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Review

Effect of atmospheric particulate matter on the functional state of mitochondria

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Abstract: The health risks associated with outdoor air pollution are of global concern. Atmospheric air pollution negatively affects a number of key aspects of human health, including the functioning of the respiratory, cardiovascular and central nervous systems, but many issues remain unresolved about the relationship between atmospheric air pollution and the development and course of pathologies. The review analyzes data from Russian and foreign sources on the effect of atmospheric particulate matter on the functional state of mitochondria. The effect of air pollution on structural changes in mitochondria, ATP synthesis, production of reactive oxygen species, damage to mitochondrial DNA, and mitochondrial membrane potential has been shown. The data presented in the review indicate the need for further studies of the functional state of mitochondria under the impact of solid particles in atmospheric air.

Keywords: mitochondria, mitochondrial dysfunction, mitochondrial membrane potential, fatty acids, mitochondrial DNA damage, atmospheric particulate matter.

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Many substances of natural and anthropogenic origin that are in the air as a result of forest fires, traffic, industrial activities (emissions from thermal power plants, boiler houses, as well as soil and water pollution by enterprises of various hazard classes) are classified as air pollution factors [1, 2]. Air pollution negatively affects some key aspects of human health, including the functioning of cardiovascular, respiratory and central nervous systems [3]. Atmospheric particulate matter (APM) in the air consists of many toxic pollutants (organic carbon species and alkanes, metals, sulfates, nitrates, etc.) [4, 5]. Usually, APM is subdivided into particles with an aerodynamic diameter of up to 1 μm (PM1), 2.5 μm ($PM_{2.5}$) and 10 μm (PM10) [6]. PM10 particles are mainly composed of oxides and dust particles, $PM_{2.5}$ particles are composed of carbon, sulfates, nitrates and silicates.

In recent years, increased attention has been paid to the harmful effects of particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$). The health risks associated with outdoor air pollution are of global concern. A large amount of literature data indicates that exposure to fine particulate matter ($PM_{2.5}$) poses a serious threat to public health from the environment and is considered one of the main factors associated with global mortality [4]. According to the World Health Organization (WHO), 92% of people worldwide live in areas where $PM_{2.5}$ concentrations exceed the limits of 10 μg/m^3, which leads to three million deaths annually [7]. However, many issues concerning the relationship between air pollution and human health still remain unresolved [3]. Exposure to APM and, in particular, to $PM_{2.5}$ particles is associated with adverse effects on the respiratory (bronchial asthma, chronic obstructive pulmonary disease), cardiovascular (coronary artery disease, heart failure) and nervous systems, and also contributes to the development of oncological diseases (lung cancer) [8].

The effect of APM on the functioning of tissues and cells has been extensively studied in vitro and in vivo. The lungs are the immediate target of exposure to APM. Consequently, forming reactive oxygen species, causing oxidative stress, activating cellular signaling pathways, and changing the processes of antioxidant protection result in inflammation and dysfunction of the respiratory system. In addition, cellular changes resulting from exposure to APM can cause epigenetic modifications and changes in gene expression [2, 9-14]. Apart from the respiratory system, APM also affects other body systems. The particles contained in the atmospheric air mainly enter the cardiovascular system and the brain by direct transport through the alveolar membranes. This causes local activation of immune cells in the lungs, which leads to the transmigration of these cells, the release of cytokines and the development of systemic inflammation. The adverse effects of APM on the cardiovascular system are based on the processes of inflammation, oxidative stress, endothelial dysfunction, and increased blood pressure, which are typical triggers of cardiovascular diseases, such as myocardial infarction or acute coronary syndrome [2, 15]. An indirect effect on the cardiovascular system is due to the activation of APM neurons, which leads to an increase in the level of circulating stress hormones and vasoconstrictors. The adverse effect of APM on the brain is based on three major mechanisms, including chronic respiratory and systemic inflammation, along with oxidative damage to the blood-brain barrier, leading to changes in

permeability, stimulation of specific mechanoreceptors in the lungs, followed by sympathetic activation with the release of vasoconstrictors, such as catecholamines [3, 15-16]. Hence, many adverse effects of APM are associated with the induction of oxidative stress, which manifests itself at the cellular level, increased processes of lipid peroxidation of membranes, impaired functioning of mitochondria, and the development of mitochondrial dysfunction [3] (see *Figure* 2 in [15], https://doi.org/10.1016/j.abb.2020.108662).

