MITOCHONDRIAL DYSFUNCTION IN PESTICIDE-INDUCED LIVER INJURY

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ABSTRACT

Objective: To investigate the mechanisms of mitochondrial dysfunction during liver exposure to pesticides and to assess the consequences for hepatocyte cell function. Methods: Literature review in in vitro and in In vivo studies of organophosphate , pyrethroid , and other pesticide classes were conducted; parameters such as mitochondrial membrane potential leakage, respiratory chain activity, ATP production, oxidative stress, and apoptosis were assessed. The results show that pesticides induce multiple disturbances: decreased membrane potential, loss of cristae , disruption of respiratory complexes, increased ROS production, mitochondrial DNA damage, and activation of apoptotic pathways.

Introduction. Pesticides are widely used in agriculture and can enter the human body through food, water, air, and occupational exposure. The liver is a key detoxifying organ, and its cells (hepatocytes) are particularly sensitive to the toxic effects of chemicals. One of the key mechanisms of damage is mitochondrial dysfunction, leading to disruption of energy metabolism, increased oxidative stress, apoptosis, and cell death. Despite growing research in this area, gaps remain in the details: which specific pesticides cause which changes at what stages, threshold doses, the effects of chronic low-dose exposure, and the potential for recovery.

The aim of this study is to systematize the available data on mitochondrial dysfunction caused by pesticide exposure to the liver, to describe the molecular and cellular mechanisms, and to discuss the prospects for protection and therapy.

Methods.

The following approaches were used to prepare the review:

1.Literature search - articles published in PubMed , Scopus , Web of Science over the past ~20 years, using keywords : *pesticide* , *liver* , *mitochondrial dysfunction* , *hepatotoxicity* , *oxidative stress* .

2.Comparative analysis of data in in vivo (on animals) and in in vitro (cell cultures, isolated mitochondria), including data on respiratory chain activity, oxidative stress, apoptosis, and changes in ultrastructure.

3.Critical selection - attention was paid to the quality of the methods: dose control, exposure time, appropriate control measures, measurements of mitochondrial functional parameters (e.g., membrane potential, ATP synthesis, respiratory chain complex activity).

Results.

1. Disruption of the respiratory chain and ATP synthesis. Studies have shown that many pesticides (especially organophosphates) inhibit enzymes of the liver mitochondrial respiratory chain. Thus, exposure to organophosphates reduces the activity of complexes I, III, and IV, decreasing mitochondrial respiratory capacity, which leads to a decrease in ATP production.

2. Decreased membrane potential and ion/protein leakage. Under the influence of pesticides, changes in membrane permeability are observed: a drop in the potential of the inner mitochondrial membrane, disturbances in calcium homeostasis, opening of mitochondrial transition pores (mitochondrial permeability transition pore , mPTP). These processes lead to the release of cytochrome C and the activation of caspases , initiating apoptosis.

3. Oxidative stress and mitochondrial DNA damage. Pesticide exposure increases the production of reactive oxygen species (ROS), which causes oxidative damage to lipids (lipid peroxide), proteins, and DNA, including mitochondrial DNA. In one study, high doses of pesticides caused significant damage to mtDNA.

4. Changes in the ultrastructure of mitochondria. Ultrastructural studies show: cristae deformation , matrix vacuolization, membrane thickening and damage, a decrease in the number of mitochondria in liver cells, and a disruption of distribution within the cytoplasm.

5. Apoptosis and cell death. Symptoms of apoptosis include an increase in the Bax /Bcl-2 ratio, activation of caspase-9 and -3, and leakage of cytochrome C. These events are the outcome of prolonged or severe mitochondrial dysfunction.

Discussion.

The collected data suggest that mitochondrial dysfunction is the central mechanism of pesticide-induced liver damage. Acute exposure often results in acute symptoms: a rapid decline in ATP synthesis, changes in membrane potential, and apoptosis. With chronic, low-dose exposure, cumulative effects become more prominent: accumulation of ROS, gradual damage to mtDNA , and a slow decline in mitochondrial function, which can lead to steatosis, impaired glucose and lipid metabolism, and ultimately fibrosis or carcinogenesis .

However, there are significant gaps:

- There is little data on the threshold doses of pesticides at which mitochondrial dysfunction begins in the human liver;
- the effects of mixed exposure (several pesticides simultaneously), low-dose and long-term exposure have not been sufficiently studied;
- few models of recovery: what are the possibilities for interventions (antioxidants, mitochondrial biogenesis, mitochondrial membrane stabilizing agents).

Prospects include the development of biomarkers of mitochondrial dysfunction, assessment of genetic predisposition (polymorphisms of enzymes regulating red oxidative status, mitochondrial proteins), and testing of therapeutic agents.

Conclusions:

- Mitochondrial dysfunction is one of the key mechanisms of liver damage due to pesticide exposure;

• It manifests itself at different levels: structural (ultrastructure), functional (respiratory chain, ATP synthesis), molecular (ROS, mtDNA , apoptosis);

Early detection and prevention, including through exposure limitation, monitoring, and research into possible protection, are important for harm reduction..

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