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LIPID PEROXIDATION AND ANTIOXIDANT SYSTEM OF THE ANIMAL ORGANISM UNDER THE INFLUENCE OF TOXIC FACTORS

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Due to the progressive deterioration of the environmental situation, the number of chemicals ingested by humans, animals and poultry has increased and causes damage to the body. These include industrial poisons, carcinogens, pesticides and mineral fertilisers, some medicines, antioxidant food additives, dyes, etc.

Xenobiotics disrupt physiological metabolic processes in the body, causing poisoning and even death [7, 8]. In the course of evolution, animals have developed mechanisms for neutralising (detoxifying) toxic substances, mainly in the liver, where about 2/3 of their total amount is metabolised. These mechanisms consist of metabolic transformations of xenobiotics that make them more water-soluble, which accelerates their excretion with bile through the intestines or urine through the kidneys.

The process of neutralising toxic substances is divided into two phases. In the first phase of biological transformation, xenobiotics undergo oxidation, reduction, hydrolysis, and other reactions catalysed mainly by enzymes of the liver endoplasmic reticulum (microsomal oxidation and reduction enzymes). The microsomal oxidative system, which includes cytochrome P-450 and the flavin enzyme NADPH cytochrome P-450 reductase, catalyses the hydroxylation of substrates according to the equation

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+.$$

In the second phase, the functional group of the xenobiotic (–OH, –COOH, –SH, – NH_2) is joined to glucuronic or sulfuric acids, amino acids, methyl or acetyl groups, and the tripeptide glutathione. For most toxic compounds, the neutralisation process involves reactions of both phases, but in some cases only one phase - the first or second.

The endoplasmic reticulum of hepatocytes contains flavin enzymes that reduce foreign substances - nitro- and azo-compounds to amino compounds, with NADPH serving as a hydrogen donor.

The mechanism that plays a key role in the development of toxic liver damage is the accumulation of reactive oxygen species in the tissues and the resulting activation

of lipid peroxidation. There is a certain balance between ROS and the activity of the antioxidant system enzymes, so all changes in metabolism that occur with the participation of ROS at any stage of the body's development should be considered in terms of the unity of the opposites of these processes [6].

Fluoride compounds pose a certain threat to the body, the spread of which is due to significant emissions from industrial enterprises and the presence in Ukraine of biogeochemical provinces with an excess of inorganic fluoride compounds in drinking water and soil. Under the influence of sodium fluoride, the liver of rats shows a decrease in retinol content and accumulation of lipid peroxidation products that affect the activity of Krebs cycle enzymes and disrupt the structural integrity of mitochondrial membranes.

There is also the problem of environmental pollution by halogenated hydrocarbons. The introduction of tetrachloromethane into the body of rats causes a sharp disruption of respiration and phosphorylation processes in hepatocyte mitochondria, and the content of ROS products in blood serum and liver increases. The activity of SOD and CAT decreases by 40 % after 48-hour exposure to carbon tetrachloride, while the relative stability of glutathione-dependent enzymes and GSH levels almost double.

There are a number of reports in the literature on the effects of heavy metals, in particular cerium and cadmium, on the body. In particular, Cadmium can accumulate in tissues, especially in the liver, kidneys and bones. Its ions are able to react with sulfhydryl groups of protein molecules, causing oxidative stress and inhibiting a number of biocatalytic processes. The manifestations of Cadmium toxicity are more pronounced in a young organism and are maximal on the 4th day after intoxication.

In experiments on rats, it was found that cobalt chlorides, against the background of intensification of lipid peroxidation processes, cause an increase in the activity of GPO in the liver and kidneys and an increase in the content of non-protein thiols in the liver. Mercuric chloride intake causes a decrease in the content of protein and non-protein thiols in liver tissues, as well as the accumulation of TBA-active products and activation of glutathione transferase in the liver, kidneys, and aorta. Activation of glutathione-dependent enzymes is also caused by plumbum acetate.

Intoxication with hydrochloric acid hydrazine is accompanied by an increase in the intensity of spontaneous and induced chemiluminescence in blood plasma and liver and a decrease in the functional activity of enzymatic (SOD, CAT) and non-enzymatic (GSH) components of the AOS only at the early stages of the study. Ethyl alcohol potentiates the pro-oxidant effect of hydrazine and leads to significant abnormalities in the membrane structures of rat liver cells.

