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REVIEW

Cellular Mechanisms of Brain Hypoglycemia

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Abstract—Data on intracellular processes induced by a low glucose level in nerve tissue are presented. The involvement of glutamate and adenosine receptors, mitochondria, reactive oxygen species (ROS), and calcium ions in the development of hypoglycemia-induced damage of neurons is considered. Hypoglycemia-induced calcium overload of neuronal mitochondria is suggested to be responsible for the increased ROS production by mitochondria.

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Homeostasis of blood and cellular glucose is an important factor of body functioning as a whole and the nerve system in particular. In a healthy human, the blood level of glucose is maintained in a rather narrow range from 3.1 to 5.21 mM (determination with glucose oxidase) [1]. This important parameter depends, on one hand, on the glucose inflow to blood (mainly from the intestine, liver, and kidney) and, on the other hand, on its outflow to the operating and depositing tissues. These processes associated with glucose transport and metabolism are controlled by a complex of hormonal factors, which may be conventionally divided into three types.

The first type of hormones stimulates glucose utilization by tissues and its deposition as glycogen but suppresses gluconeogenesis and, thus, decreases the blood level of glucose. Insulin is a hormone of this type.

The second type of hormones stimulates glycogen decomposition and gluconeogenesis and, thus, increases the blood level of glucose. This type of hormones includes glucagon, secretin, vasoactive intestinal peptide, and epinephrine.

The third type of hormones stimulates gluconeogenesis in the liver, suppresses glucose utilization by various cells, and, as a result, increases the glucose level in blood. Glucocorticoids and somatotropin–somatomedins are hormones of this type [2].

It seems that glucose metabolism and energy homeostasis of the body are also regulated by the nerve system and special glucose-sensory neurons with action potential depending on the glucose level in the extracellular medium [3, 4]. The glucose-excitable neurons elevate their activity with an increase in the external glucose concentration, and the glucose-suppressible neurons are activated with a decrease in its level. These specialized neurons use glucose and products of its intracellular metabolism for regulation of their activity and release of a neurotransmitter [3-5]. The mechanism of this regulation is not clear, but glucokinase and potassium ATP-sensitive channels are known to be involved in this regulation.

From the extracellular space, glucose is transported by the specific transporter GLUT3 into excitable neurons, where it is phosphorylated by glucokinase. This enzyme is one of main regulators of ATP synthesis and is located near mitochondria under the cytoplasmic membrane containing ATP-sensitive potassium channels. The produced ATP binds with these channels and inactivates them, and this results in depolarization of the cell membrane, entry of calcium into the cytoplasm through potential-dependent channels, and increase in neuronal activity. Local changes in the glucose concentration near axonic terminals can also initiate these processes and cause neurotransmitter release. Glucose-sensitive neurons organize and respond to changes in a number of hormonal, metabolic, transmitter, and peptide signals

Abbreviations: AMPA) amino-3-hydroxy-5-methyl-4-isoxazole propionate; NMDA) N-methyl-D-aspartate; PARP-1) poly(ADP-ribose)-polymerase-1; ROS) reactive oxygen species.

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involved in the regulation of energy homeostasis and other biological functions [4].

A decrease in glucose blood content below a minimal level that the body is adapted to, or hypoglycemia [6], is especially dangerous for cells of the central and peripheral nerve system even under conditions of normal partial oxygen pressure. Hypoglycemia and glucose deprivation as its extreme expression are very interesting, because in the nerve system glucose is not only the main source of energy necessary for its functioning, but also a substance capable of preventing glutathione oxidation and reducing the damage to mitochondria caused by glutamate neurotoxicity [7]. It should be noted that disorders in the transport and metabolism of glucose are an important signal for triggering the apoptotic cascade [8].

