ОГЛЯДИ

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Common mechanisms in the damaging effects of hypoxia and hyperglycemia on neuronal function

Порушення функціонування нейрональних структур є найбільш поширеним ускладненням цукрового діабету. Ці порушення мають багато спільного з ушкоджучими ефектами ішемії/гіпоксії, і тому їх часто класифікують як псевдогіпоксію. В огляді висвітлюються спільні зміни в основних мітохондріальних метаболічних шляхах, що ведуть до накопичення відновлених елементів, генерації реактивних кисневих сполук і вільних радикалів (оксидативний стрес). Відповідні порушення іонного гомеостазу, продукції АТФ та активності іонних помп, що виникають внаслідок цих змін, є характерним наслідком обох патологічних станів; вони призводять до змін збудливості нервових клітин, синаптичної передачі сигналів і відповідних неврологічних синдромів. Важливим є те, що значна група хімічних препаратів (як комерційних, так і експериментальних) ефективно впливають на різні аспекти мітохондріальних функцій, змінюючи їх метаболічні механізми, антиоксидантні системи, синтез АТФ і різні ланки іонного обміну, сприяючи полегшенню порушень нейрональних функцій. В огляді висвітлюються відомі механізми впливу таких препаратів; разом з тим підкреслюється, що у внутрішніх механізмах взаємодії діабетичної гіперглікемії та ішемії/гіпоксії та у розробці засобів їх запобіганню залишається багато питань, які вимагають подальшого експериметального дослідження.

Hypoxia and hyperglycemia are the most frequent reasons for the development of neurological disorders. Obviously, the mechanisms leading to such disorders have many features in common and can interact with each other. Therefore the comparison of changes induced in brain neurons under the action of both factors is definitely of great interest for the understanding the mechanisms of diabetic neuropathic complications.

Systemic changes. One of the general mechanisms involved in the origin of diabetic neuropathy is related to the development of hypoxia/ischemia as a result of occlusive or non-occlusive microvascular changes (the so called "hypoxia/ischemia" hypothesis of the development of neuropathy). Altered vasoregulation is the basic reason for such changes. It leads to reduced nerve blood flow, increased endoneural vascular resistance and endoneural hypoxia [50]. Such changes in the endoneural vascular structures as basement membrane thickening, endothelial cell swelling, platelet aggregation and loss of small myelinated nerve fibers were noted [19]. A correlation between basement membrane thickening and changes in myelinated nerve fiber density has been documented. They correlate with functional deficits in nerve conduction velocity [69]. Peripheral nerves are especially susceptible to reduced oxygen supply induced by increasing intercapillary distance. It has been shown that ischemic lesion in diabetes is confined to the mid-thigh level of the sciatic nerve which contained darkly stained axons [67]. They usually lead to the development of subclinical

peripheral neuropathy with corresponding electrophysiological abnormalities, changes in biosynthesis and histological changes [64]. If ishemia/hypoxia is of brief duration, three consecutive stages can be separated: 1) the initial one with rapidly developing bioenergetic failure; 2) the interval when the bioenergetic state is restored and synaptic activity recovers; 3) the secondary cell death [39]. Long-lasting ischemia can cause the impairment of the blood-brain barrier functioning. The above noted changes in sciatic nerve may be closely connected with the changes in ionic homeostasis and neurotransmitters release [8]. Oxygen supplementation can partly prevent these changes [44].

An important injuring role is played by the state of reperfusion after hypoxia. For such injury the delivery of oxygen to the tissues must be restored [42]. Hypoxia can alters tissue in such a way that after reperfusion it start to generate active substances intimately that has been previously attributed to the lack of oxygen.("oxygen paradox"). Such oxygen reactive species (ROS) can be generated in the mitochondria of the different cells, for instance endothelial cells, neutrophils, macrophages and, probably, neurons. ROS can damage cells either directly or indirectly by oxidizing cellular macromolecules. The state of ischemia/reperfusion induces nerve fiber changes of different severity and, probably, different type than those caused by ishemia alone. They include: endothelial swelling, endoneural edema, demyelination, intramyelinic edema, axonal degeneration and vessel trombosis [53].

