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METABOLIC AND MORPHOLOGICAL CHANGES IN RAT TISSUES UNDER THE EFFECT OF ELECTRONIC CIGARETTES

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Introduction. Electronic cigarettes are widely used as a potentially less harmful alternative to conventional smoking, generating aerosol without exothermic combustion. Exposure to e-cigarette aerosols increases reactive oxygen species and lipid peroxidation products, which modify key metabolic enzymes and disrupt energy and lipid homeostasis. These effects are reflected in elevated lactate dehydrogenase (LDH) and creatine kinase (CK) activities, altered glucose levels, and morphological tissue changes confirmed by histology.

Aim of the study. To establish organ-specific changes in energy and lipid homeostasis indicators, as well as morphological alterations in rat tissues under conditions of chronic exposure to electronic cigarette aerosols.

Materials and Methods. Twenty adult male Wistar rats were divided into the experimental (n = 10) and the control (n = 10) groups. Experimental animals were exposed to aerosol from an Elf Bar 1500 Ultra e-cigarette for 20 minutes daily over three months; animals in the control group were not exposed. Animals were euthanized one hour after the final session, and tissue samples from the lungs, liver, heart, kidneys, and brain were collected for biochemical assays and histological examination.

Results. Chronic exposure increased LDH and CK in lungs and liver, indicating anaerobic glycolysis activation and cytolytic injury, accompanied by inflammation, edema, and alveolar disruption. Reduced tissue glucose and suppressed enzymatic activity in the heart and kidneys were associated with microcirculatory disturbances. Lipid accumulation correlated with inflammatory and edematous reactions, while brain histology revealed increased vascular permeability.

Conclusions. Chronic e-cigarette aerosol exposure induces organ-specific metabolic and structural alterations, disrupting energy and lipid metabolism and causing histological damage, most pronounced in the lungs.

Keywords: electronic cigarettes, biochemical markers, toxicity, organ-specificity, histology.

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МЕТАБОЛІЧНІ ТА МОРФОЛОГІЧНІ ЗМІНИ У ТКАНИНАХ ЩУРІВ ЗА ДІЇ ЕЛЕКТРОННИХ СИГАРЕТ

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Електронні сигарети широко використовуються як альтернатива традиційному тютюнопалінню, однак їх аерозолі містять низку токсичних компонентів, здатних індукувати метаболічні та запальні порушення. Метою роботи було оцінити органоспецифічні зміни показників енергетичного та ліпідного гомеостазу, а також морфологічні зміни в тканинах щурів за умов хронічної експозиції парами електронних сигарет.

Встановлено, що хронічна експозиція аерозолями електронних сигарет зумовлює виражені метаболічні порушення в окремих органах. Гістологічні дослідження виявили розвиток запальних, судинно-набрякових і структурних змін. Отримані результати свідчать про системний характер токсичної дії аерозолів електронних сигарет та їх здатність викликати поєднані метаболічні й морфологічні порушення.

Ключові слова: електронні сигарети, біохімічні маркери, токсичність, органоспецифічність, гістологічні дослідження.

Introduction

Electronic cigarettes have become increasingly widespread in recent years as an alternative to conventional tobacco smoking; however, their aerosols contain nicotine, aldehydes, formaldehyde, heavy metals, and other toxic compounds potential to induce metabolic and oxidative disturbances. The investigation of biochemical changes in tissues under exposure to electronic cigarette aerosols is important for understanding the potential risks to human health.

Exposure to electronic cigarette aerosols may induce mitochondrial dysfunction in tissues (for example, in the liver and myocardium), resulting in decreased β-oxidation of fatty acids. This, in turn, leads to triglyceride accumulation in tissues, a simultaneous decrease in adenosine triphosphate (ATP) levels and compensatory activation of glycolysis, as well as increased release of cytosolic enzymes, namely lactate dehydrogenase (LDH) and creatine kinase (CK), into the tissue supernatant.

