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Pathomorphological Changes in the Lungs of Rats During the Development of Reperfusion Syndrome against Exposure to Ionizing Radiation

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Abstract A study of the lungs of Wistar rats revealed ontogenetic morphological features of the lung parenchyma in animals of immature, mature and presenile ages. The maximum content of unchanged lung parenchyma was found in mature rats. In other age groups of animals, against the background of a decrease in the number of intact parenchyma, the percentage of emphysematous areas and areas of distelectasis increased.

Keywords Acute and chronic radiation exposure, Rat, Experiment, Lungs

1. Introduction

Respiratory diseases are an urgent problem of our time, due to the significant prevalence of this pathology among the population, the progression and aggravating effect on concomitant lesions. According to the World Health Organization, respiratory pathology occupies a leading place in the structure of morbidity of the adult population [3]. In this regard, it has recently become increasingly important to improve the quality of life of patients achieved by using various therapies. However, the applied methods of therapy and rehabilitation do not always achieve optimal results, which requires the search for new methods of treatment. A promising direction of modern treatment based on understanding the causes and mechanisms of lung damage and their recovery is the use of biologically active substances of various classes. To date, there is evidence of a beneficial effect on the lungs of vasopressin [1], corticoliberin [1], somatostatin [1], melanocyte stimulating hormone [5], melatonin [1], ghrelin [2], hepatocyte growth factor [9], epidermal growth factor [1], endothelial growth factor [6], erythropoietin [1] and others. These and many other biologically active substances were found in the composition of cerebrospinal fluid [1]. At the same time, the concentration of certain substances in the cerebrospinal fluid significantly exceeds the plasma concentration [1,2], which makes it possible to consider the cerebrospinal fluid as a natural substrate of interest in terms of a potential therapeutic agent for the correction of pulmonary pathology.

In addition to studying the composition and properties of cerebrospinal fluid, experience has been accumulated in the use of cerebrospinal fluid for therapeutic purposes in a number of pathological conditions: blood loss [6], infectious diseases [5], metabolic disorders [1], radiation sickness [3], burns [5]. The positive effects of the use of xenogenic cerebrospinal fluid in gynecology [5], dermatology [1], endocrinology [7,10], neurology and psychiatry [5] are described. The effect of CSF on the red bone marrow [1,5], lymph nodes [2], brain [1], endocrine organs (ovaries, thyroid gland, pituitary gland [7, 8], adrenal glands [2]) has been established. As part of the study of the properties of xenogenic cerebrospinal fluid and its effect on the organs and systems of the body, as well as regenerative abilities, it became necessary to study the effect of xenogenic liquor on the lungs in the ontogenetic aspect and in modeling pathological conditions.

The routes of entry of substances into the lungs can be divided into exogenous (airways, transthoracic) and endogenous (bloodstream). Through these pathways, the respiratory part of the lungs may be damaged directly (exogenous pathway) and indirectly through blood vessels (endogenous pathway). Thus, Savchuk R.M. [7] carried out a study to study the effect of aeropolutants contained in the atmospheric air of an industrial city on the microcirculatory bed. In the capillaries, he determined a violation of the integrity of the vascular wall 13 up to the exposure of the basement membrane. In places of vascular wall damage, the author observed adhered platelets, erythrocyte aggregates, which in combination with edematous endotheliocytes caused narrowing of the capillary lumen. In another study [1], during chronic inhalation of phosphor containing lead phthalate, the formation of airless areas alternating with emphysematous areas, polymorphocytic infiltrates with incipient pulmonary fibrosis were found.

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In a study devoted to the study of experimental acute respiratory distress syndrome of exogenous genesis (intra-tracheal administration of a suspension of Staphylococcus aureus), thickening of the interalveolar septa due to interstitial edema and infiltration in combination with intraalveolar edema and alveolar hemorrhages was noted. Macrophages, edematous fluid, fibrin were traced in the alveoli. The development of areas of dis- and atelectasis, the number of which increased over time, thickening of the basement membrane due to the formation of collagen fibers was established [3]. Studying the consequences of another exogenous pathway of damage, thermoingalation, a decrease in the specific gravity of phosphatidylcholine in bronchoalveolar flushes, which is the most superficially active fraction of the surfactant system, was revealed [4]. Another way to influence the lungs is to directly affect the parenchyma through the chest wall.

