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CHANGES IN REDOX HOMEOSTASIS IN LUNG TISSUE UNDER CONDITIONS OF DMH-INDUCED COLON ADENOCARCINOMA

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The study is dedicated to the experimental assessment of the parameters of the redox system in the lung tissue of rats under conditions of modelled cancerogenesis.

Materials and methods. The experiment involved 110 adult male outbred white rats. Colon adenocarcinoma in situ was modelled by the weekly administration of N,N-dimethylhydrazine hydrochloride for 30 weeks.

Results. The most pronounced changes in redox reactions in the lung tissue of the experimental animals were observed starting from stage 4 of the study. Accordingly, the level of POM_{370} exceeded the control group results by 1.7 times (stage 4) and 2.8 times (stage 7). The activity of Cat in the lung tissue significantly decreased throughout all observation stages by 1.1 times at stage 1 and 2.0 times at stage 7. It should be noted that the activity of SOD in the lung tissue of the experimental animals increased at stages 1–3. However, starting from stage 4, this indicator significantly decreased. During stages 1–3, the concentration of CP in the lung tissue was almost identical to that of the control group. From stage 4 onwards, this indicator significantly increased, exceeding the control group values by 1.5 times (stage 4) and 2.8 times (stage 7). Analysis of non-enzymatic biological markers of the antioxidant system revealed that the GSH content in the lung tissue during stages 1–3 was virtually identical to the control group. Starting from stage 4, this indicator significantly decreased at all subsequent stages of carcinogenesis. A similar pattern was observed in the mediators of the glutathione system of antioxidant defense. At the final stage of observation, the GPx level was 1.5 times lower, and the GP level was 1.5 times lower compared to the control values.

Conclusions. The development of the chronic neoplastic intoxication syndrome, due to the excessive formation of toxic metabolites, creates significant strain on the antioxidant system and leads to a decrease in the activity of antioxidant enzymes as well as a substantial reduction in the concentration of non-enzymatic antioxidant mediators.

Key words: induced carcinogenesis, antioxidant system, redox balance, lungs.

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ЗМІНИ ОКИСНО-ВІДНОВНОГО ГОМЕОСТАЗУ В ТКАНИНІ ЛЕГЕНЬ ЗА УМОВ ДМГ-ІНДУКОВАНОЇ АДЕНОКАРЦИНОМИ ТОВСТОЇ КИШКИ

Тернопільський національний медичний університет імені І. Я. Горбачевського Міністерства охорони здоров'я України, Тернопіль, Україна

Досліджено параметри окисно-відновної системи в тканині легень щурів за умов змодельованого канцерогенезу. В експерименті використано 110 білих статевозрілих аутбредних щурів-самців. Аденокарциному товстої кишки in situ моделювали введенням N,N-диметилгідразину гідрохлориду один раз на тиждень впродовж 30 тижнів.

На початкових етапах канцерогенезу функціональна спроможність антиоксидантної системи була достатньою для запобігання розвитку оксидативного стресу. Починаючи з 4-го етапу дослідження відзначено достовірне зростання показників оксидативного стресу, а також концентрації продуктів окислювальної модифікації білків плазми крові. Розвиток синдрому хронічної неопластичної інтоксикації за рахунок надлишкового утворення токсичних катаболітів спричиняє істотне навантаження на ланки антиоксидантної системи та призводить як до зниження активності антиоксидантних ферментів, так і до суттєвого зменшення концентрацій неферментативних антиоксидантних медіаторів.

Ключові слова: індукований канцерогенез, антиоксидантна система, окисно-відновний баланс, легені.

Introduction. Colorectal cancer (CRC) is a complex condition influenced by various factors. While the precise cause remains elusive, research underscores the impact of lifestyle elements such as diet, smoking, stress, alcohol consumption, and exposure to toxins [1; 2]. Oxidative stress (OS) precipitates inflammatory responses in the intestinal mucosa, genetic predisposition, alterations in intestinal immune responses, and notably, dysbiosis-changes in the composition of gut microbiota, which were recognized as integral to CRC development. Numerous studies validate the role of free radicals in initiating, promoting, and progressing multistage carcinogenesis. Oxidative stress within intestinal mucosal cells is likely pivotal in CRC pathogenesis [3–5]. Free radical-induced oxidative damage can trigger metabolic pathways, leading to the production of other proteins that influence cell proliferation and inflammation processes [6]. Given the biological unity of the body's organs and systems, we can confidently state that oxidative stress is harmful to the entire body in the case of colon neoplasia.