Reactive oxygen species, the levels of which also increase under exposure to electronic cigarette aerosols, as well as lipid peroxidation products, covalently modify key metabolic proteins (for example, mitochondrial enzymes and enzymes involved in β-oxidation), which may cause functional decompensation of energy metabolism and altered lipid homeostasis; this simultaneously contributes to membrane damage, as evidenced by increased activity of LDH and CK [1; 2].

The exact mechanisms by which e-cigarettes vaping induces vascular defects remain unknown, but they are likely multifactorial and predominantly atherogenic. It is believed that the atherogenic effect is mediated by nicotine and carbon monoxide present in cigarette smoke [3; 4]. It has also been hypothesized that these vascular injuries may result from smoking-induced oxidative stress, since cigarette smoke contains a large number of potentially reactive oxygen and nitrogen species [5].

Organ-specific enzymes are used to assess tissue destruction in various diseases, and CK is regarded as a reliable marker for evaluating myocardial, muscular, and cerebral injury. Creatine kinase is a cytosolic enzyme that catalyzes the reversible phosphorylation of creatine using ATP, while the transfer of a high-energy phosphate group represents an important step in various physiological processes. The determination of LDH and CK in tissues makes it possible to assess local cellular damage and the state of energy metabolism. Glucose level is an important indicator of energy balance, and its alterations may be associated with the effects of nicotine and other smoke components on the regulation of carbohydrate metabolism. Measuring LDH, CK, and glucose levels allows for the assessment of the metabolic changes occurring in the body.

Aim of the study. To establish organ-specific changes in energy and lipid homeostasis indicators, as well as morphological alterations in rat tissues under conditions of chronic exposure to electronic cigarette aerosols.

Materials and Methods

In our study, a passive smoking model was implemented. According to this model, the experimental animals receive toxic substances through exposure to e-cigarette aerosol within an inhalation chamber (Fig. 1).

The system consisted of a 5 L inhalation chamber, a 300 mL syringe, an Elf Bar 1500 Ultra electronic cigarette, and a one-way valve allowing the syringe to be filled with aerosol from the electronic cigarette and subsequently delivered into the inhalation chamber for animal exposure [6]. Two animals were simultaneously placed in the chamber.

The experiment was performed on 20 sexually mature male Wistar rats aged 8–10 weeks and weighing 180–220 g. The animals were divided into two groups: the experimental group (10 rats) and the control group (10 rats). Rats of the experimental group were daily exposed to electronic

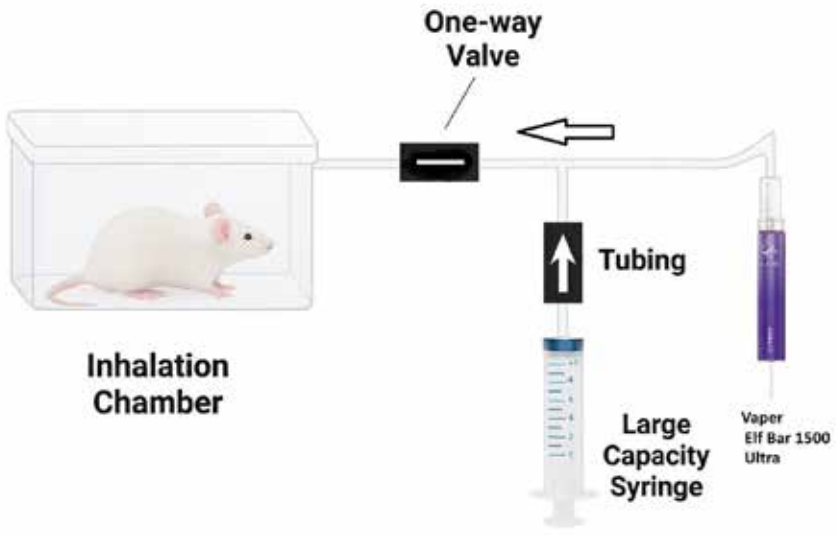

Fig. 1. Passive smoking model

cigarette aerosol inhalation (100 mL/min, 20 min), whereas the control group animals were not subjected to vaping exposure.