Possible mechanisms in reperfusion injury include the generation of free radicals, the activation of polymorphonuclear lymphocytes and the release of cytokines [67]. The same duration of ischemia without reperfusion fails to reveal obvious pathological changes.

All these data indicate that the states of hypoxia/ischemia and hypoxia/reperfusion can both play a systemic role in the development of different nerve changes, including diabetic neuropathy (under hyperglycemic conditions). It should be noted that in normal rats exposure to hyperbaric oxygen also produces metabolic and functional changes in the peripheral nerve system and slowdown in nerve conduction velocity [44].

Changes at cellular level. Under ishemia/hypoxia/anoxia states, changes in neuronal membrane potential of mammalian neurons were recorded as early as in 15-90 sec. Both effects of hyperpolarization and depolarization have been observed in CA1 hippocampal neurons [8]. In insect motor neurons, a 5 min hypoxia state caused a reversible multiphase depolarization (10-25mV). It consisted of an initial transient depolarization followed by a partial repolarization and then a slower phase of further depolarization [12] The first phase of depolarization was characterized by spontaneous prolonged action potentials ("plateau potentials") and increased frequency of inhibitory postsynaptic potentials. The second, slower phase, was marked by the absence of plateau potentials or postsynaptic potentials [12]. In mammalian neurons during the first minutes of hypoxia the main change was a slow rise of external potassium concentration ($[K^+]_0$). The neurons were usually depolarized to -20mV, probably, due to this effect. The threshold for action potential generation was reached, and activation of K^+ channels involved in the repolarization of the action potential enabled further K^+ efflux. This promoted further depolarization by increasing $[K^+]_0$ [21]. Such chain of reactions resulted in a positive feedback loop leading to increasing of $[K^+]_0$. In any case, the response to hypoxia involves K^+ efflux from nerve cells, according to the experiments that have been done with a K^+ channel blocker TEA [8].

Cerebral hypoxia induces also an increase in intracellular Na^+ concentration due to the inhibition of the Na^+/K^+-ATPase. The changes in the activity of Na^+/K^+-ATPase may be due to reduced ATP content in the brain neurons during hypoxia. Survival during hypoxia/ischemia is dependent on the ability of animals to maintain normal ATP levels and normal level of glycolysis [47]. In addition, Na^+/K^+-ATPase is sensitive to low temperature [8] This is might

be one of the reasons why hypoxia is reversible in normal animals, and becomes more grave under hyperglycemia.

It is of interest that in motor neurons of insects cell depolarization which occurs during hypoxia is not reduced by a sodium channel blocker tetrodotoxin (TTX) and results from the influx of Na^+ through TTX-insensitive channels [12].

The changes in the Na^+ permeability are also followed by entry into the cells of Cl^- ions, probably, to prevent an imbalance in intracellular osmolarity. At the same time, Cl^- entry can be due to the activation of γ-aminobutyric acid (GABA) receptors [29, 38]. Under conditions of increased level of inhibitory neurotransmitter the energy consumption of the brain may be reduced [7].

During hypoxia-induced membrane depolarization, the Ca^{2+} entry into the cells will also be changed. It may be due to the changes in the activation of voltage-operated calcium channels (VOCC). In normal conditions, amplitude of calcium transient increases very steeply with depolarization: even a small depolarization induces a nearly maximum response. This reflects the generation of Na^+-driven action potentials. In case if Na^+ permeability is blocked, the dependence of calcium transient amplitude versus membrane potential becomes much smoother, reflecting gradual activation of plasmalemmal calcium channel by depolarization [37]. At different potentials different subsets of plasmalemmal calcium channels are responsible for calcium transient generation. In case of prolonged depolarization that occurs during ishemia/hypoxia, the calcium channels inactivation also will be prolonged. [15,30]. Calcium currents due to high-voltage activated (HVA) Ca^{2+} channels express slow calcium-dependent inactivation, while the inactivation of low-voltage activated (LVA) channels is dependent only on the level of membrane potential [36]?

