also destroys the abnormal cells and tissues. The principle immune-modulated effect of the drug is shown by influencing a macrophage link, which is responsible for the reparation of the damaged cells and restoration of the functional activity of the organs and cells. Besides, the drug effect is also pronounced by NK-cells (the natural killers, CD3-16+56+) and T-killers (CD3+16+56+). However, the most significant effects of the drug are the improving metabolism and microcirculation at the myocardium, raising the myocardium liability to hypoxia. If the ischemic damages occur, so this drug application is directed to the reparation of cardiac myocytes and restoration of their functions, these all can be used to eliminate prenatal hypoxia [18].

To sum up, the drug therapy of hypoxia requires rational application of the medications for reducing metabolic changes of the organism or for preventing these complications during the posthypoxic period, so called the anti-hypoxic drugs. Application of the modern anti-hypoxic drugs should, at least, correct the energy-supply process and stabilize cellular and subcellular membranes. The efficacy of medicines of the anti-hypoxic type may be realized by the stabilization of membranes, reduction of the oxygen-required level for tissues and energy potential, inhibition of the calcium channels, inhibition of arachidonic acid metabolism and lipid peroxidation. In one word, these drugs should influence on the major effects of hypoxia. This statement is proved by the results of research. The authors of the paper believe that the main strategy to protect the cells from hypoxia effects should be the complex pathogenetic approach for pharmacologic correction of many established complication [1, 4, 21, 31]. Perhaps, up to day the major part of existed anti-hypoxic drugs are still not widely applied to the clinical practice. There is insignificant information (not enough clinical data) about the cardiac-protective and therapeutic effects for prevention and treatment of complications after antenatal hypoxia. The most perspective for performing these functions are the peptide-contained drugs, which are characterized by high effectiveness and a little number of the side-effects. However, the significant pharmacologic and physicologic aspects of their efficacy are still underinvestigated.
References


ЗАСТОСУВАННЯ АНТИГІПОКСАНТІВ В КОРРЕКЦІЇ АНТЕНАТАЛЬНОЇ ГІПОКСІЇ З ПОЗИЦІЙ ЇЇ МОРФО-ФУНКЦІОНАЛЬНИХ ОСОБЛИВОСТЕЙ

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Проблема гіпоксії протягом багатьох років є надзвичайно актуальною і привертає увагу фізіологів і клініцистів враховуючи механізми розвитку різних патологічних станів. Ефекти антенатальної гіпоксії на організм новонародженого залежать від термінів та важкості її впливу, індивідуальної толерантності та терміну внутрішньоутробного розвитку. У зв'язку з тотальною поширеністю серцево-судинної патології вивчення впливу антенатальної гіпоксії на серце, а також можливості її корекції, представляють інтерес з позицій як теорії, так і практики. Одним з можливих шляхів усунення негативних наслідків гіпоксії є використання різноманітних антигіпоксантов, у тому числі пептидних комплексів.

Ключові слова: антенатальна гіпоксія, антигіпоксанти, кардіоміоцити, пептиди, медіатори.

ПРИМЕНЕНИЕ АНТИГИПОКСАНТОВ В КОРРЕКЦИИ АНТЕНАТАЛЬНОЙ ГИПОКСИИ С ПОЗИЦИЙ ЕЕ МОРФО-ФУНКЦИОНАЛЬНЫХ ОСОБЕННОСТЕЙ (ОБЗОР ЛITERATУРЫ)

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Проблема гипоксии на протяжении многих лет является чрезвычайно актуальной и привлекает внимание физиологов и клиницистов с точки зрения механизмов развития различных патологических состояний. Эффекты антенатальной гипоксии на организм новорожденного зависят от сроков и тяжести ее воздействия, индивидуальной толерантности и срока внутриутробного развития. В связи с тотальной распространенностью сердечно-сосудистой патологии изучение влияния антенатальной гипоксии на сердце, а также возможности ее коррекции представляют интерес с позиций как теории, так и практики. Одним из возможных путей устранения негативных последствий гипоксии является использование антигипоксантов различного механизма действия, в том числе пептидных комплексов.

Ключевые слова: антенатальная гипоксия, антигипоксанты, кардиомиоциты, пептиды, медиаторы.