The Elf Bar 1500 Ultra electronic cigarette (China) consisted of four main components: propylene glycol, glycerin, nicotine salt (50 mg/mL), and flavoring agents. The liquid volume was 4.8 mL.

Experimental studies were conducted in accordance with generally accepted bioethical standards. The animals were maintained under standard vivarium conditions in compliance with the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). The experimental protocol was reviewed and approved by the Department of Molecular Biology, Biochemistry, and Genetics of Odesa I. I. Mechnikov National University (Protocol No. 4, 2025).

After 3 months, the rats were withdrawn from the experiment under thiopental anesthesia (20 mg/kg): 1 hour after completion of the final inhalation session in order to record the most relevant morphological and biochemical changes in tissues. Following euthanasia, animal tissues were isolated, weighed, and homogenized in 0.9% NaCl solution at a ratio of 1:10. The homogenates were centrifuged at 10,000 g for 15 min, after which the supernatant was used for biochemical analyses.

A marker of chronic exposure in the study was the regular and repeated exposure to electronic cigarette aerosol throughout the entire experimental period, corresponding to accepted approaches used in vape inhalation models [7]. The observed metabolic and structural changes confirm the systemic toxicity of chronic e-cigarette exposure.

The catalytic activity of LDH and CK was determined according to International Federation of Clinical Chemistry recommendations using kinetic spectrophotometric methods at a wavelength of 340 nm (37°C), whereas glucose concentration was measured by the hexokinase method. Total cholesterol and triglycerides were determined enzymatically with photometric registration of the results [8].

Statistical processing of the obtained results was performed using Student's t-test with Microsoft Excel software. Differences were considered statistically significant at $p \leq 0.05$ according to Student's tables [9].

For histological examination of tissue material, samples of the lungs, brain, and liver were isolated and prepared for further analysis using generally accepted methods [10]. The material was stained with hematoxylin and eosin, and subsequent histological examination was performed using a light microscope equipped with an image capture camera.

Research results and their discussion

Chronic inhalation exposure to electronic cigarette aerosols induced pronounced organ-specific changes in energy metabolism parameters in rat tissues. Analysis of LDH and CK activity, as well as glucose levels, indicates remodeling of cellular energy supply and the development of metabolic stress under conditions of prolonged aerosol exposure (Table 1).

In lung tissue, a moderate decrease in glucose concentration (by 10.2%) was observed, accompanied by a significant increase in LDH (+20.8%) and CK (+47.1%) activity. Such a combination of changes may reflect upregulation of glycolysis in response to increased cellular energy demand, as well as damage to cellular membranes with the release of cytosolic enzymes. The obtained data are consistent with the concept of local metabolic and structural stress development in the lungs as the primary organ exposed to inhaled aerosol.

Similar metabolic alterations have been described in experimental models of electronic cigarette aerosol exposure and are associated with cellular stress and impaired energy homeostasis in the pulmonary epithelium. Although direct markers of oxidative stress were not assessed in the present study, the detected changes are consistent with pre-

Table 1

Biochemical parameters of energy metabolism in rat tissues following chronic electronic cigarette aerosol exposure

Tissue	Parameter	Control group	Experimental group	Δ (%)
Lungs	Glucose (mmol/g)	0.00490 ± 0.0005	0.00440 ± 0.0005	−10.2
	Lactate dehydrogenase (mmol/min/g)	0.674 ± 0.05	0.816 ± 0.78*	+20.8
	Creatine kinase, (mmol/min/g)	0.606 ± 0.04	0.891 ± 0.82*	+47.1
Cardiac muscle	Glucose (mmol/g)	0.01040 ± 0.001	0.00530 ± 0.0005*	−49.0
	Lactate dehydrogenase (mmol/min/g)	6.853 ± 0.61	6.066 ± 0.60	−11.4
	Creatine kinase, (mmol/min/g)	16.45 ± 1.54	12.02 ± 1.18*	−27.0
Kidneys	Glucose (mmol/g)	0.00440 ± 0.0005	0.00410 ± 0.0005	−6.9
	Lactate dehydrogenase (mmol/min/g)	0.951 ± 0.08	0.671 ± 0.07*	−29.4
	Creatine kinase, (mmol/min/g)	0.978 ± 0.08	0.858 ± 0.08	−12.2
Liver	Glucose (mmol/g)	0.07190 ± 0.007	0.05710 ± 0.005*	−20.6
	Lactate dehydrogenase (mmol/min/g)	11.910 ± 1.23	16.740 ± 1.68*	+40.4
	Creatine kinase, (mmol/min/g)	0.402 ± 0.03	0.593 ± 0.05*	+47.5