The changes in the intracellular calcium homeostasis under hypoxia are not entirely clear but may involve changes in the intracellular Ca^{2+} turnover. As the activation of VOCCs is closely connected with the intracellular second messengers and proteins (cAMP, PLA_2, calmodulin, G-proteins, PKC), the dysfunction of intracellular calcium-regulated messenger mechanisms can be also involved in the case of hypoxia [12].

An important question is the influence of prolonged ischemia on the function of intracellular structures; such as endoplasmic reticulum (SR) and mitochondria. Several authors have shown that ischemic state impairs both endoplasmic reticular Ca^{2+} uptake and endoplasmic reticular Ca^{2+} release [61]. It must be mentioned that one of the antagonist of InP_3-sensitive reticulum is *heparin* - a clinically used substance. On the other hand, the Ca^{2+}-induced Ca^{2+} release from the reticulum can be influenced by cardiac glycoside *digitoxin* [37].

Considering possible involvement in toxic effects during hypoxia/ishemia Ca^{2+} ions the possible role of ligand-gated NMDA receptor must be mentioned. Under physiological condition the plasma membrane transporter prevents extracellular glutamate concentrations from reaching neurotoxic levels. Its function is dependent upon the transmembrane gradient of Na^+ ions. During ischemia this transporter can invert its direction, and large amounts of glutamate can be accumulated extracellularly [72]. This mediate rapid increases of $[Ca^{2+}]_i$ that may lead to overloading the neurons by calcium [62]. All these features make NMDA receptors the most prominent ligand-gated channels which can promote the toxic effects of calcium under ischemia/hypoxia. In any case, under the state of insult some authors try to use antiNMDA drugs [8]. Several investigations have also shown changes of $[Ca^{2+}]_i$ in mammalian sensory neurons due to activation of metabotropic receptors during diabetic hyperglycemia [65] and hypoxia [8].

According to the "excitotoxic" theory of hypoxic-ishemic neurotoxicity [8], the AMPA– and kainate (KA) glutamate receptor complex may also have a role in the toxic effect of glutamate. AMPA receptor activation under hypoxia/ishemia has been shown in hippo-

campal and cerebellar Purkinje neurons, while KA (kainate) glutamate receptor complex does not seem to be a major contributor to glutamate-induced Ca^{2+} influx under the state of hypoxia. [6,27]

Glutamate-induced Ca^{2+} influx leads to the activation of a variety of potentially toxic Ca^{2+} events [10,14, 41]. Probably, the functional role of Ca^{2+} entry through NMDA channels is connected with prolonged activation of PKC, which in turn is responsible for the phosphorylation of a series of membrane proteins involved in the long-term changes of neuronal activity. The well known neurodegenerative processes induced by excessive extracellular concentrations of excitatory amino acids during hypoxia/reperfusion result from the substantial and prolonged elevation of cytosolic Ca^{2+} [37]. Some of these effects of glutamate may be modified under hypoxia/hyperglycemia (see below).

AMPA, KA, and NMDA receptor channels can mediate glutamate toxicity by a rapid increase of Na^+ entry which can directly produce neuronal damage [34] or cell swelling [5 may be Reversal of Na^+/Ca^{2+} exchanger or disruption of various Na^+ -dependent transporters may be the side effects of the Na^+-entry [1,6]. Na^+/Ca^{2+} exchanger is electrogenic and voltage sensitive. Under normal conditions the exchanger extrudes Ca^{2+} from the cell. When depolarization occurs it catalyzes Ca^{2+} influx. Under hypoxia/ishemia the exchanger operates in an inverse mode, importing Ca^{2+} into the cell [60] Probably, the functions of glutamate transporter and the sodium-calcium exchanger depend upon the transmembrane gradient of Na^+ ions. It has been shown that changes in $[Na^+]_0$ can exert diverse effects on hypoxia-induced elevations of $[Ca^{2+}]_i$ [71, 72]. Such opposite direction of the activity of the exchanger is involved in the elevation of $[Ca^{2+}]_i$ and thereby in hypoxia-induced brain damage. The results of reversed exchanger activity have been shown for the cortical white matter, and its inhibition protected this structure from hypoxia/ induced injury [60]. At the same time inhibition of the exchanger in the gray matter enhanced toxic effects of glutamate [59]. In the dorsal root ganglion neurons the changes in the activity of the sodium-calcium exchanger may play a less significant role under the state of hypoxia/ hyperglycemia [4].