Causes of hypoglycemia vary greatly. In particular, this state can arise because of starvation, development of tumors from the insulin-producing pancreatic islet cells, and in children because of a decrease in the secretion of ACTH or growth hormone that promote an increase in blood sugar level. Hypoglycemia can also be caused by injection of insulin in an amount above the therapeutic dose, which strongly lowers the glucose level in blood. This phenomenon is often observed in patients treated with high doses of insulin. The development of hypoglycemia is associated with a decrease in the glucose inflow to the brain, which can cause convulsions, coma [9], and even death. Therefore, studies on damages of the central nerve system under conditions of hypoglycemia are very important for clinical medicine. According to data of electroencephalography, decrease in the blood glucose level below 2 mM is associated with a decrease in brain activity, which can recover on normalization of the blood glucose level. A decrease in the glucose level below 1 mM results in ATP decrease in the brain tissue and irreversibly damages the central nerve tissue [10].

Functioning of the brain is much more dependent on glucose inflow from blood compared to other organs. First, this is explained by small reserves of this carbohydrate in the brain tissue compared with high rate of its consumption. If the entire glucose in the brain is used only for oxidation, its stores can be completely exhausted within 4-6 min [11]. Nerve tissue is characterized by a very high level of glucose consumption: it utilizes 70% of the glucose produced in the liver and released into the blood [11]. Exhaustion of glucose stores leads to a decrease in the glycolysis rate and, as a result, to lowering the entry of pyruvate into the tricarboxylic acid cycle in mitochondria and a decrease in the ATP generation by these organelles. Hypoglycemia is associated with a rapidly appearing disturbance of ionic balance in the cytoplasm of neurons, where the concentration of Ca^{2+} increases and that of K^+ decreases. Under conditions of long-term hypoglycemia, oxidative stress develops, excitatory amino acids and adenosine are released, their receptors and poly(ADP-ribose)-polymerase-1 (PARP-1) are activated (with inhibition of glycolysis as a consequence), and the redox potentials of the NAD/NADH, GSG/GSSG, NADP/NADPH couples are shifted toward the oxidized forms. All these processes are terminated by necrosis or apoptosis of neurons. Such severe pathological states of the nerve system, as ischemia, hypoglycemia, and Alzheimer's disease [12-14] accompanied by necrotic and apoptotic death of neurons are indicated by a common sign: the progress of these diseases is associated with the intracellular glucose insufficiency as a result of its decreased concentration in the intercellular medium or disorders in the transport into the cell.

Glucose is transported into the brain across the blood–brain barrier mainly by specific carriers, and only 5% of its total amount is transported by passive diffusion [11]. Therefore, the glucose starvation of neurons can be caused not only by a decrease in the blood contents of glucose but also by disorders in functions of these carriers. In particular, in Alzheimer's disease the normal functioning of the glucose transporter GLUT3 in neurons is disturbed because of β-amyloid accumulation in the brain [12, 15]. It is suspected that the death of neurons in lateral amyotrophic sclerosis and schizophrenia is also accompanied by disorders in glucose transport into neurons [8, 16].

Moreover, glucose plays an important role in the central nerve system as a precursor (along with glutamine) of glutamate, which is the most widespread excitatory neurotransmitter [17].

CONTRIBUTION OF EXCITATORY AMINO ACIDS TO DEGENERATION OF NEURONS IN HYPOGLYCEMIA-INDUCED DAMAGE

Changes in the contents of excitatory neurotransmitters and their precursors in nerve tissue have been found in different models under conditions of hypoglycemia. It is now an axiom that hyperstimulation of glutamate receptors by excitatory amino acids is a leading pathogenic factor of damage to neurons during the development of various neurodegenerative diseases. As a neurotransmitter, glutamate can interact with N-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) membrane receptors. The specific agonists of these receptors are, respectively, N-methyl-D-aspartate, kainic acid, and AMPA [18, 19]. Quinolinic acid can also activate NMDA receptors [20]. Each type of these receptors is associated with a specific ionic channel. In addition to the above-listed ionotropic subtypes of glutamate receptors, there is a group of metabotropic receptors activating the production of secondary transmitters [19]. The different glutamate receptors contribute differently to the progress of neurocytotoxic impact on neurons. It seems that a princi-

pal role in the death of neurons belongs to NMDA receptors, because their inhibition by selective antagonists prevents nearly completely the destruction of neurons [21-23]. Hyperactivation of ionotropic glutamate receptors results in disorders in ionic balance of the cytoplasm of neurons, morphofunctional disturbances of their mitochondria, and, finally, their death [24].