Intake of ^{137}Cs with activity of 3000 Bq per day in chickens contributed to an increase in the amount of lipid peroxidation products in the skin of chickens. The digestive organs of chickens have a powerful antioxidant defence, as evidenced by the stable content of ROS products after radionuclide intake. In the liver of rats, ^{137}Cs on the 22nd day of exposure caused a 64 % increase in the intensity of spontaneous ROS, which was accompanied by an increase in the activity of the enzymes of the SOD (GP, glutathione-S-transferase, $NADP^+$-malate dehydrogenase) in the liver and inhibition of the activity of enzymatic and non-enzymatic SOD in the blood.

Under conditions of exposure to ionising radiation, emotional and painful stress and hypercholesterolaemia, accumulation of ROS products and inhibition of the activity of SOD, CAT, GR enzymes of plasma membranes of cardiomyocytes, erythrocytes and platelets are observed.

The presence of T-2 toxin in the feed of laying hens leads to an increase in the content of TBA-active products in the liver of embryos and day-old young animals by 13-22 %, while there is a decrease in the activity of key enzymes (SOD, CAT, GP) and a decrease in the content of vitamins with antioxidant effects, in particular, A, E, C.

Experiments conducted on rats during their maximum physical activity by running in a trembler or swimming "to failure" caused activation of lipid peroxidation (increased content of TBA-active products) in the brain and myocardium, and to a much lesser extent in the liver, spleen and intestines.

Hypergravity (2 and 5 g), which was created in experiments on rats by spinning them in a centrifuge, causes the accumulation of ROS products in the liver, spleen, brain and blood, with a reactive mobilisation of the enzymatic activity of SOD and CAT. The dynamics of lipid peroxidation corresponds to the stages of the general adaptation syndrome.

The development of livestock and poultry farming is inevitably associated with transshipment, regrouping, and veterinary measures, which leads to mental and physical overload of the organism, and the development of stress. Under transport stress at the stage of anxiety, a sharp decrease in the activity of antioxidant enzymes in the mucous membrane of the small intestine of bulls is observed. Immobilisation stress promotes the activation of lipid peroxidation in liver homogenates, the effectiveness of which is higher in old rats than in young animals.

Glutathione-deficient state significantly activates lipid peroxidation and oxidation of protein SH-groups, and the activity of the process depends on the morphological and functional organisation of tissues [4].

The introduction of large amounts of mineral fertilisers and pesticides into the soil and the existence of about 3000 filtering wastewater storage facilities in Ukraine has led to the emergence of significant areas of groundwater contamination with nitrates and nitrites. It is estimated that on average 17 % of nitrates are ingested through drinking water. Nitrates are formed in the soil, as well as in surface and groundwater, as a result of the natural decomposition of organic nitrogen-containing substances by microorganisms. Some of them are absorbed by plants, while others are released into open water bodies. The toxic effect of nitrates is manifested only through their reduction products, nitrites. After entering the bloodstream, NO_2^- ions quickly penetrate red blood cell membranes. Within the first 5 minutes after internal administration of $NaNO_2$ (in a dose of 2 to 7 mg per 100 g of body weight), a sufficiently high level of methemoglobin in the blood is formed - from 10 to 45 %.

The nature of the toxic effect of nitrites is ambiguous. Oxidants (nitrites and nitrates, ferricyanide, amyl nitrate, nitrobenzene, thiosulfate) can combine with haemoglobin to form meta-haemoglobin containing trivalent Fe. The oxidation of haemoglobin to meta-haemoglobin leads to the formation of superoxide anion radical

($O_2^{\cdot-}$), which causes blockage at certain stages of redox reactions and causes hypoxia in tissues:

$$Hb(Fe^{2+}) + O_2 \rightarrow Mt\text{-}Hb(Fe^{3+}) + O_2^{\cdot-}.$$

As a result of interaction with nitrites, certain characteristics of haemoglobin change: the dissociation of oxyhaemoglobin is disrupted, and the transport function decreases. Even after the complete disappearance of MetHb, the oxygen carrying capacity of the blood decreases. Metahemoglobin formation leads to changes in the concentrations of radical metabolites $O_2^{\cdot-}$, $OH^{\cdot}$, and $NO_2^{\cdot}$. The latter have a pronounced oxidative effect, interacting with SH groups of proteins, reduced forms of coenzymes, and physiologically active polyunsaturated compounds. As a result, the oxygen carrying capacity of the blood decreases, the basal metabolism increases, and tissue hypoxia develops.