* – $p < 0.05$ compared to the control group.

viously described oxidative stress-mediated effects of electronic cigarettes [11; 12].

In cardiac muscle tissue, a marked decrease in glucose content (49.0%) was detected in combination with suppression of both LDH (−11.4%) and CK (−27.0%) activity. Such a pattern of changes may indicate impaired glucose delivery or utilization, decreased glycolytic activity, and functional exhaustion of enzymatic systems. Reduced CK activity, which plays a key role in rapid ATP resynthesis in cardiomyocytes, indicates potential myocardial energy instability and increased susceptibility of cardiac tissue to functional disturbances.

In the kidneys, the changes were less pronounced; however, they were characterized by a tendency toward decreased tissue glucose levels (−6.9%) and a substantial reduction in LDH activity (−29.4%), which may indicate suppression of glycolytic processes in nephron cells. The detected alterations indicate the sensitivity of renal tissue to the systemic effects of electronic cigarette aerosol components and possible impairment of energy supply to the tubular apparatus.

The liver exhibited a distinct metabolic response pattern: a decrease in glucose levels (−20.6%) was combined with a significant increase in LDH (+40.4%) and CK (+47.5%) activity. Such dynamics may reflect activation of anaerobic glycolysis against the background of impaired mitochondrial oxidation, as well as structural hepatocyte damage accompanied by the release of intracellular enzymes. Considering the central role of the liver in the regulation of energy and lipid metabolism, such alterations may have systemic consequences for the metabolic homeostasis of the organism.

Similar organ-specific disturbances of energy metabolism have been described in experimental models of electronic cigarette aerosol exposure and are associated with the development of cellular stress and mitochondrial dysfunction. Although direct markers of oxidative stress were not determined within the scope of this study, the identified biochemical alterations are consistent with previously described oxidative stress-mediated mechanisms of electronic cigarette toxicity.

The next stage of the study involved the investigation of changes in lipid homeostasis in rat tissues under conditions of chronic e-cigarette aerosol exposure (Table 2). A general tendency toward increased levels of total cholesterol and triglycerides was established in all examined organs compared with the control group.

The most pronounced relative increase in cholesterol concentration was observed in cardiac muscle tissue (+41.2%), which may indicate disruption of intracellular lipid balance and the potential development of lipotoxic effects in cardiomyocytes. Elevated tissue cholesterol levels may adversely affect cellular membrane stability, mitochondrial function, and contribute to the activation of apoptotic processes.

The greatest accumulation of triglycerides was recorded in renal tissue (+32.0%), which may be associated with impaired β-oxidation of fatty acids or increased lipid deposition in tubular epithelial cells. Such alterations potentially create conditions for the development of local inflammation and renal functional disturbances during prolonged exposure.

In the liver and lungs, the increase in cholesterol and triglyceride content was moderate, which may reflect a combination of the local effects of inhaled aerosol and systemic metabolic effects induced by nicotine and inflammatory mediators. Considering the key role of the liver in lipid metabolism, even moderate alterations may be clinically significant under conditions of chronic exposure. The obtained results are consistent with data from other experimental studies demonstrating alterations in tissue lipid composition following exposure to electronic cigarette aerosol or nicotine [13].