The involvement of endogenous excitatory amino acids in development of acute pathological states of the central nerve system is witnessed by sharply increased extracellular concentrations of glutamate and aspartate in brain tissue [21, 25]. The accumulation of these neurotransmitters outside the cells is considered to be a result of both their enhanced release from the nerve terminals and disorders in functioning of ATP-dependent systems of the re-uptake of these transmitters by the cells [26].

As shown in the table, in all models hypoglycemia of nerve tissue is associated with an increase in the extracellular aspartate level, and accumulation of quinolinic acid in the *corpus striatum* of rats was found in insulin-induced coma [27, 28]. So far, quinolinic acid has not been shown to function as a transmitter, but this substance is an agonist of the NMDA-subtype of ionotropic glutamate receptors and can be toxic for glutamatergic neurons. Data on the glutamate level in brain tissue under conditions of hypoglycemia are inconsistent. Accumulation of this neurotransmitter was shown in brain cortex of 1-2-week-old piglets with insulin-induced coma [29], in cerebrospinal fluid of newborns with hypoglycemia [30], and in culture of hippocampus tissue with iodoacetate-inhibited glucose metabolism [31]. In other works, a reduced level of this neurotransmitter or its precursor glutamine was shown in hypoglycemia in various structures: forebrain culture, retina, and *striatum* [32-35]. The authors suggest that this decrease in the glutamate and glutamine contents is associated with the glucose deficiency-caused increase in the expenditure of amino acids in deamination reaction and their subsequent utilization in the tricarboxylic acid cycle [32, 33]. Note that a decrease in the glucose level in the culture medium increased the neuron sensitivity to toxic effect of glutamate [36]. The increased sensitivity was retained for a long time after the recovery of glucose inflow to the cascade of glycolytic reactions [37]. This cascade seemed to be caused by PARP-1 activation in hypoglycemia. During catalysis, PARP-1 utilizes cytosolic NAD, which is a cofactor of glycolysis. Therefore, the hypoglycemia-induced activation of PARP-1 can suppress glycolysis, even upon the recovery of the glucose level in the cell [38, 39]. In turn, the activity of PARP-1 is determined by phosphorylation of this enzyme by ERK1/2 (External signal Regulated Kinases 1/2). An increase in the ERK1/2 activity can be triggered by reactive oxygen species (ROS), damage of to DNA, or a p53-independent mechanism [40].

PARP-1 is also activated by a hypoglycemia-induced vesicular release of zinc ions from nerve terminals and its accumulation in the body of postsynaptic neurons. The activation of PARP-1 by zinc ions is supposed to be associated with the ability of zinc to stimulate ROS production by mitochondria of neurons [41]. Possibly, ROS

Effect of hypoglycemia on the contents of excitatory neurotransmitters and their precursors in nerve tissue

Model	Structure or tissue	Changes in the contents of agonists of glutamate receptors or their precursors	Source
Tissue culture, hypoglycemia	rat telencephalon	aspartate↑, glutamine↓, glutamate↓	[32]
Glucose deprivation	isolated eye retina	aspartate↑, glutamate↓, glutamine↓	[33]
Brain sections under conditions of hypoglycemia	rat hippocampus	glutamate↓, glutamine↓	[34]
Dissociated tissue culture, inhibition of glycolysis by iodoacetate	hippocampus of rat embryos	glutamate↑ (a slight increase)	[31]
Neonates with hypoglycemia	human cerebrospinal fluid	glutamate↑, aspartate↑	[30]
Insulin-induced coma	rat striatum	quinolinic acid↑	[27, 28]
—"—	rat hippocampus and striatum	aspartate↑, glutamine↓, glutamate↓	[35]
—"—	cortex of hemispheres of piglets	glutamate↑, aspartate↑	[29]

involved in this process initially induce ERK1/2, which then phosphorylates PARP-1.