Both hypoxia/ischemia and an early increase in $[K^+]_o$ can lead to the changes in intracellular and interstitial pH (pH_i and pH_0). Decrease in pH_0 during brain ishemia begins within 15 sec after its onset [24] , with intracellular pH declining to 6,5 – 6,8 [8]. The decrease in $(pH)_0$ has been shown *in vitro* to precede the anoxic depolarization when measured in the same neuron, i.e the intracellular pH changes, probably, start at the time when ATP levels are still high. If this is the case, the oxygen stores in the brain can support normal O_2 consumption for only a few seconds [24]. Once this O_2 is consumed, a stimulation of anaerobic way of glycolysis via the Pasteur effect results in the enhanced lactate production. Lactate, in turn, reduces the amount of intracellular HCO_3^- and concomitantly causes an increase in CO_2 that cannot be removed by blood flow. If ischemia is complicated by preischemic hyperglycemia, a greater acidification occurs (pH=6.1 in neurons and pH=5.5 in glia) [8,55]. However, NMDA receptor ion-channel activity in cultured neurones is inhibited by a decrease in pH_0 [8].

At the same time in the literature there are little support of the view that acidosis by itself is damaging. Several authors found hypoxia is damaging but acidosis is surprisingly benign, and acidic medium can even protect against anoxic damage [8,42].

The most important damaging role of hypoxia is attributed to changes in the cellular respiratory pathways, especially to the impairment of oxidation of NADH to NAD^+ and corresponding elevation of the $NADH/NAD^+$ ratio. This induces an increase of oxygen free radicals production coupled with reduced protection against them ("oxidative stress"). The damaging effect of oxidative stress depends on the balance between the pro-oxidant states and the defense against free radicals [43].

Common metabolic changes. In general, the consideration of glucose as a neurotoxic factor must be wide and include shifts in cytoplasm and mitochondrial redox complexes, changes in electrolyte balance and corresponding deficits in neuronal functions [20]. Similar shifts can also be characteristic of hypoxia, and therefore the evaluation of possible interaction between both states is very important for both the understanding of the basic mechanisms of induced pathological changes and the prediction of possible ways of their treatment.

If the level of hyperglycemia is quite high in type I diabetes mellitus, a state of ketoacidosis during which the metabolic acidosis and pH changes can occur. Diabetic ketoacidosis (DKA) can result from the increased glucagon/insulin ratio and/or the excess of catecholamines, cortisol and growth hormone; the convertion of free fatty acids (FFA) to ketone bodies.. Subsequently loss of bicarbonate and other body buffers and decrease in pH_0 (usually less than 7.2 in diabetic patients), changes in the cellular functions and ion distribution between the intracellular and extracellular compartments. At first a movement of hydrogen ions from the extracellular to the intracellular compartment and of potassium in the opposite direction takes place. Besides, the release of phosphate from cells is noted which reduces the ionized calcium concentration in the serum. A flux of water from the intracellular to the extracellular compartment would be expected to produce a lowering of the serum sodium concentration. Magnesium deficiency in the serum can also be expected. Even if it is not high, it can lead to the impairment of secretion and action of parathyroid hormone, and symptomatic hypocalcemia [33]. In animals with experimental diabetic acidosis (metabolic acidosis) may also develop and affect the intracellular and extracellular ion concentration. A mild state of ketoacidosis has been recorded in rats with streptozotocin-induced diabetes [57]. Whether the changes in serum and intracellular ion concentration are similar to human one is a question. It must be noted that in diabetes the state of ketoacidosis can be corrected by insulin.