One of such factors is irradiation affecting the components of the aerogematic barrier with the development of radiation pulmonitis with the outcome of fibrosis [1]. When rats are irradiated, changes occur in the lungs in the form of stroma sclerosis with ventilation circulatory disorders in the alveoli and reactive hyperplasia of lymphoid tissue, and when combined with cyclophosphamide administration, the degree of sclerosis and delimphatization significantly increases [5]. Uzlenkova N.E. when studying the features of collagen changes in the lungs, she revealed a decrease in collagen formation and an increase in its proteolysis at an early stage of radiation damage, which was replaced by a gradual increase in its synthesis with inhibition of collagen fiber proteolysis at a late stage [5,15]. Among the endogenous sources, it is possible to conditionally distinguish a damaging effect due to violations of the functioning of a separate organ or a systemic damaging effect. Thus, in experimental modeling of acute renal failure in rats, Klisch I.P. he noted thickening of the basement membrane, edema of endotheliocytes, the appearance of aggregated and adhered platelets and leukocytes in the lumen of capillaries [2,12].

These changes lead to vasoconstriction, disrupting tissue trophism. The effect of heart failure, in particular chronic, was studied by Klimenko N.A. with co-authors [2,3]. Chronic heart failure led to sclerotic changes in the interstitial lung tissue, accompanied by an increase in the formation of collagens, primarily young type III collagen and, to a lesser extent, mature type I collagen, and the synthesis of type IV collagen increased in the basal epithelial membranes. Experimental modeling of chronic liver failure in rats, conducted by A.A. Alekseenko. et al., demonstrated the presence of a compensatory phase with activation of the functional activity of type II alveolocytes and their proliferation, passing into the decompensation phase with increased vascular permeability, the development of hemorrhages, microthrombosis, areas of distelectasis and atelectasis, progression of sclerosis of the interalveolar septa with the outcome of small-focal pneumofibrosis [3]. In the event of severe acute pancreatitis, damage to the pulmonary parenchyma was induced due to the influence of endothelium-dependent mediators (eselectin, intercellular adhesion molecule-1, tissue thromboplastin, Willebrand factor 15) [7,11], accompanied by an increase in matrix metalloprotease-9 [17].

The systemic damaging effect on the lungs is due to the influence of pathological agents coming both from the outside, which do not have a direct traumatic effect on the lungs, and formed during endogenous processes without the influence of external factors. Ukrainian researchers have established the appearance of adaptive compensatory and destructive changes in the aerogematic barrier after receiving a thermal injury. Narrowing of the lumen and filling of the capillaries were characteristic. Type I alveolocytes are characterized by significant swelling and enlightenment of the cytoplasm, hypertrophy and destruction of organelles. The basal membrane of the blood vessels was significantly unevenly thinned from the side of the aerogematic barrier, and, at the same time, the expansion of the interstitial connective tissue stroma with fuzzy contours. Signs of edema and vacuolization were noted in type II alveolocytes. An increased number of alveolar macrophages was observed in the lumen of the alveoli [3,12]. The described changes are accompanied by an increase in the activity of the NO-ergic system in the lungs of rats with the accumulation of NO2 - with its maximum reaching during burn shock [5,15].

Gravitational overloads also have a negative impact on the lungs in the form of circulatory disorders, severe intracellular edema, dystrophic and destructive processes [5,9]. In a number of studies aimed at studying the toxic effects of heavy metal salts on the lung tissue of rats, structural changes were noted in the form of accelerated development of emphysematous processes against the background of the formation of pneumosclerosis with thickening of the interstitial space of the aerogematic barrier [11,14]. Intravenous use of narcotic substances revealed an increase in the content of lipid peroxidation products (diene ketones and conjugated trienes) in the exhaled air condensate with a simultaneous decrease in antiradical activity, accompanied by 16 metabolic changes in the lungs due to the activation of anaerobic processes [9]. Similar data were obtained in patients with acute respiratory distress syndrome on the background of abdominal sepsis [20], as well as in acute respiratory distress syndrome modeled by the method of G. MatuteBello, Michael Matthay, 2013. (intratracheal administration of 0.1 normal hydrochloric acid) [18], in acute hypoxic hypoxia and acute blood loss [2,19,21]. Analyzing another study [5,14,16] devoted to modeling acute hypoxic pulmonary edema, the development of attenuation of serotonin inactivation in the lungs due to a reduction in monoamine oxidase activity was noted, leading to a decrease in oxidative deamination of serotonin in the lungs and an increase in its concentration in lung tissue.