The contribution of glutamate receptor hyperactivation to neurodegenerative processes in hypoglycemia was also supported by experimental data obtained in animals or tissue culture: injection of antagonists of NMDA receptors protected neurons against damage. In the insulin-induced coma of animals, an antagonist of NMDA receptors considerably decreased the damage of neurons [42-44]. Similar data were obtained in a culture of brain neurons. Blockade of NMDA receptors prevented the death of neurons induced by glucose deprivation [45-48].

Inhibition of other subtypes of glutamate receptors did not prevent the death of neurons under conditions of hypoglycemia [45-47]. However, when hypoglycemia was modeled by iodoacetate-induced inhibition of glycolysis, the data were ambiguous. In this model, the blockade of NMDA receptors prevented the iodoacetate-caused death of the hippocampal neurons in culture [31], whereas in retina cultures such a blockade failed to protect the cells [49]. Moreover, NMDA receptors were shown to be unimportant for neuron depolarization in hypoglycemia [50]. Under conditions of glucose deprivation of neurons, the removal of glutamine (the precursor of glutamate synthesis) from the culture medium aggravated the damage to neurons and decreased the protective effect of NMDA antagonists [48]. Thus, notwithstanding considerable advances in understanding of the role of glutamate receptor in mechanisms of neuronal damage in hypoglycemia, the problem needs further studies.

INVOLVEMENT OF ADENOSINE IN NEURON DEGENERATION UNDER HYPOGLYCEMIA-INDUCED DAMAGE

An important role of endogenous adenosine was recently revealed in disturbance of neurotransmission in hypoglycemia [51, 52]. Turner et al. observed that hypoglycemia was associated with an increased release of adenosine from cortical neurons, changes in $[Ca^{2+}]_i$, and expression of the proapoptotic enzyme caspase-3 correlated with a decrease in neuron viability. Early disorders in $[Ca^{2+}]_i$ and activation of the apoptotic marker caspase-3 were completely prevented by treatment with antagonists A(1) of the adenosine receptor (A(1)AR) [53]. Activation of this type of receptors can inhibit various types of neurons on the postsynaptic level due to induction or modulation of ion currents and on the presynaptic level through reducing the release of neurotransmitters. In the A(1) receptor signalization, G-proteins coupled with ion channels, adenylate cyclase, or phospholipase are involved [54]. Further studies of these authors showed that A(1)AR plays an important role in development of hypoglycemic damage of neurons. It was shown on hippocampal sections from young mice that a decrease in the glucose concentration in the medium caused severe damage of the neurons. The treatment of the sections with an antagonist of A(1)AR diminished the hypoglycemic damage, whereas agonists increased it. Moreover, insulin-induced hypoglycemia in A(1)AR(−/−) mice did not cause cell damage, but in A(1)AR(+/−) mice a pronounced damage of the neurons was recorded [55]. Although these observation show that A(1)AR activation is involved in the hypoglycemia-induced damage of the brain, the true role of these receptors in this process is unclear, because in the study [56] agonists and not antagonists of A(1)AR displayed a protective effect under conditions of glucose deprivation.