Particular attention should be paid to the hypothesis of lipotoxicity in cardiac tissue: elevated intracellular cholesterol levels may impair membrane stability, mitochondrial function, and promote apoptotic processes in cardiomyocytes, potentially increasing the risk of functional disturbances during prolonged exposure. Similar mechanistic concepts regarding the effects of nicotine and associated metabolic disturbances on cardiovascular tissues have been described in both classical and contemporary studies. A significant increase in triglycerides in the kidneys may reflect impaired β-oxidation of fatty acids or enhanced lipid deposition in renal tubules, accompanied by local inflammation and potential impairment of renal function during chronic exposure [14; 15].

Thus, the obtained results indicate the systemic nature of metabolic disturbances induced by electronic cigarette aerosols, accompanied by the development of organ-specific alterations in energy and lipid homeostasis. The identified biochemical changes are in good agreement with the described morphological alterations in tissues and

Table 2

Biochemical parameters of lipid homeostasis in rat tissues following chronic electronic cigarette aerosol exposure

Tissue	Parameter	Control group	Experimental group	Δ (%)
Lungs	Total cholesterol (μmol/g)	33.6 ± 3.41	35.2 ± 3.76	+4.8
	Triglycerides (μmol/g)	47.6 ± 5.01	54.1 ± 5.74	+13.7
Cardiac muscle	Total cholesterol (μmol/g)	27.2 ± 2.98	38.4 ± 4.09*	+41.2
	Triglycerides (μmol/g)	45.4 ± 4.97	54.1 ± 5.74*	+19.2
Kidneys	Total cholesterol (μmol/g)	56.0 ± 5.72	60.8 ± 5.83	+8.6
	Triglycerides (μmol/g)	101.6 ± 9.56	134.1 ± 12.73*	+32.0
Liver	Total cholesterol (μmol/g)	35.2 ± 3.76	40.0 ± 4.02	+13.6
	Triglycerides (μmol/g)	95.2 ± 9.07	103.8 ± 9.85	+9.0

** – $p < 0.05$ compared to the control group.*

complement current understanding of the toxic potential of electronic nicotine delivery systems.

In the lung tissue of rats from the control group (Fig. 2A, I), mildly expressed inflammatory changes were observed. Uneven congestion of the microcirculatory vessels with isolated diapedetic hemorrhages was noted. Moderate peribronchial and perivascular lymphohistiocytic infiltration with predominance of lymphocytes and isolated polymorphonuclear leukocytes was detected. The infiltration was predominantly diffuse in nature without the formation of massive cellular aggregates.

The interalveolar septa were focally moderately thickened due to the cellular component. The architecture of the alveolar space was generally preserved. The detected alterations indicate the presence of a low-grade background inflammatory process, which should be taken into account during the interpretation of experimental results.

In animals of the experimental group (Fig. 2A, II), the morphological pattern was characterized by markedly more pronounced lesions with the formation of a broncho-interstitial pattern. Pronounced vascular congestion with multiple focal hemorrhages of varying size was observed. Peribronchial infiltration was intense, with the formation of dense cellular cuffs around the bronchi; the cellular composition was represented predominantly by lymphocytes with admixture of histiocytes and isolated neutrophils. Perivascular infiltration was moderate or focally pronounced.

The interalveolar septa were unevenly thickened due to pronounced lymphohistiocytic infiltration and edema. Areas of alveolar collapse (atelectasis) alternating with foci