Oxidative stress arises from an imbalance between pro-oxidant molecules and the cell's antioxidant defense mechanisms. This imbalance triggers damage to cells in the digestive tract, encompassing DNA injury, protein aggregation, and membrane dysfunction. It is established that reactive oxygen species (ROS), through interactions with cellular macromolecules like proteins, nucleic acids, and lipids, disrupt vital cellular processes. For instance, oxidative DNA damage may manifest as base oxidation, single- and double-strand breaks, or the formation of abasic sites. Furthermore, unrepaired oxidative DNA damage heightens the risk of mutagenesis, potentially affecting crucial genes governing cell growth, such as tumor suppressor genes and proto-oncogenes, thereby contributing to cancer development [7–8].

Given the above, the present paper is **devoted to the study** of the parameters of the redox system in lung tissue in rats with DMH-induced colon adenocarcinoma.

Materials and methods

Animals

The study was conducted on 110 white, sexually mature, outbred male rats weighing 190 ± 5 g. The experimental animals were kept in standard vivarium conditions. The survival and body weight of the animals were monitored throughout the study. The rats had free access to drinking water and a basic diet *ad libitum*. All animal experiments used in this study complied with generally accepted international standards and were approved by the Bioethics Committee of the Ternopil National Medical University (Minutes No. 75 of 01.11.2023).

Rats were randomly divided into 2 groups: Group 1 – 50 control animals, Group 2 – 60 animals with induced colorectal adenocarcinoma *in situ.* The N,N-dimethylhydrazine (DMH) colorectal cancer model is a well-known and widely used model of chemically induced colon cancer in animals. It shares a number of morphological and molecular characteristics with sporadic CRC in humans. DMH-induced colon adenocarcinoma was modelled by administration of N,N-dimethylhydrazine hydrochloride (Sigma-Aldrich Chemie, Japan, series D161802) dissolved in isotonic sodium chloride solution. The carcinogenic substance was injected subcutaneously into the inter-lobar area at a dose of 7.2 mg/kg body weight (by active ingredient) once a week for 30 weeks [9; 10]. Animals in the control group were injected subcutaneously with saline with the above frequency at a daily dose calculated by animal weight similar to animals in the experimental group to model possible stress effects.

All animal manipulations were performed in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes Strasbourg, 1986 [11].

Histologically, at the 30-week mark of DMH administration, colon adenocarcinoma in situ was diagnosed in all rats treated with DMH.

Blood sampling and analysis

Blood samples were collected and analysed one day after the last administration of DMH, along with control animals of the same age. Animals were deeply anesthetized with thiopental (50 mg/kg, intraperitoneally, Arterium, NUA/3916/01/02) and euthanized by exsanguination. For the convenience of analysis and presentation of research results, samplings were conducted in stages 1–7 (each stage consisting of a 30-day observation period).

Analysis of indicators of prooxidant-antioxidant homeostasis in lung tissue

The course of oxidative processes in lung tissue homogenate was evaluated by changes in the concentrations of TBA – reactive substances (TBARS), diene and triene conjugates (DC, TC), Schiff bases (SB), blood plasma proteins oxidative modification: aldehyde and ketone derivatives products of neutral (POM_{370}) and basic (POM_{430}) origin. The effectiveness of the enzymatic and non-enzymatic links of the antioxidant system was analysed by determining the activities of catalase (Cat), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), ceruloplasmin content (CP), and reduced glutathione (GSH) according to generally accepted methods [10].

Statistical analysis of experimental data was performed using the computer program Microsoft Excel XP (USA). The obtained qualitative results were processed by the method of variation statistics using a one-factor analysis of variance ANOVA with the Originpro 7.5 program. Differences between the mean values were considered significant if the probability of the alternative hypothesis was at least 0.95.