CHANGES IN ION BALANCE IN BRAIN TISSUE UNDER HYPOGLYCEMIA

A set of recent data demonstrates that brain hypoglycemia is associated with a massive depolarization, release of potassium ions from cells, and a rapid decrease in the level of intercellular calcium. On a model of hypoglycemic coma of rats, the extracellular Ca^{2+} level was shown to decrease from 1.2 to 0.07 mM even for 0.2 min of the coma and to 0.02 mM for 15 min [57]. Under conditions of hypoglycemic coma, the extracellular K^+ level changed from 3.2 ± 0.2 to 55 ± 5 mM [58]. These disorders in the extracellular ion balance were reversible; thus, the level of extracellular K^+ became normal even 5 min after the coma was terminated by injection of glucose into the animals. The extracellular Ca^{2+} level normalized more slowly. Five minutes after the coma was terminated, it recovered to $27 \pm 10\%$ of the control level and 15 min after to 76% [57].

Note that blockade of the NMDA receptors did not prevent these changes in the extracellular ion contents in hypoglycemia. The authors of [58] concluded that the activation of NMDA receptors was not important for hypoglycemic depolarization. The decrease in the extracellular calcium level suggested an increase in the intracellular calcium, and this was confirmed experimentally on a model of insulin-induced hypoglycemia in cats. In this study, free cytosolic calcium was measured in cortex cells with the fluorescent calcium probe indo-1. Hypoglycemia induced a significant increase in the intracellular calcium level and its rapid recovery upon the injection of the animals with glucose [59]. Similar data were also obtained in a culture of hippocampal neurons. As in the experiments on animals, hypoglycemia induced an elevation of the intracellular calcium, which was not recorded during cell incubation in calcium-free medium. The findings of this work suggested that under conditions of hypoglycemia, calcium ions could enter the neurons through the plasma membrane [60, 61]. However, the pathways of calcium ion entry in neurons are not identified more accurately.

Some authors believe the increase in intracellular calcium in hypoglycemia to be associated with its entry in the cell through NMDA channels and its release from the endoplasmic reticulum [31]. It seems that the calcium ion contents in the neuron can increase also as a result of a decrease in its ATP-dependent release from the cell because of ATP deficiency arising in hypoglycemia.

No doubt, calcium overload of neurons in hypoglycemia contributes significantly to the death of neurons. A decrease in the level of extracellular calcium or its binding by a chelator (BAPTA-AM) markedly increased the survival of cultured hippocampal neurons upon inhibition of glycolysis by iodoacetate [31]. A long-term decrease in the level of intracellular potassium, as well as an increase in the level of extracellular calcium, can affect the post-hypoglycemic viability of neurons. The decrease in the level of intracellular potassium can lead to activation of caspases [62] and further to a programmed cell death (apoptosis) [63].

The progress of hypoglycemia in hypoglycemic coma in rats was associated with a rapid decrease in pH by 0.1 unit within the first minutes, but then pH increased by 0.2 unit [64]. The elevation of pH in hypoglycemia occurred not only in the extracellular space, but also inside the cells (the cytoplasmic pH). The increase in cytosolic pH under hypoglycemia seemed to be associated with a lactate deficiency arising in the cells [65] and also with oxidation of endogenous amino acids and accumulation of ammonia [65-68].

CHANGES IN THE FUNCTIONAL STATE OF MITOCHONDRIA IN HYPOGLYCEMIA

The major function of mitochondria is oxidation of organic compounds (fatty acids and pyruvate) and utilization of the energy released from oxidation of these compounds for generation of the proton-moving force in mitochondria, which is used for the synthesis of ATP. Exhaustion of glucose stores in hypoglycemia lowers the glycolysis rate and the entry of pyruvate into the tricarboxylic acid cycle of mitochondria with a resulting decrease in the membrane potential in the mitochondria and the ATP generation by them [33, 61, 69]. It seems that decrease in the mitochondrial membrane potential in neurons in hypoglycemia is significantly associated with the increase in the level of intracellular calcium, because cultivation of neurons in a Ca^{2+}-free medium prevents the increase in the intracellular $[Ca^{2+}]$, dysfunction of mitochondria, and damage of neurons subjected to hypoglycemia [61].