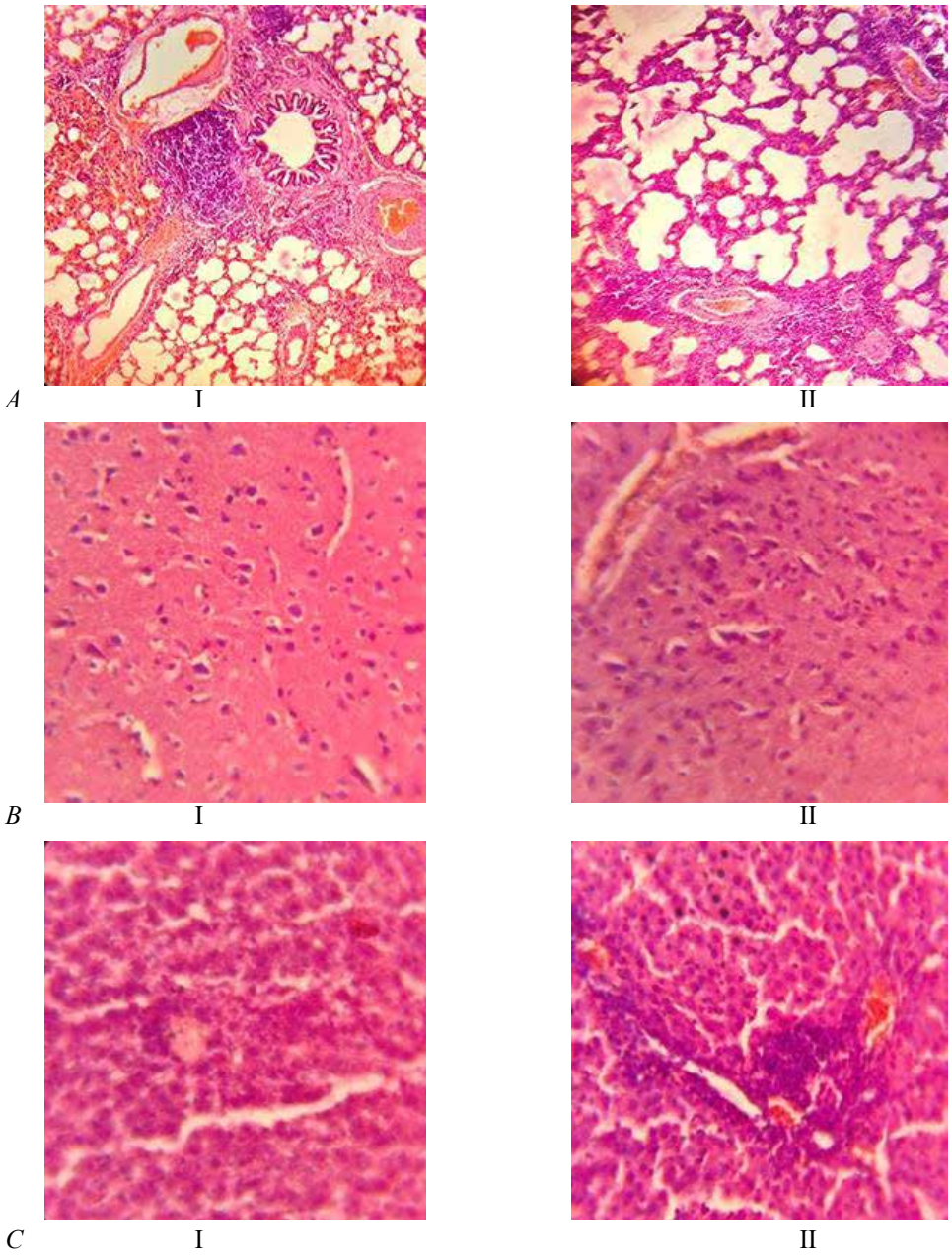

Fig. 2. Transverse sections of rat lungs, brain, and liver (A–C):
I – the control group, II – the experimental group. Hematoxylin and eosin staining, magnification ×40

of acute alveolar emphysema were identified, indicating marked heterogeneity of ventilation processes. In addition, moderate interstitial edema was observed. Collectively, these alterations correspond to severe inflammatory and vascular injury accompanied by disruption of alveolar architecture and remodeling of pulmonary tissue.

It is important to note that mildly expressed inflammatory changes in the control group were likely associated with background housing conditions of the animals. Therefore, the interpretation of the results was based on comparative analysis of the severity of pathological changes, which were substantially more intense in the experimental group.

