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Mitochondrial Dysfunction of Neurons Under the Toxic Effects of Arsenic and Aluminum

Fliuryk SV[1]*, Dremza IK[2], Bon LI[3] and Burak IN[4]

[1]*Grodno State Medical University, Assistant of the Department of Pathological Physiology named D.A. Maslakov Grodno State Medical University, Belarus*

[2]*Grodno State Medical University, PhD of Biological Sciences, Associate Professor, Associate Professor of the Department of Pathological Physiology named after D.A. Maslakov, Belarus*

[3]*Grodno State Medical University, PhD of Biological Science, Associate professor of Chair of pathological physiology of the name of D.A. Maslakov, Belarus*

[4]*A 3rd year student of the group number 1 of faculty of General Medicine Grodno State Medical University, Republic of Belarus*

***Corresponding author:** Fliuryk SV, Grodno State Medical University. Assistant of the Department of Pathological Physiology named D.A. Maslakov Grodno State Medical University, Belarus

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SUMMARY

Introduction: Exposure to neurotropic chemicals (aluminum, arsenic, etc.) as a result of pollution of environmental objects can cause disruption of the bioenergetics of nerve cells. The purpose of the study is to analyze and summarize the literature data on the mechanisms of the effects of arsenic and aluminum on the structure and functions of neuronal mitochondria. Sources of Data: literary sources reflecting the mechanisms of action of these neurotoxicants on neuronal mitochondria.

Methods: The basis of this study was a review of the literature on this topic.

Results: The effect of arsenic compounds on nerve cells causes mitochondrial dysfunction due to the activation of oxidative stress, an increase in the intracellular level of Ca^{2+}, a decrease in the mitochondrial membrane potential and the level of calpain 1, and aluminum compounds increase the formation of ROS and disrupt the activity of cytochrome coxidase and the energy-producing function of mitochondria in various types neurons.

Conclusions: The presented information deepens our knowledge about the mechanisms of neuronal bioenergetics disorders under the influence of arsenic and aluminum compounds, which is the basis for further research in order to develop effective methods of prevention, detoxification and antioxidant therapy for arsenic and aluminum poisoning and to implement the results obtained in practical healthcare.

Introduction

Mitochondria play a key role in physiological and pathological processes in the cell, including energy metabolism, calcium homeostasis, lipid biosynthesis and apoptosis [1]. The main function of mitochondria is the synthesis of ATP, which is achieved by coupling oxidation and phosphorylation. The oxidation of energy substrates is carried out in the mitochondrial matrix and is associated with the formation of NADH+, which, in turn, transfers electrons and protons to the electron transport chain (ETC) of the inner mitochondrial membrane. ETC consists of four main metal-containing protein complexes of electron and proton carriers

(I-IV). Electrons are transferred longitudinally to the membrane from complex I to complex IV and then to molecular oxygen, while protons move transversely into the intermembrane space, which leads to the formation of a proton gradient, the energy of which is used in the ATP synthase complex (complex V) for ATP resynthesis.

During the functioning of the mitochondrial ETC, due to the so-called "leakage" of electrons to molecular oxygen, a by–product is formed - the superoxide-anion radical ($O^{2\cdot-}$), which is unstable and with the participation of mitochondrial superoxide dismutases (MSD) quickly turns into hydrogen peroxide (H_2O_2), which, in turn, is transformed into other reactive oxygen species (ROS) in the cytoplasm of the cell. Excessive formation of ROS in mitochondria can cause oxidative stress, oxidative damage to ETC complexes, mitochondrial membranes, as well as cellular proteins, lipids and DNA. The human brain at rest uses about 20% of the ATP produced by the mitochondria of the body, while it accounts for only about 2% of body weight, and the main amount of energy produced by neurons is spent on maintaining the membrane potential. An important function of mitochondria is the deposition of calcium ions, which mediate the dynamics of neurotransmitter release in neurons. It is known that mitochondrial dysfunction of brain neurons is one of the causes of a number of neurodegenerative diseases: Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), autism and amyotrophic lateral sclerosis (ALS) and other forms of neurodegeneration [2].