Results and discussion

Evaluation of redox processes in lung tissue during induced carcinogenesis

The development of a tumor is always accompanied by changes in oxidative-reductive balance and the formation and accumulation of reactive oxygen species (ROS). This leads to activation of lipid peroxidation (LPO) and disruption of the antioxidant system. It has been scientifically proven that the activity of free radical reactions in the human body significantly changes during tumor development. Activation of LPO in such pathology may be caused by the development of a stress response. Stress is an adaptive reaction of the organism to various stimuli. Prolonged stress, especially during the development of pathological processes, leads to increased ROS levels. As a

result, processes of free radical oxidation are activated. All these reactions suppress the capabilities of cellular defense systems, which can lead to considerable damage not only to the target organ but also to other organs and systems of the body [11; 12; 13].

An excess of ROS leads to an increase in the quantity of primary molecular products of LPO – DC, TC, and SB. The rapid breakdown of DC and TC, formed in large quantities, leads to the appearance of a wide range of toxic catabolites (TBARS, aldehydes, ketones).

Thus, under conditions of induced carcinogenesis, we observed a statistically significant increase in the concentration of DC, TC, and SB in the lung tissue homogenate. However, it should be noted that the increase in the content of these compounds in lung tissue was observed starting from stage 4 of the study. It can be hypothesized that at the initial stages of carcinogen exposure, the functional capacity of the antioxidant system was sufficient to prevent the development of oxidative stress.

By the end of the modelling (stage 7), the concentration of DC exceeded the corresponding indicator in the group of intact animals by 2.6 times ($p<0.001$); TC – by 2.5 times ($p<0.001$); SB – by 2.5 times ($p<0.001$). The concentrations of TBARS increased under conditions of experimental carcinogenesis, starting from stage 1 of observation, and at stage 7 and final stage, this indicator exceeded the control by 4.0 times ($p<0.001$) (Fig. 1).

Unlike lipid peroxidation products, carbonyl derivatives of proteins are much more stable and specific, making them convenient markers for oxidative stress intensity and opening possibilities for their use in diagnostics and prognosis of pathology development. Considering this, it was pertinent to investigate the content of POM in lung tissue of experimental animals under pathological conditions.

The results of the conducted research indicate that the intensity of protein oxidation in the lung tissue of white rats increases throughout all observation periods. POM_{370}, encompassing neutral aldehyde and ketone derivatives, exceeded the corresponding indicator in control animals by 1.3 times (stage 1), 1.5 times (stage 2), 1.6 times (stage 3), 1.7 times (stage 4), 1.8 times (stage 5), 2.5 times (stage 6), and 2.8 times (stage 7).

The concentration of basic POM_{430} derivatives also exceeded the respective control group indicator throughout all experiment terms. However, a significant increase in basic POM_{430} derivatives was observed starting from stage 4 of observation, by 1.4 times. Subsequent increases persisted: by 1.8 times at stage 5, by 2.1 times at stage 6, and by 2.2 times at the final stage 7 of observation (Figure 2).

The biological role of catalase (CAT) involves the degradation of H_2O_2 formed in cells because of superoxide dismutation, ensuring effective protection of cellular structures against damage caused by H_2O_2. Ceruloplasmin (CP) is an acute-phase protein, and its levels increase in patients with malignant neoplasms of various localizations. Changes in CP concentration serve as markers of the effectiveness of applied treatment-lower CP levels correlate with more successful chemotherapy and radiotherapy of oncological diseases [14].

During DMH-induced carcinogenesis, the activity of CAT in lung tissue decreased statistically significantly over the course of 7 stages of modelling: by 1.1 times at