Mitochondria are organelles involved in major cell functions, including nutrient metabolism and energy production – i.e., adenosine triphosphate (ATP), formation and removal of reactive oxygen intermediates (ROIs), activation of the caspase protease family, and regulation of intracellular Ca2+ homeostasis and apoptosis [17-18]. Air pollution negatively affects the structure and functioning of mitochondria, including changes in the amount of mitochondrial DNA (mtDNA) [19], ultrastructural disorders of mitochondria [20], signs of mitochondrial oxidative stress, such as inhibition of aconitase activity [21-22], reduced activity of succinate dehydrogenase, changes in the MMP, and disruption of oxidative phosphorylation processes [23] (*Figure* 1).

Research in recent decades has provided insight into the adverse effects of air pollution on human health. However, many issues of the relationship between air pollution and development/course of pathologies remain unresolved. Despite the significant interest in this problem, most publications were devoted to the effect of APM on the mitochondrial apparatus of cells in certain nosological forms of diseases. They did not sufficiently reveal the systemic mechanisms of pathological effects and considered a rather narrow range of parameters characterizing the functional state of mitochondria. Our review analyzes the results of current domestic and foreign studies of the APM effect on the structural and functional state of mitochondria, thereby making it possible to assess the development of mitochondrial dysfunction under the impact of APM and to identify the main mechanisms. Various ideas and hypotheses about the formation of environmentally dependent pathologies based on disorders of the considered cellular ultrastructures are systematized.