The changes in intracellular glucose metabolism in diabetic conditions are most important. During hyperglycemia the $NADH/NAD^+$ becomes increased, like in anoxia; but in this case it is due to the an opposite reaction – an increased rate of reduction of NAD^+ to NADH. That is may be the result of the increased sorbitol pathway activity or anaerobic glycolis. Under hypoxic condition the same changes may be the result of impaired mitochondrial oxidation of NADH to NAD^+[66]. Increased metabolism of glucose via the sorbitol pathway is important for such a change, as this process is coupled to the rate of oxidation of sorbitol to fructose (the second step of the sorbitol pathway). An increase in cytosolic $NADH/NAD^+$ is also observed in tissues exposed to elevated glucose levels at normal tissue pO_2. The hyperglycemia-induced redox imbalance is a characteristic feature of poorly controlled diabetes that mimics the effects of true hypoxia on vascular and neuronal function ("pseudohypoxia"). Cytosolic reducing equivalents are also transported into the mitochondria by electron transport chain, but the increase in cytosolic $NADH/NAD^+$ may or may not be accompanied by the corresponding enhancement in mitochondrial $NADH/NAD^+$. In hypoxia the redox imbalance originates in mitochondria (because of the decreased pO_2), but it also affects the cytosol because reducing equivalents generated in the cytosol can no longer be oxidized in the mitochondria. The same changes in the mitochondrial $NADH/NAD^+$ can occur under diabetic ketoacidosis as a result of increases in the ratio of b-hydroxybutyrate/acetoacetate (so-called keton bodies) These keton bodies receive a long-chain fatty acid as a substrate for their formation in the liver [16].

The effects of both hypoxia and hyperglycemia-induced pseudohypoxia on vascular and neuronal structures are mediated by the imbalance of lipid metabolism and the state of oxidative stress (an increased free radical production and decreased NO production). As it has been shown in the case of pseudohypoxia

and ischemia the described changes in NADH/NAD^+ ratio can lead to the depression of Na^+/K^+- and Ca^{2+}-ATPases, electrophysiological dysfunction, increase in vascular permeability and even DNA damage [66].

In vitro studies on ischemic nerve preparations from diabetic rabbits have also shown that reduced creatine phosphate levels and increased lactate concentrations persisted when the oxygen tension became lower. Such changes represented a loss of total creatine from the tissue. All these features characterize distal symmetric diabetic neuropathy [19].

Probably, the damage of tissues under ischemia/reperfusion is more closely connected with the state of "oxygen paradox" than with acidosis. Its damaging effect can be based on the action of the superoxide radical and other reactive oxygen species which can be generated in the tissue, mitochondria, vascular endothelial cells, neutrophils and macrophages [3]. The oxygen species damage cells directly or indirectly by oxidizing cellular macromolecules, including membrane lipids, enzymes, structural proteins [42, 54]. A relative role of these changes has been evaluated by different investigators in different ways..

In hyperglycemia (diabetes mellitus), a similar state of "oxidative stress" can develop which is characterized by formation of free radicals and subsequent lipid peroxidation (conjugated dienes, lipid hydroperoxides). The possible potential sources for increased free radicals are as follows: hyperglycemic peroxidation, increased mitochondrial leak, catecholamine oxidation and, probably, increased infiltration of the tissue by leukocytes [43].

The effects of oxidative stress depend on the balance between oxidative stress, pro-oxidant status and free radical generation. In sciatic nerve the pro-oxidant status is increased due to an increase of polyunsaturated fatty acid with excessive lipolysis [73]. Another common feature of ischemia/hypoxia and hyperglycemia are the changes in the activity of ATP-dependent ionic pumps, including the Na^+/K^+ and calmodulin-modulated Ca^{2+}-ATPases [8].