A study conducted by Messeir E.M. et al. revealed the protective effect of alpha-tocopherol on type II alveolocytes from oxidative stress, genotoxicity and inflammation induced by the action of cigarette smoke [1,8,10,12]. In

addition, there was a decrease in acute inflammatory infiltration and collagen formation in the lung tissue during inhalation chemical damage [2,16]. A positive effect of alphatocopherol was also found in lung injury induced by the effects of irradiation and lipopolysaccharide [7,17]. Thus, there is no doubt about the predominantly positive effect of certain biologically active substances contained in the cerebrospinal fluid on the morphological structure of the lungs. However, it remains unknown what the resulting effect will be the use of xenogenic cerebrospinal fluid on the structure of the lungs with its parenteral administration normally. In addition, taking into account the available data on the beneficial effect of xenogenic cerebrospinal fluid in the treatment of acute radiation sickness [1,8], and the lack of data in available literature on the effect of xenogenic cerebrospinal fluid on damaged lungs, our study was supplemented by the study of the effect of xenogenic cerebrospinal fluid on the lungs of Wistar rats exposed to exogenous (one-time total irradiation) and endogenous (the use of itraconazole) effects.

The aim of the study was to study the content of products of spontaneous oxidative modification of proteins in the blood serum and lung tissue of rats after local irradiation of the projection area of the lungs with gamma radiation.

2. Material and Methods of Research

Outbred Wistar rats were used in the experiments. For more than 5 years they have been used in a number of laboratories of the Research Institute of Oncology, their various parameters and, above all, the frequency and spectrum of spontaneous tumors, life expectancy, sensitivity to the action of various carcinogenic agents and other modifying factors have been well studied. In total, 55 mature female rats aged 3-4 months, with a body weight of 140-160 g were used in the dissertation study. The animals were kept in a barrier–type vivarium under standard light conditions (12/12), at a room temperature of 20-23℃ and a relative humidity of 54-58%. The rats were in polypropylene cages with a metal lattice lid, no more than 6 animals in a cage. The change of litter (sawdust) and drinking (tap) water was carried out 3 times a week. The usual cleaning of the premises was carried out daily, a complete cleaning of the premises with washing of floors and shelves was carried out 2 times a week.

Wistar rats of the I7-K series were intramuscularly injected with placebo three times and removed from it on the 7th day of the experiment. The average weight of animals in this group was 41.00±2.04 g, the average total lung volume was 2.46±0.30 cm^3.

When studying the morphometry parameters of the lungs of rats of the I-7-K series, the following results were obtained: the percentage of unchanged parenchyma was 59.82±1.86%, emphysematous areas were 33.39±1.6%, distelectases were 6.52±0.30%, hemorrhages were 0.27± 0.01%. When the lungs were stained with picrofuxin in the interalveolar septa, collagen fibers were visualized as single thin, intermittent strands with an increase in the number around the vessels.

Rats of the Wistar line of the I7-E series were parenterally injected with CSF three times and removed from the experiment on day 7. With triple administration of RWCF, the average weight of animals increased by 3.00 g ($p > 0.05$), and the total lung volume decreased by 0.44 cm^3 ($p>0.05$). In animals, the presence of areas of emphysema with areas of distelectases was noted. There are isolated areas of hemorrhages in the lumen of the alveoli and interalveolar septa, consisting of hemolysed erythrocytes. The percentage of emphysematous areas decreased by 15.95% ($p <0.05$) with an increase in the percentage of unchanged parenchyma by 14.35% ($p<0.05$) and hemorrhages by 0.69% ($p <0.05$).

Rats of the I-30-K series were given a placebo tenfold parenterally and removed from it on the 30th day of the experiment. In animals of the control series during the 30-day experiment, the average weight was 36.00 ± 1.5 g, the total lung volume was 2.96 ± 0.32 cm^3. Histological examination of the lung tissue revealed the presence in almost equal proportions of unchanged parenchyma and areas of emphysema, which were 45.70 ± 1.38% and 48.70 ± 1.26%, respectively. The areas of distelectasis and hemorrhages accounted for an insignificant part (2.38 ± 0.11% and 3.85 ± 0.15%). After staining the lungs with picrofuxin, collagen fibers are presented in the form of thicker strands located in the interalveolar septa, perivascular spaces.