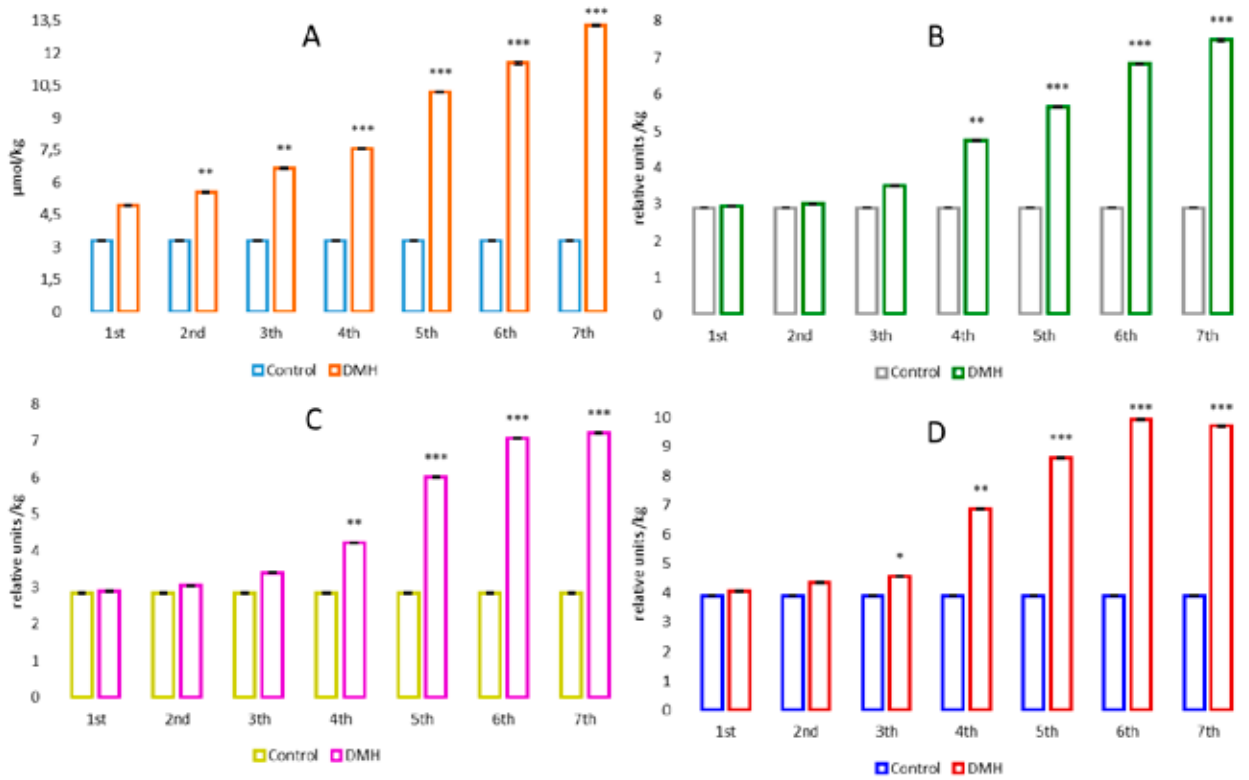

Fig. 1. Dynamics of oxidative stress development in lung tissue of white rats under conditions of induced carcinogenesis (A – TBARS; B – DC; C – TC; D – Schiff bases)

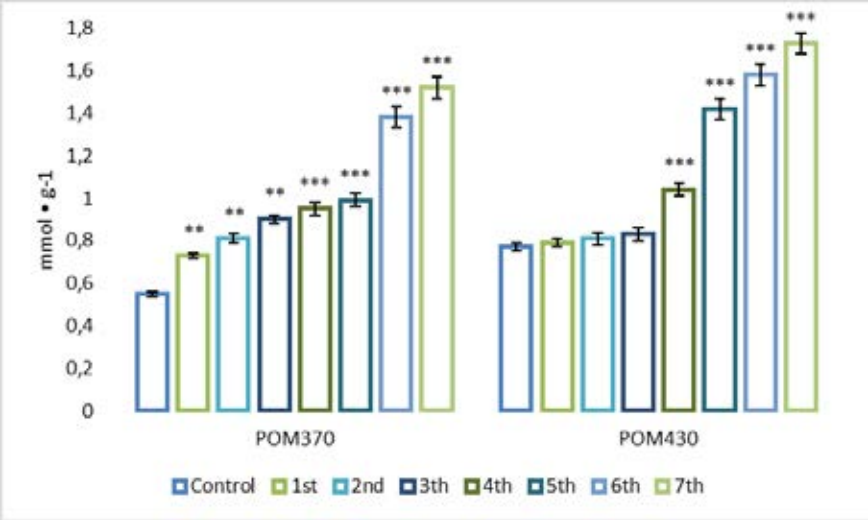

Fig. 2. Dynamics of changes in the concentration of aldehyde and ketone derivatives of neutral (POM_{370}) and basic (POM_{430}) nature in the lungs of white rats with induced carcinogenesis