Mitochondria as a link for protection against described changes. An important mechanism by which hypoxia can influence the cells are changes in the activity of mitochondria and alteration in ATP synthesis. A decrease in ATP concentration inhibits the Na^+/K^+-ATPase activity leading to a progressive increase in the concentration of cytosolic Na^+ and a concomitant increase of extracellular K^+. Na^+ ions activate mitochondrial Na^+/Ca^{2+} and Na^+/H^+ exchangers resulting in accumulation of Ca^{2+} and protons in the cytosol. Besides, the rise in the intracellular Na^+ may lead to depolarization of the cell membrane. All the events caused by hypoxia are very close to those induced by hyperglycemia. It must be noted that acidosis associated with a low mitochondrial Ca^{2+} concentration, according to some investigators, protects against ischemic injury [18] and prevents the opening of the mitochondria transition pores (PTP).

On the contrary, during reperfusion PTP are opening; that causes cell swelling, collapse of the mitochondrial membrane potential and finally a total inhibition of the mitochondrial function. In addition, a sudden influx of oxygen leads to generation of bursts of reactive oxygen species (ROS) [56, 63], depletion of mitochondrial pyridine nucleotides and glutathione. It must be noted that during ischemia nearly all ATP is produced by the oxidation of fatty acids (this state is also close to that of diabetes mellitus) [51].

There are several substances that can affect different lines of the above mentioned events. They can be subdivided into those acting directly effect on the mitochondria and on those which have an indirect influence. Among the substrates with direct action one group can modulate mitochondrial metabolism by acting on the fatty acid metabolism. Their mechanism of action is connected with the inhibition of fatty acid oxidation which is accompanied by the secondary increase of the glucose oxidation. For instance, the antiischemic substance *trimetazidine* inhibits the activity of the last enzyme involved in fatty acid oxidation – 3-ketoacyl-

coenzyme A thiolase. Concomitantly, it decreases the inhibitory effect on pyruvate-dehydrogenese caused by accumulation of acetyl-CoA [55]. *Ranolazine* limits the effect of palmitoyl-l-carnitine, indirecly stimulating pyruvate-dehydrogenase [49]. Another way to reduce fatty acid oxidation and secondary increase of glucose utilization by mitochondria can be modulation of mitochondrial action by inhibitiing of carnitine palmitoyltransferase (CPT inhibitors *etomoxir,oxfenicine, perhexiline, amiodarone*) [9, 41, 70].

Several pharmacological substances can influence the respiratory chain of mitochondria by acting on their electron transport and, probably, PTP opening induced by Ca^{2+} overload. Some of them (for instance, exogenous coenzyme Q_{10} and its derivative *idebenone*) act as electron shuttle between complex I of the respiratory chain (oxidation of NADPH) and complex II (oxydation of succinate) and cytochrome system of the complex III [22]. Their effects lie in influencing the ATP and phosphocreatine concentration and protectiing creatine kinase during reperfusion [23].

The role of mitochondria in the described events can also be related to the production of reactive oxygen species (ROS). The production of free radicals is a physiological process; however, the cell is effectively protected from them by a whole group of enzymes (glutathione reductase, glutathione peroxidase, superoxide dismutase etc). The degradation of this system both in hypoxia and hyperglycemia leads to a release of superoxide radicals (O_2^-) in the mitochondrial matrix. Such events entail the formation of the hydroxyl radicals (OH^-) and toxic lipid peroxide products. This process can be exacerbated by the rise of mitochondrial Ca^{2+} occurring during reperfusion [2, 11]. A very close situation in the antioxidant system and ROS formation occurs during hyperglycemia and diabetic neuropathy. The drugs that can diminish these changes are plant products of *Ginkgo biloba.* Their action is connected with the inhibition of the complex I and complex III activity [64]. A seleno-organic drug *ebselen* which protect the cells from lipid peroxidation also belongs to this group [52].