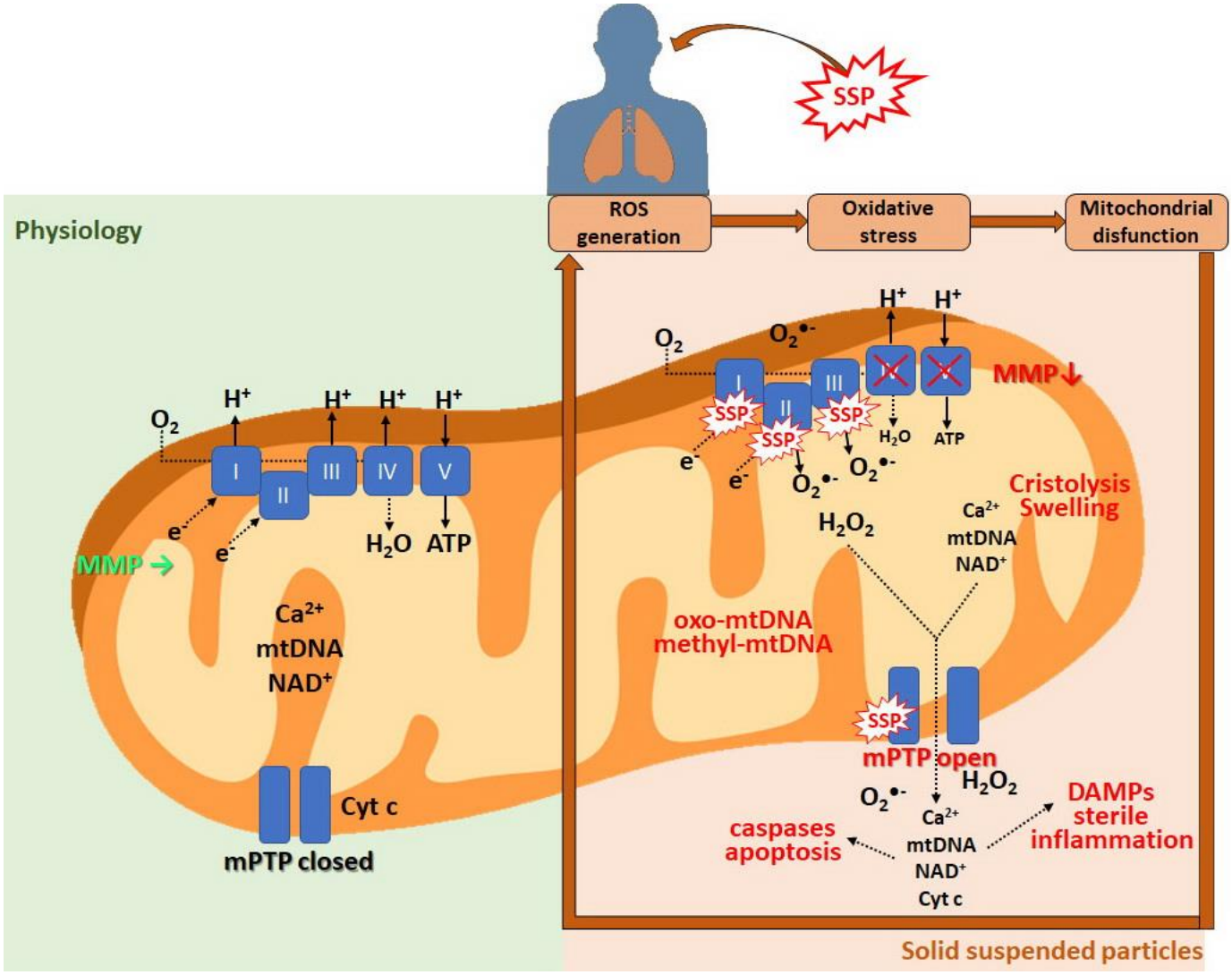

Figure 1. Mitochondrial dysfunction under the impact of APM (modified from A. Daiber et al. 2020 [15])

$PM_{2.5}$ particles cause ultrastructural damage to mitochondria. When exposed to $PM_{2.5}$, the number of mitochondria increases, which causes disruption of the mitochondrial membrane and cristae, mitochondrial vacuolization, and swelling [24-28]. When studying the effect of fine particles of atmospheric air on the membranes of platelet mitochondria, it was discovered that the lipid matrix of mitochondrial membranes became denser and their permeability decreased, which was characterized by the accumulation of saturated fatty acids (12:0, 14:0, 16:0, 18:0) and n -6 polyunsaturated fatty acids (20:3n-6, 20:4n-6, 22:4n-6), as well as a deficiency of n-3 polyunsaturated fatty acids. These data may imply, on the one hand, the development of mitochondrial dysfunction under unfavorable environmental conditions. On the other hand, a change in the structure of mitochondrial membranes occurs as a result of the activation of special adaptive mechanisms and the formation of a compensatory response, manifested by an increase in the proportion of saturated fatty acids, along with a redistribution among the acids of the n-6 and n-3 families towards the accumulation of 20:4n-6 and 22:4n -6 [29-31].

The mitochondrial pathway is one of the main pathways of apoptosis, in which significant changes in mitochondrial structures occur already in the early stages. Because of increased permeability of the outer mitochondrial membrane, soluble proteins are released into the cytoplasm. A decrease in the mitochondrial transmembrane potential and an increase in the permeability of the outer membrane triggers the release of cytochrome C, which regulates energy metabolism, and, when interacting with proteins in the cytosol, triggers caspase activation, which ultimately leads to apoptosis [16]. At the same time, a significant increase in mitochondria-induced apoptotic signaling is noted, which is reflected in an increase in the activity of caspase-3 and caspase-9 [15].

Besides, the normal functioning of mitochondria provides Ca2+ signaling and transport, and the accumulation of Ca2+ in mitochondria leads to cell apoptosis as well. Exposure to high concentrations of APM causes depolarization of mitochondrial membranes. Mitochondrial dysfunction induced by APM is accompanied by a decrease in the potential of the mitochondrial membrane and the opening of the mitochondrial pore [16]. It was shown that mitochondria exposed to APM required significantly less Ca2+ to induce mitochondrial pore opening versus the control [32-33]. Also, the MMP decreased under the impact of APM, which indicated a disruption in the functioning of the mitochondrial membrane [27-28]. On the other hand, a study of the effect of APM on people living in areas with aggravated environmental stress exhibited an increase in the content of leukocytes with reduced MMP, which implied a disorder in the functioning of mitochondria [29, 34-35]. Therefore, an increased content of APM in the air leads to a constant tension of the mitochondrial apparatus in cells, which contributes both to the development of the body's resistance to adverse factors and the formation of compensatory processes, and, ultimately, can lead to disruption of compensatory processes and the development of chronic diseases [29-31, 34-35].