stage 1, by 1.3 times at stage 2, by 1.5 times at stage 3, by 1.6 times at stage 4, by 1.8 times at stage 5, by 1.9 times at stage 6, and by 2.0 times at stage 7 of DMH administration compared to the corresponding indicator in the control group of animals. Experimental findings indicate that during the development of adenocarcinoma of the colon, SOD activity in lung tissue initially increases in the first months of DMH administration, but significantly decreases starting from the 4th month. The lowest SOD activity observed at stage 7 of carcinogen administration was 2.6 times lower than that in the intact group of animals ($p<0.001$). Under DMH-induced carcinogenesis, the concentration of CP in lung tissue significantly increased starting from the 4th month of observation, surpassing the control animals' indicator by 1.5 times. In subsequent experimental stages, CP concentration exceeded the control value by 2.1 times (stage 5), 2.5 times (stage 6), and 2.8 times (stage 7) ($p<0.001$). This described dynamic change in CP concentration indicates the progression of the pathological process (Figure 3).

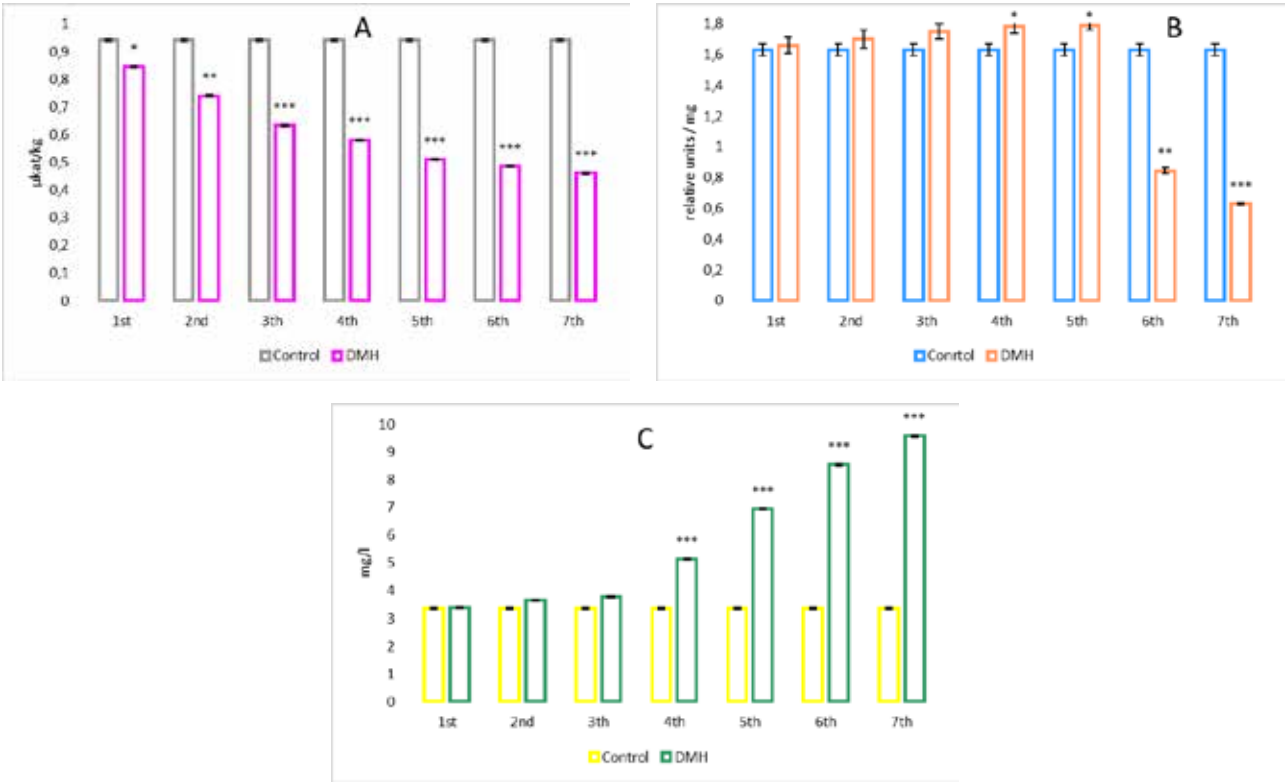

Fig. 3. Dynamics of changes in antioxidant system enzymes in the lung tissue of white rats under modelled carcinogenesis (A – Cat; B – SOD; C – CP)