Histological examination of brain tissues in the control group animals (Fig. 2B) revealed moderate venous congestion of vessels within the pia mater. Moderate perivascular and pericellular edema was observed. No signs of pronounced cellular infiltration or destructive changes in the neuroparenchyma were detected.

In animals of the experimental group (Fig. 2B, II), markedly pronounced venous congestion with dilation of microcirculatory vessels was observed. Perivascular and pericellular edema was diffuse in nature and substantially more intense compared with the control group. Moderate lymphoid infiltration with predominance of lymphocytes, occasionally forming small perivascular aggregates, was detected in the pia mater.

The morphological pattern corresponded to enhancement of vascular-edematous syndrome with signs of a neuroinflammatory response without evident manifestations of massive neuronal injury.

The least pronounced alterations induced by electronic cigarette exposure were identified during the examination of liver specimens (Fig. 2C). In the liver of rats from the control group (Fig. 2C, I), uneven congestion of sinusoids and central veins was observed. Isolated small hemorrhages were detected. Hepatocytes preserved their typical trabecular organization, and no signs of pronounced cellular destruction or inflammatory infiltration were observed.

In animals of the experimental group (Fig. 2C, II), the predominantly vascular nature of alterations persisted, with greater variability in sinusoidal congestion. In certain areas, isolated perivascular and interstitial lymphocytic aggregates were identified, indicating a mildly expressed inflammatory response. No signs of massive hepatocellular necrosis or pronounced dystrophic alterations were detected.

Overall, the morphological pattern corresponded to moderate congestive-vascular alterations with initial manifestations of immune activation.

Damage induced by electronic cigarettes is often less pronounced than that caused by conventional cigarettes; however, it differs in nature and may lead to unique pathological conditions. Electronic cigarettes induce tissue injury through oxidative stress, inflammation, toxic degradation products, and immune dysregulation. Although the risks may be lower, electronic cigarettes are not safe for body tissues, and their long-term consequences remain insufficiently studied.

According to the performed pathohistological investigations, exposure to electronic cigarettes is associated with a significant increase in vascular disturbances and inflammatory changes in the brain and lungs compared with the control group, more pronounced interstitial (perivascular and peribronchial) lymphoid infiltration, edema, and local disturbances of alveolar architecture (atelectasis and acute emphysema). In the liver, the alterations were predominantly vascular and mildly inflammatory, being less pronounced than those observed in the respiratory system. The obtained results are fully consistent with the available literature data [16; 17].

The detected biochemical alterations are closely associated with the identified morphological disturbances in the examined tissues. Increased LDH and CK activity in the lungs and liver reflects activation of anaerobic glycolysis and cytolytic cellular injury, which is consistent with histological signs of inflammation, edema, vascular congestion, and disruption of alveolar architecture. Decreased tissue glucose levels and suppression of enzymatic activity in cardiac muscle and kidneys were accompanied predominantly by vascular and congestive morphological alterations, indicating impaired microcirculation and cellular energy supply. Accumulation of cholesterol and triglycerides in tissues correlated with the development of edematous and inflammatory reactions. The edema and inflammation detected in the brain are consistent with systemic metabolic alterations and indicate increased permeability of vascular barriers under conditions of chronic exposure.

Conclusions

Chronic e-cigarette aerosol exposure causes disturbances of energy metabolism in rat tissues, manifested by alterations in LDH and CK activity, as well as glucose levels.

Increased LDH and CK activity in the lungs and liver against the background of decreased tissue glucose levels indicates activation of glycolysis, mitochondrial dysfunction, and cellular injury.

Alterations in lipid metabolism (accumulation of cholesterol and triglycerides) indicate metabolic remodeling and the systemic nature of aerosol effects on the organism.

Histological investigations revealed enhanced neurovascular and pulmonary inflammation accompanied by edema and vascular disturbances; structural alterations of pulmonary architecture (atelectasis, acute emphysema, and septal thickening) as key markers of adverse effects. The presence of alterations in the brain, lungs, and liver indicates systemic inflammation and congestion, with the greatest severity observed in the lungs.

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