The mechanism of mitochondrial deeenergization caused by hypoglycemia is actively discussed in the literature. Some authors believe that hypoglycemia induces mitochondrial nonspecific permeability (MNP) [70, 71]. This was indirectly confirmed by data obtained on rats with insulin-induced hypoglycemia: the activities of caspase-3 and similar enzymes were increased in the hippocampal denticulated fascia and in the CA1 region, which is not observed in the presence of cyclosporin A [71]. Moreover, pretreatment with cyclosporin before the insulin-induced hypoglycemia considerably reduced the damage of rat brain. The hypoglycemic insult was associated with mitochondrial swelling, but in the cyclosporin-treated animals the mitochondria retained their normal state during both the hypoglycemic insult and after it. Studies on the kinetics of mitochondrial swelling isolated from the hippocampus revealed that cyclosporin A inhibited Ca^{2+}-induced MNP. The authors suggested that mitochondria and MNP may be involved in the development of hypoglycemia-induced damage of rat brain [70].

It should be noted that various growth factors can markedly reduce the damaging effect of hypoglycemia on neuronal mitochondria. As shown in [61], nerve growth factor (NGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor II (IGF-II) prevented a disturbance of $[Ca^{2+}]_i$ homeostasis, a decrease in the mitochondrial transmembrane potential, and protected hippocampal neurons against hypoglycemic damage, but were unable to prevent hypoglycemia-caused decrease in ATP level. The authors emphasized that disorders in $[Ca^{2+}]_i$ homeostasis could be a crucial event resulting in mitochondrial damage and neuronal death caused by reduced energetic functions of their mitochondria. Prevention of disorders in $[Ca^{2+}]_i$ homeostasis seems to be a general mechanism responsible for the neuroprotective action of growth factors.

HYPOGLYCEMIA AND OXIDATIVE STRESS

It has been recently shown that hypoglycemia induces oxidative stress in nerve tissue [72] and increases the production of ROS in cultured neurons and cells of neuronal origin [73-75]. In the cells, ROS are mainly generated by the mitochondrial electron transport chain, which produces these active molecules even under conditions of normal metabolism [76, 77]. Therefore, mitochondria have occupied a central place in studies on mechanisms of ROS production under hypoglycemia. After 2 h of insulin-induced hypoglycemia, the mitochondria isolated from the brain cortex of newborn pigs increased by 60 and 100% the production of superoxide-anion radical and hydrogen peroxide, respectively, than the mitochondria of the control animals [78]. However, mitochondria are not only principal cellular organelles initiating oxidative stress of the cell, but also targets of this pathologic process. The same authors recorded increased lipid peroxidation in brain mitochondrial membranes after hypoglycemia, and this did not occur in synaptosomes or nuclear membranes. Hypoglycemia also caused

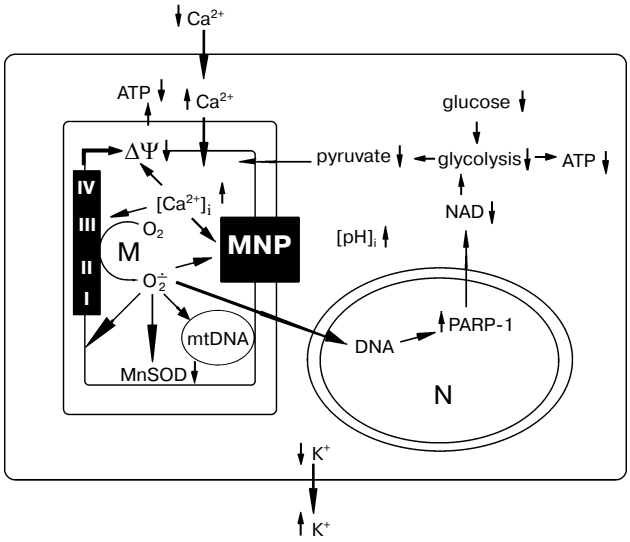
fragmentation of mitochondrial DNA (mtDNA). The authors concluded that the damage to mitochondria was caused by an increase in the ROS production, which was the early event in the development of hypoglycemic damage of the brain [79].