The human body can be exposed to toxic effects of various chemical elements, including heavy metal ions such as arsenic (As), aluminum (Al), cadmium (Cd), lead (Pb), copper (Cu), manganese (Mn), etc. Being natural components of the earth's crust, they enter the biosphere as a result of various human activities. The main ways of their entry into the human body are the gastrointestinal tract, lungs and skin. Brain neurons are able to effectively neutralize the negative effects of low concentrations of these substances, but their long-term intake into the body can lead to accumulation in brain tissue and cause mitochondrial disorders with subsequent neurodegeneration. Depletion of ATP reserves and increased formation of ROS can ultimately lead to neuronal death through apoptosis and/or necrosis [monograph]. The metabolism of neurotoxic metals in the brain and their role in the etiology of various types of neurodegeneration have recently been actively studied, as evidenced by a large number of works devoted to this problem. However, the effects of various metals and the specific mechanisms of their damaging effect on mitochondrial processes in neurons have not been fully elucidated. In this review, we analyzed the latest data on the mechanisms of mitochondrial dysfunction in in arsenic and aluminum-induced neurotoxicity.

Arsenic (As) is a widespread toxic metalloid that poses a danger to approximately 200 million people in more than 24 countries worldwide. It can be absorbed into the blood through the skin, gastrointestinal tract and enter the body when breathing. In animals and humans, As can accumulate in various organs, including the kidneys, lungs, liver and spleen [3]. Its accumulation in various areas of the brain is especially dangerous [4]. *In vivo* studies have shown that excessive exposure to arsenic compounds causes increased apoptosis of neurons, leading to impaired development of the nervous system in ontogenesis and cognitive functions in adult rats [5]. Epidemiological studies have also shown that in adults and elderly people living in rural areas, arsenic levels of 3–15 μg/l in water are negatively correlated with cognitive function and memory, which indicates its neurotoxicity and is a risk factor for AD [6]. However, the mechanisms of As-induced neurotoxicity remain unclear to date. To date, As-induced neurotoxicity has been associated with overproduction of amyloid Aß, inflammatory reactions [7], thiamine deficiency, oxidative stress, impaired neurotransmitter formation [8], impaired cytoskeletal gene expression, mitochondrial dysfunction, and impaired cholinesterase activity. Mitochondrial dysfunction plays a key role among these pathogenetic factors of As-neurotoxicity.

In vitro experiments, numerous studies have shown that arsenic can have an adverse effect on mitochondrial functions. Thus, Haga, et al. [9] showed that treatment of A172 cell culture with arsenic trioxide (As_2O_3, 50 μM for 8 hours) led to the formation of mitochondrial aggregates. Subsequently, other researchers also showed that treatment with sodium arsenite ($NaAsO_2$) or As_2O_3 caused mitochondrial dysfunction by increasing intracellular Ca^{2+} levels, reducing mitochondrial membrane potential (MMP) or calpain 1 levels in N2A cell culture, SHSY-5Y cells, primary astrocytes and rat neurocytes. Moreover, *in vivo* studies have also confirmed the critical role of oxidative stress and mitochondrial dysfunction in arsenic-induced neurotoxicity. It is well known that mitochondria is the main source and main target of ROS [10]. Oxidative stress induced by as compounds is closely related to mitochondrial dysfunction. Thus, an increase in ROS levels and increased lipid peroxidation after exposure to $NaAsO_2$ for 28 days was accompanied by a decrease in the activity of mitochondrial manganese-dependent superoxide dismutase (MnSOD) and catalase (CAT) in the mitochondrial fraction of different brain regions (including the striatum, hippocampus and frontal cortex) of rats. In addition, the activity of MnSOD, CAT, glutathione peroxidase (GP), glutathione reductase (GR) and glutathione transferase (GT) decreased in the mitochondrial fraction of the rat brain under sub chronic exposure to As. Moreover, various researchers have shown that as directly disrupts tissue respiration through oxidative stress.

As-induced oxidative stress inhibited the activity of complexes I, II, and IV in rat brain mitochondria. These results have been confirmed earlier by other laboratories. Thus, arsenic reduced the activity of mitochondrial respiration and phosphorylation in the mitochondria of the brain, which ultimately led to a decrease in ATP synthesis. In addition, sub chronic exposure to low as levels reduced the expression of mitochondrial complexes II, IV and V genes in the brains of mice.