Tissue hypoxia delays the oxidation and reduction of NADP, which is a coenzyme of a large number of dehydrogenases. Nitrates and nitrites are precursors of highly carcinogenic nitroso compounds. Normally, the blood of animals contains 2-5 % of methemoglobin, which is maintained by the redox system and erythrocyte methemoglobin reductase. Young animals are more sensitive to nitrite than adults, due to the lower activity of methemoglobin reductase [10].

A direct correlation has been established between the amount of nitrates and nitrites in feed and the level of methemoglobin in the blood of animals. To maintain the physiological level of methemoglobin in the blood, the amount of nitrates in feed should not exceed 30-50 mg/kg.

When animals eat feed containing nitrates, the latter are absorbed through the mucous membrane of the digestive tract. The absorption of nitrates begins in the oral cavity, and most of them are adsorbed and partially reduced to nitrite in the distal part of the small intestine. Absorbed nitrates enter the bloodstream, disrupt the ionic balance and then enter the liver via the portal vein system and are distributed to tissues and organs: most of them accumulate in the liver and kidneys. Nitrates are excreted from the body in urine (60 %) and bile (1 %).

Acute intoxication with sodium nitrate leads to increased methemoglobin formation, activation of free radical reactions and a decrease in the antioxidant status of the body, oxidative modification of proteins, and destruction of plasma and cytoplasmic membranes, At the same time, the energy supply of liver cells is impaired and the activity of lysosomal hydrolases increases, which leads to a deterioration in the functional state of the liver, its ability to bioconvert and the entry of a large number of toxic compounds into the systemic circulation.

Hemoglobin and myoglobin, which are subjected to oxidative attack, are converted to meta-haemoglobin and metmyoglobin, respectively, releasing $O_2^{\cdot-}$, which is neutralised by SOD and CAT. Sodium nitrate causes an increase in the content of MtHb, DC, TBA-active products, and NO_3^- and NO_2^- in the blood. Acute sodium nitrite poisoning causes an increase in the content of CP and CAT activity in erythrocytes and liver. In vitro experiments have shown that catalase activity decreases in the presence of sodium nitrite in the incubation medium. Nitrates reduce the functional activity of

liver mitochondria, which leads to a deficiency of macroenergetic compounds in the tissues.

Subtoxic doses of nitrate cause latent nitrate-nitrite toxicosis, accompanied by increased methemoglobin formation and accumulation of ROS (NO_2^-, NO-, O_2^-), which cause activation of lipid peroxidation: in the blood serum, the content of GPP increases by 75 %, the activity of GP and CAT increases by 17 and 79 %, respectively. Sodium nitrite in microsomal (physiological) concentrations in the presence of chlorides, thiocyanates and bromides can inhibit the enzymatic activity of catalase [11].

In chronic toxicosis, nitrates and nitrites block the transformation of carotene into vitamin A. Nitrates in the amount of 0.5-1.5 % in the diet of chickens do not affect the absorption of feed protein, but reduce the absorption of vitamin A, which results in a deterioration of the incubation properties of eggs.

It has been established that the processes of lipid peroxidation in animals, poultry and microorganisms are affected by a number of factors [1, 2, 3, 5, 9, 12].

Thus, the key to the occurrence of toxic effects on the body is to reveal the mechanisms of pathogenic effects of nitrates and nitrites on animals, i.e., the imbalance between the activity of free radical processes and the functional state of the antioxidant defence system. Some studies that have comprehensively investigated the impact of physicochemical factors on various organs and systems of the body have not paid enough attention to the mechanism of oxidative stress development and methods of its correction. All these issues are of scientific and practical interest, and therefore require serious attention and further study.

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