The mechanism of the increase in the mitochondrial generation of ROS in neurons under conditions of hypoglycemia is still quite unclear. The protein GRP75 mainly located in mitochondria is involved in the regulation of ROS production in hypoglycemia. Elevated expression of this protein increased the survival of PC12 line cells under conditions of hypoglycemia but did not influence the decrease in the ATP level and mitochondrial membrane potential [80]. The ROS generation in neurons seems to be also associated with the nonspecific permeability of the mitochondrial membrane. MNP induction is accompanied by an increase in ROS generation, but the mechanism is still not elucidated [81-83]. The mechanism of increase in ROS generation by mitochondria in neurons under conditions of hypoglycemia may be similar to the mechanism of ROS production in neurons under conditions of glutamate toxicity, with the calcium overload of neuronal mitochondria as an important step [84]. This hypothesis is indirectly confirmed by similarity of intracellular pathophysiological processes in neurons under conditions of both hypoglycemia and glutamate toxicity. Both glutamate and hypoglycemia induce in neurons calcium overload, activation of PARP-1, and lowering of the mitochondrial membrane potential and of ATP level. Moreover, the toxicity of excitatory amino acids seems to be a component of the hypoglycemic damage of nerve tissue. Note that zinc ions are accumulated after hypoglycemia in neurons in some brain structures. Thus, in the hippocampal CA1 cell bodies [41] zinc ions interacting with mitochondria can induce production of ROS [85, 86].

The excessive level of ROS in the cells can arise not only because of their increased generation in the electron transport chain of mitochondria, but also because of a decrease in the activity of antioxidant systems. The latter statement has been already confirmed experimentally. A pronounced increase in the activities of mitochondrial catalase and manganese superoxide dismutase has been recorded in different brain regions under conditions of hypoglycemia [14].

The data presented in this review on disturbance in the intracellular homeostasis of neurons in hypoglycemia can be generalized in the following scheme.

A massive depolarization of neurons is one of the first events occurring in brain hypoglycemia, the release of potassium ions from the cells, and a rapid decrease in the intercellular calcium level as result of its entry into the neurons through potential-dependent, glutamate, and, possibly, other channels. The reduced influx of glucose in glycolysis causes a decrease in the production by this enzymatic system of ATP and pyruvate, which is the main energy substrate for neuronal mitochondria. The pyruvate deficiency forces the mitochondria to use endogenous amino acids as substrate, and this leads to accumulation of ammonia and elevation of intracellular pH values. The incoming excessive calcium ions are transported into mitochondria at the cost of their membrane potential energy. The accumulation of calcium ions inside the mitochondria increases the generation of ROS by these organelles. ROS cause the damage of mitochondrial DNA and membranes, and decrease in activities of various mitochondrial enzymes, in particular those responsible for defense against ROS (e.g. superoxide dismutase). The decrease in the pyruvate level in the cell and calcium overload of the mitochondria result in a decrease in ATP synthesis by them. The continuous production of ROS by the mitochondria, especially on the background of elevated level of free intramitochondrial calcium, can itself induce MNP in the inner membrane of the mitochondria leading to their complete deenergization. Moreover, ROS can also affect nuclear DNA that causes a rapid activation of PARP-1 involved in DNA repair. However, the intensive functioning of PARP-1 results in a rapid exhaustion of NAD, which is necessary for various processes, in particular, glycolysis. Therefore, upon normalization of the glucose influx into neurons after hypoglycemia, the glycolysis cycle cannot rapidly recover its activity because of NAD deficiency.



Scheme of disorders in neuron intracellular homeostasis under conditions of prolonged hypoglycemia. M) mitochondrion; N) nucleus

This review is dedicated to the memory of our colleague N. A. Andreeva, Ph.D.

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