Our data suggest that, on one hand, there is an increase in the sensitivity of proteins to oxidative modification during the development of the oncological process, and on the other, a decrease in their degradation rate through proteolysis. This may result from changes in the structural organization of protein molecules, disruption of the ratio of variable valence metals, and a decrease in the activity of components of the first line of the body's antioxidant system.

Research into the glutathione antioxidant system is of interest due to the fact that GSH is a primary component that rapidly mobilizes in response to increased peroxide levels and restores them through reactions accompanied by the formation of oxidized glutathione (GSSG), which is toxic to cells. The intracellular content of GSH depends on the balanced rates of opposing processes such as de novo synthesis involving γ-glutamylcysteine synthetase and efflux into the extracellular space, as well as regeneration through reduction of GSSG and utilization in the neutralization of H_2O_2 and secondary peroxidation products [15; 16].

Under the conditions of induced injury modelling, a significant decrease in GSH concentration in lung tissue was observed starting from stage 4 of observation, followed by subsequent significant decreases during stages 5, 6, and 7 of induced carcinogenesis modelling compared to the indicator in the control group of animals (Figure 4).

An important component of the enzymatic antioxidant defense system is glutathione peroxidase (GP). The GPx peptide chain contains a selenocysteine residue, a cysteine analog in which the sulfur atom is replaced by a selenium atom. Selenocysteine is part of the enzyme's active center. GPx can reduce hydroperoxides of free fatty acids, hydroperoxides of phospholipids, and esterified fatty acids. The enzyme is regenerated by NADPH-dependent glutathione reductase (GR). Two molecules of the reduced form form a disulfide upon oxidation [17, 18].

Experimental findings have established that during the development of adenocarcinoma of the colon, GPx activity in lung tissue also significantly decreases, starting from stage 4 of the experiment ($p<0.01$). The lowest GPx activity was observed at stage 7 of DMH administration and was 1.5 times lower compared to the indicator in the group of nearly healthy animals ($p<0.001$).

Inactivation of GPx is only possible under conditions of reduced optimal levels of intracellular GSH, which serves not only as a substrate for the reaction but also as a necessary factor for continuous restoration of the catalytic center's enzyme selenol groups that undergo oxidation.

A similar trend of activity reduction was observed in the study of GR activity in rat lung tissue with experimental carcinogenesis. From stage 4 of the study, a decrease by 7.3% compared to the corresponding control indicator was noted. In all subsequent terms of the experiment, there was a tendency towards further inactivation of this indicator, with the lowest activity observed at stage 7 of induced carcinogenesis (a decrease by 55.8%) compared to GR activity in the control group of animals.

Under physiological conditions, activation of GP in response to excess hydroperoxides stimulates GR activity for the regeneration of oxidized glutathione. The opposite changes in GR and GPx were influenced