Rats of the I-30-E series were parenterally injected tenfold with CSF and removed from the experiment on day 30. After tenfold administration of RWCF, the average weight of animals decreased by 1.17 g ($p>0.05$), and the total lung volume - by 0.14 cm^3 ($p>0.05$). In the lungs of animals of the I30-E series, along with unchanged alveoli, there are alveoli with an enlarged lumen and thinned walls, as well as hemolysed erythrocytes intraalveolar and their walls. The percentage of emphysema sites decreased by 3.58% ($p>0.05$), against the background of an increase in the percentage of unchanged parenchyma by 2.71% ($p>0.05$), distelectasis sites – by 0.31% ($p>0.05$), and hemorrhages – by 0.56% ($p>0.05$). Collagen fibers, presented perivascularly and in the interalveolar septa, looked like thinner fragments and were less common in comparison with rats of the control group.

Thus, it was found that the introduction of CSF causes changes in the lungs of immature Wistar rats: an increase in the percentage of unchanged parenchyma due to a decrease in the percentage of emphysematous areas, a decrease in the severity of collagen formation. These changes are more pronounced when administered three times.

During ultramicroscopic examination, the nuclei of type I alveolocytes had an ovoid shape with a smooth or wavy contour. Chromatin was diffusely located over the entire surface of the nucleus, but could be grouped near the karyolemma in the form of elongated solid lumps, creating

an inhomogeneous density of karyoplasm. Mitochondria of various sizes of oval or spherical shape were localized mainly around the nucleus, but in small numbers were also found in the cytoplasm of the processes. Among the membrane structures of the cytoplasm, one could see a granular endoplasmic network covered with numerous ribosomes, less often a Golgi complex. The thinned peripheral part of type I alveolocytes contained a large number of micropinocytic vesicles. A significant volume part of type II alveolocytes was occupied by a nucleus with evenly spaced chromatin. Chromatin condensation was observed in some cells, which indicates the possibility of these cells to replenish the population of alveolar cells of both types.

A high level of functional activity is indicated by the presence in the cytoplasm of a large number of mitochondria, endoplasmic reticulum, ribosomes, Golgi complex cisterns, vesicles. The most characteristic of these cells is the presence of osmiophilic lamellar bodies, which had an ovoid or spherical shape, were limited by a membrane and contained plates of high electron density. The corpuscles in the same cell were at different stages of their evolution: from the formation of an endoplasmic network in the tubules to the process of release beyond the cell boundaries into the lumen of the alveoli. A characteristic feature of type II alveolocytes is the presence of microvilli on the apical surface of cells. The cytoplasm of endotheliocytes contained a moderate amount of pinocytic vesicles. The nuclei of endotheliocytes had a rounded shape with evenly spaced chromatin. The basement membrane was thin, with clear, even contours, and contained a small amount of collagen fibers. Wistar rats of the II-7-E series were parenterally injected three times and removed from the experiment on day 7. With the introduction of CSF, the average weight of animals increased by 8.33 g ($p>0.05$), and the total lung volume decreased by 2.03 cm^3 ($p>0.05$).

In animals, the presence of areas of emphysema with areas of distelectases was noted. The percentage of emphysematous sites decreased by 13.73% ($p <0.05$) along with an increase in the percentage of unchanged parenchyma by 5.07% ($p<0.05$), distelectasis sites by 9.23% ($p<0.05$) and hemorrhages by 0.57% ($p<0.05$). Thus, it was found that the introduction of CSF causes multidirectional changes in the lungs of mature Wistar rats. Triple and tenfold administration (long-term effects) leads to an increase in the percentage of unchanged parenchyma, more pronounced in the long-term effects of tenfold administration, a decrease in the content, manifested in the early effects of tenfold administration. Changes in the percentage of emphysematous areas have similar trends, except for greater severity with three-time administration. The increase in the percentage of sites of atelectasis and hemorrhages, noted with a triple administration, is replaced by a tendency to gradually decrease with a tenfold administration in long-term effects. The introduction of CSF reduces the severity of collagen formation.

3. Conclusions

1. A study of the lungs of Wistar rats revealed ontogenetic morphological features of the lung parenchyma in animals of immature, mature and presenile ages. The maximum content of unchanged lung parenchyma was found in mature rats. In other age groups of animals, against the background of a decrease in the number of intact parenchyma, the percentage of emphysematous areas and areas of distelectasis increased.

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