Uncoupling agents are also limiting the mitochondrial damage by dissipating the mitochondrial proton gradient. As it is known, high transmembrane gradient of H^+ increases the probability of ROS formation [53]. Induction of a mild proton leak across the inner membrane can lead to an increase in oxygen consumption and lowering of ROS production. At the same time it can also limit Ca^{2+} entry into the mitochondria [53]. It is of interest that proteins with such kind of action (thyroid hormones) can also act as a glutamate toxicity protector.

Protection against hypoxia and hyperglycemic damage can also be also closely connected with the inhibition of the mitochondrial PTP opening. At the molecular level such pore may be formed by the adenine nucleotide translocator (ANT) modulated by cyclophilin (CyP-D). According to some authors,it can also be modulated by a multiprotein structure located at the interface between the inner and outer mitochondrial membrane [13, 25]. They can be opened by Ca^{2+} overload or oxidative stress.

The drug that effectively inhibits PTP formation is cyclosporin A (CsA) which prevents the interaction between CyP-D and ANT [68]. CsA also delays the glutamate-induced mitochondrial depolarization; it may inhibit the Ca^{2+}-calmodulin dependent phosphatase (calcineurin) as well. Unfortunately, pharmacokinetic characteristics are against the clinical use of CsA. However, some drugs act at a micromolar range (*amiodarone, trifuoperazine, cinnarizine)*, and their action on mitochondria may be involved in their antiischemic effect. Of interest might be a group of drugs (*nitrons*) which can also interfere with PTP and show protection against the glutamatergic-induced neural cell death *in vivo* [40, 58].

The second large group of antiischemic drugs is represented with those having an indirect mechanism of action on mitochondria. They modulate mitochondrial ionic homeostasis and affect mitochondrial membrane potential. Such drugs as *diltiasem* and *clonasepam* cause

inhibition of the Na^+/Ca^{2+} exchanger by decreasing Ca^{2+} efflux from the mitochondria. They indirectly modulate the activity of mitochondrial dehydrogenases (pyruvate dehydrogenase, isocitrate dehydrogenase and a-ketoglutarate dehydrogenase). Drugs inhibiting the Ca^{2+} mitochondrial overload are widely used in scientific experiments (for instance, *ruthenium red*). Other substances modulate the mitochondrial activity by decreasing its membrane potential. This type of action is characteristic of the drugs which increase the proton permeability of the inner membrane (uncoupling agents like *2-4-dinitrophenol)* or open K^+_{ATP} channels on the inner membrane of mitochondria (*diazoxide)*. It must be noted that some of K^+_{ATP} channel modulators can cause not only opening of mitochondrial channels but also opening of similar sarcolemmal channels [17, 51]. Some investigators report that activation of the K^+_{ATP} channels can lead to a decrease of the ATP synthesis and hence to release of cytochrome C in the cytosol - two events which have been associated with the induction of apoptosis [13, 26]. It is of interest that the corresponding channels were also shown to be important for the ischemic preconditioning (IPC) response. In heart such mitochondrial channels reduced infarct area as compared to control and preserved postischemic diastolic function. Therefore the group of drugs directed to the correction of K^+_{ATP} channels may also have a cardioprotective role.

Conclusions. Changes in the functioning of neuronal elements are the most common complication of diabetic hyperglycemia. They are comparable with the damaging effect of ischemia/hypoxia, and their mechanisms are often classified as pseudohypoxia, because on the cellular level both demonstrate similar changes in main mitochondrial metabolic pathways, leading to accumulation of reduced elements, generation of reactive oxygen species and free radicals (oxidative stress). Alteration of ionic homeostasis, changes in production of ATP and activity of ionic pumps are consequently characteristic for both pathological states. It is important that a large group of drugs (both commercial and experimental) can act on different mitochondria functions under different pathological conditions. They can influence the metabolic aspects of mitochondria activity, antioxidant systems, ATP generation and different steps of ionic homeostasis. However, many questions about the intrinsic mechanisms of their interaction and correspondingly about possible ways of correction still remain open, and their further clarification is of high importance.

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