The mitochondrial respiratory chain creates the electrochemical gradient necessary for the production of ATP and is the target of APM. The study of the effect of APM contained in diesel exhaust on mitochondria revealed a reduction in ATP production and a significant decline in the activity of complex I of the respiratory chain [15, 36]. In addition, the effect of APM reduces mitochondrial respiration mainly via decrease in the activity of complex II: mitochondria depolarize and ATP production decreases.

Another sign of a respiratory chain disorder is an increased production of ROIs, which may be associated with a decrease in the activity of antioxidant enzymes under the influence of APM: Cu/Zn superoxide dismutase, Mn superoxide dismutase, glutathione peroxidase, and glutathione reductase [37]. Under physiological conditions, the level of ROI formation ranges from low to moderate and plays a key role in routine cellular signaling. ROI generation is one of the likely molecular mechanisms linking the effects of APM with the development of various diseases [2, 38]. When studying the effect of air pollution on white and brown adipose tissue in mice, it was shown that in the group exposed to concentrated APM, the production of superoxide anion increased [39-40]. On the other hand, the physicochemical characteristics of $PM_{2.5}$ (the size and heterogeneity of the components) provide the capability of these particles to cause the formation of ROIs. Chemical reactions in the atmosphere lead to the appearance of free radical components in $PM_{2.5}$. Thus, in $PM_{2.5}$, a large number of semiquinone radicals were found, which are capable of producing hydroxyl radicals in the absence of biological tissue [41]. Many organic compounds absorbed by the APM surface contribute to an increase in the formation of ROIs, turning into metabolites of the electrophilic reaction. It has been established that organic components of APM provide up to 60% of the ability to generate ROIs of APM water-soluble components [2]. ROIs are very active substances and are capable of initiating and modulating a wide range of molecular reactions that cause damage and dysfunction of cells, tissues and organs, which could lead to the progression of various diseases.

When ROI production exceeds the antioxidant capabilities of the defense system, oxidative stress occurs, which manifests itself in the form of protein and lipid oxidation, as well as RNA and DNA damage, which, in turn, causes dysfunction of cells and tissues [38]. Biomarkers of oxidative stress typically include ROIS-induced modifications (oxidative low-density lipoprotein [Ox-LDL], 4-hydroxynonenal [4-HNE], malondialdehyde [MDA], 8-hydroxy-2'-deoxyguanosine [8-OHdG], etc.), ROI formation markers (xanthine oxidase, myeloperoxidase, etc.), as well as markers of antioxidant protection (transcription factor Nrf2, glutathione peroxidase [GSH-Px], etc.) [2].

Mitochondrial damage caused by ROIs is characterized by three key processes: damage to mtDNA, protein oxidation, and activation of lipid peroxidation processes. In cases when superoxide dismutases cannot catalyze ROIs, the latter break mtDNA strands. This phenomenon can be observed in cells exposed to pollutants or in people living in a highly polluted environment [42-44].

The mtDNA is an indicator of oxidative stress; it is located in the inner mitochondrial membrane near the site of ROI formation. Without histone protection and in the absence of reliable DNA repair ability, mtDNA is more susceptible to oxidative stress attack than nuclear DNA [45]. Moreover, damaged mtDNA can cause excessive generation of ROIs, which, in turn, contributes to further aggravation of mtDNA damage [46]. The amount of mtDNA decreases with age [47] and is considered a biomarker of oxidative stress and mitochondrial dysfunction [45]. It was found that long-term exposure to $PM_{2.5}$ is associated with a decrease in the number of mtDNA copies [48-49]. There is evidence of a decrease

in the amount of mtDNA in leukocytes when exposed to coal particles formed when coal is burned indoors [50], as well as in the blood when exposed to carbon generated by road traffic [19]. According to other data, exposure to APM can increase the amount of mtDNA, causing damage to mitochondria, and, as a result, enhances the formation of oxidative compounds [51]. $PM_{2.5}$ can induce changes in mtDNA through methylation and strand breaks, as well as activate mitochondria-mediated apoptosis in lung tissue [52-57]. It has been shown that exposure to air pollutants during prolonged exposure to APM can cause changes in the DNA methylation profile, which can affect mitochondrial functions and immune responses [48-49].