Thus, the sources of literature analyzed by us showed that the mechanisms of oxidative stress play a key role in As-induced neurodegeneration, leading to disruption of the energy-producing function of mitochondria. Numerous studies have shown that the most important mechanism of as neurotoxicity in the CNS is mitochondrial dysfunction. It includes a violation of Ca^{2+} homeostasis, a decrease in membrane potential, mitochondrial membrane permeability, and mitochondrial respiration [11], which ultimately leads to damage and death of neurons along a mitochondrial-dependent pathway. Aluminum (Al) is a ubiquitous metal on Earth. It can be readily absorbed through skin contact, inhalation and ingestion. Aluminum sulfate is widely used for water purification, in the food and pharmaceutical industries, in medicine and other industries, which creates conditions for its entry into the human body. Numerous studies show that Al can accumulate in various organs of mammals, including bones, kidneys, lungs, liver, spleen, and brain [12]. A growing body of literature also suggests that Al accumulation in various brain regions can cause symptoms of neurotoxicity and learning impairment [13]. Rodent studies have shown that chronic Al exposure leads to Al accumulation in the hippocampus and causes behavioral disorders [13]. Other studies have shown that Al causes degeneration of neurofibrils. Epidemiological studies have shown that Al is considered as a potential risk factor for the development of neurodegenerative diseases such as AD, PD, HD, etc. [14].

Some researchers suggested that mitochondrial dysfunction may play a crucial role in Al-toxic effects, including neurotoxicity [15]. Rao, et al. [16] showed that, after treatment with Al, ROS generation in glial cells increased, mitochondrial respiratory activity and reduced glutathione reserves decreased within 24 hours. Other researchers have also shown that Al exposure increased ROS production and disrupted cytochrome-c-oxidase activity and the energy-producing function of mitochondria in various types of neurons, including the PC12 line, SH-SY5Y neuroblastoma cells [17], and rat cerebellar granule cells [18]. Mitochondrial dysfunction has also been observed in *in vivo* studies. Acute exposure to 50 μM aluminum maltonate via intracisternal injection caused the release of cytochrome c (cyt-c) from mitochondria, which was accompanied by a decrease in the level of anti-apoptotic proteins of the Bcl-2 family and activation of pro-apoptotic proteins: Bax, p53, effector ecaspase-3, as well as DNA fragmentation in rabbit brain mitochondria. Subsequently, Kumar, et al. [19] also showed that subchronic exposure to Al for 12 weeks resulted in increased ROS production and decreased ATP synthesis and cytochrome levels in the rat brain, suggesting impaired mitochondrial function. In addition, exposure to Al reduces the activity of MnSOD and aconitase in various regions of the rat brain. The results of electron microscopy showed that exposure to aluminum causes swelling of mitochondria and their vacuolization, which leads to an increase in their diameter in neurons of the hippocampus of mice and rats [15]. Finally, Al exposure increased the activity of autophagy-associated LC3-II and Beclin-1 proteins and at the same time suppressed p62 protein expression, suggesting a link between learning and memory impairment and mitophagy [15].

Recently, oxidative stress and mitochondrial disorders have been considered as the main targets of aluminum-induced neurotoxicity. The use of the antioxidant quercetin prevented Al-induced mitochondrial swelling and chromatin condensation in the rat hippocampus [20]. Naringin also had a protective effect on memory impairment in rats with sub chronic aluminum exposure, preventing the activation of mitochondrial oxidative damage in the brain [21]. Later, it was shown that centella asiatica, which has antioxidant properties, suppresses aluminum-induced oxidative stress, increases the activity of mitochondrial enzymes in the hippocampus and cerebral cortex, and improves memory [22]. In addition, other natural antioxidants, such as crocin, curcumin, and polyphenols, have been shown to be neuroprotective in aluminum-induced neurotoxicity [23]. These studies indicate that inhibition of oxidative stress and mitochondrial dysfunction may be a major therapeutic strategy to prevent Al-induced neuronal damage.

Conclusion

Analysis and generalization of modern literature data on the mechanisms of neurotoxicity of aluminum and arsenic compounds that can accumulate in the body due to environmental pollution shows that the leading mechanism of their damaging effect is a violation of the energy-generating function of the mitochondria of neurons, which, in turn, involves the development of effective mitochondriotropic agents for the prevention and therapy of these disorders. In particular, antioxidants of plant origin and other mitochondria-protective drugs or their complexes can be used as such agents.

Conflict of Interest

No conflict of interest with any institution/organization.

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