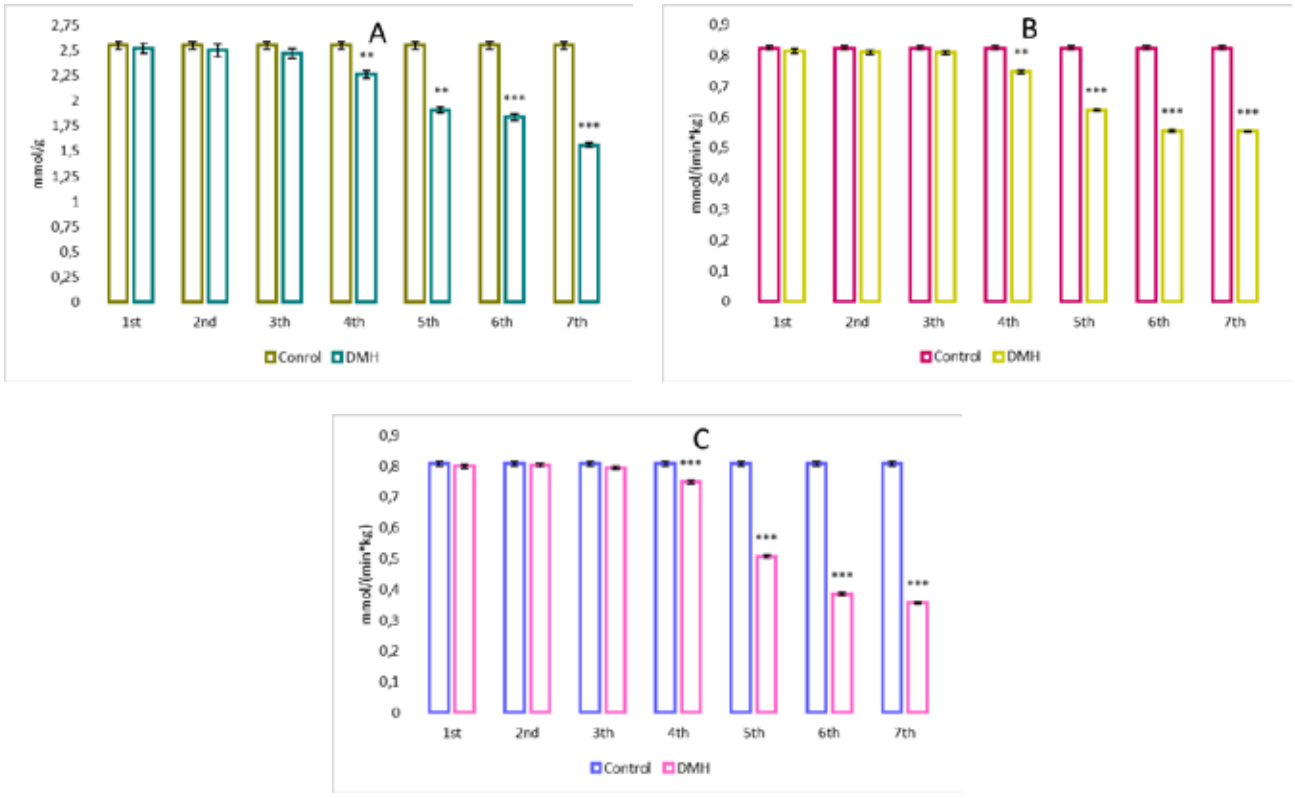

Fig. 4. Dynamics of changes in biological mediators of the glutathione antioxidant defense system in lung tissue under conditions of modelled carcinogenesis (A – GSH; B – GPx; C – GR)

by processes involving oxidation of the enzyme's active center and deficiencies in cofactors such as NADPH and selenium. The deficit of NADPH arises from the shift of the pentose phosphate pathway from oxidative glucose metabolism to anaerobic conditions, partially meeting the organism's energy demands under hypoxia during chemical carcinogenesis. Disruption in the biosynthesis of GSH leads to inadequate anti-peroxidative function of the glutathione system. Throughout the experiment, the dynamics of oxidative stress significantly disturb the synthesis of glutathione peroxidase and glutathione reductase in the endoplasmic reticulum, resulting in suppressed functional activity of the glutathione-dependent antioxidant defense system.

Thus, chemically induced carcinogenesis disrupts redox balance, manifested by significant increases in lipid peroxidation products and TBARS, alongside decreases in antioxidant enzymes and non-enzymatic antioxidant mediators' activities.

As a result, based on the experimental study, it can be stated that the development of neoplastic lesions of the colon causes significant changes in the redox homeostasis of the body of experimental animals, in particular the severity and direction of these processes in the lung tissue.

Conclusions. DMH-induced colon carcinogenesis is accompanied by severe disturbances of redox balance in the lung tissue of experimental animals, which is manifested by a significant increase in lipid peroxidation products and TBARS. Excessive accumulation of toxic catabolites causes a significant burden on the antioxidant system and leads to a decrease in the activity of antioxidant enzymes as well as a significant decrease in the concentration of non-enzymatic antioxidant mediators. The above should be taken into account when developing an adequate and pathogenetically sound "maintenance therapy" in the management of colon carcinogenesis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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