Mitochondria play an important role in the activation and regulation of innate and adaptive immune cells. Besides, it was demonstrated that mitochondrial dysfunction could cause immunodeficiency. Disorders of key mitochondrial metabolic processes, such as oxidative phosphorylation, the Krebs cycle, etc., can lead to various changes in the functionality of immune cells [57]. The mtDNA release and ROIs are involved in the regulation of immune cell transcription. Furthermore, when exposed to adverse factors, mitochondria produce other damage-associated molecular patterns, such as succinate, cardiolipin, mitochondrial transcription factor A, uric acid, mtDNA-encoded proteins, and N-formyl peptides. With the development of mitochondrial dysfunction as a result of exposure to APM, they are released into the cytoplasm and are detected by pattern recognition receptors, which causes an immune response. Various signaling mechanisms are triggered in immune cells, leading to the activation of nuclear transcription factor (NF-κB), mitogen-activated protein kinase, and regulatory factor of interferon, all of which control the expression of proinflammatory chemokines and cytokines. The interaction of mtDNA with TLR9 plays an important role in the mechanisms of forming the immune response to the release of mtDNA as a result of exposure to APM, leading to an increase in the expression of proinflammatory cytokines, such as interleukin 6 (IL-6). 6), tumor necrosis factor alpha (TNF-a) and interleukin 1 beta (IL-1β) via activation of the NF-κB pathway [57] (see *Figure* 3 in [57], https://doi.org/10.1016/j.envpol.2020.116242).

Mitochondrial proteins can be oxidized or fragmented by ROIs, resulting in impaired oxidative respiration, protein synthesis, and gene expression. Protein oxidation leads to structural deformation, dissociation of complexes, dysfunction, and degradation [58-60]. ROIs formed under the impact of APM can break mtDNA strands, oxidize and fragment proteins, which leads to disorder of oxidative respiration, protein synthesis and gene expression, as well as activation of lipid peroxidation processes, changes in their structure, disruption of the double membrane structure of mitochondria and membrane-related complexes. Violation of the structural integrity of mitochondria, along with the release of ROIs and proapoptotic agents into the cytoplasm, triggers the signaling cascade of cellular stress. Thus, lipid peroxidation is associated with apoptosis and oxidative stress [3, 57].

Mitochondria are very sensitive to environmental toxicants and air pollution. Exposure to environmental toxicants causes changes in mitochondrial respiration and metabolism, production of oxidants, mtDNA damage, and mitochondrial clearance with developed dysfunction through mitophagy and apoptosis [52]. An analysis of the literature data showed that most of the changes in mitochondria that occur as a result of exposure to APM are due to oxidative stress. Changes in ROIs cause disruption of the structure and functioning in mitochondria. An increase in ROI formation can be the result of the direct effect of APM on both mitochondria and other cellular components. In addition, mitochondria can be damaged directly by APM, which can accumulate in the matrix [15-16, 53, 61-64]. Oxidative stress, metabolic disorders, and development of inflammation trigger signaling pathways leading to cell death and, ultimately, systemic failure. Violation of the structure and functioning of mitochondria as a result of exposure to APM negatively affects the respiratory, cardiovascular, and nervous systems, and also promotes the development of type 2 diabetes mellitus and oncological diseases [3, 8].

Mitochondria constitute the key target of solid particles contained in the atmospheric air. APM activate the initiation of oxidative stress development processes by increasing ROI production. In this case, mtDNA damage, protein oxidation and activation of lipid peroxidation processes are observed. Under the influence of APM, a number of interrelated disorders in the functioning of mitochondria occur, which at the level of ultrastructural changes is expressed in an imbalance of the fatty acid composition in mitochondrial membranes and in a reduction of MMP. The data presented in our review suggest the need for further study of the functional state of mitochondria under the impact of APM and of particular mechanisms of APM effect on the key parameters of these organelles, along with the development and course of environmentally conditioned pathologies. A comprehensive assessment of the characteristics of mitochondria under the influence of APM is a promising area of research for establishing early diagnostic and prognostic criteria for the development and progression of such pathologies.

Conflict of interest

The authors declare no conflicts of interest.

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