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MORPHOHISTOLOGICAL CHARACTERISTICS OF THE HEART, LIVER AND KIDNEYS UNDER THE INFLUENCE OF DOXORUBICIN AND METABOLIC DRUGS

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Doxorubicin is one of the most effective drugs, which is often used in clinical practice. The purpose of this work was to study the structural basis of the doxorubicin toxic effects on the heart, liver and kidneys and under the influence of metabolic drugs. Results of the histological and morphometric studies indicate the potential cytoprotective properties of the studied metabolic drugs – ubiquinone-10, a complex of precursors and modulator of ubiquinone biosynthesis (vitamin E, methionine, paraoxybenzoic acid and magnesium) and tiotriazolini in the conditions of experimental doxorubicin cardiomyopathy (the cumulative dose of doxorubicin is 15 mg/kg) and can serve as an experimental justification for their feasibility as a protective agents in clinical practice.

Key words: doxorubicin, heart, liver, kidney, ubiquinone, thiotriazolini.

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МОРФОГІСТОЛОГІЧНІ ХАРАКТЕРИСТИКИ СЕРЦЯ, ПЕЧІНКИ ТА НИРОК ЗА ВПЛИВУ ДОКСОРУБІЦИНУ ТА ПРЕПАРАТІВ МЕТАБОЛІЧНОЇ ДІЇ

Доксорубицин відноситься до найбільш ефективних препаратів, які використовуються в клінічній практиці. Метою даної роботи було дослідити структурні основи токсичного впливу доксорубіцину на серце, печінку та нирки, а також за впливу препаратів метаболічної дії. Результати проведених гістологічних та морфометричних досліджень вказують на потенційні цитопротекторні властивості досліджуваних препаратів метаболічної дії – убіхінону-10, комплексу попередників та модулятора біосинтезу убіхінону (вітамін Е, метіонін, параоксибензойна кислота і магній) та тіотриазоліну при експериментальній доксорубіцинової кардіоміопатії (кумулятивна доза доксорубіцину – 15 мг/кг) і можуть слугувати експериментальним обгрунтуванням їх використання в якості протекторних засобів в клінічній практиці.

Ключові слова: доксорубіцин, серце, печінка, нирки, убіхінон, тіотриазолін.

The work is a fragment of the research project "The mechanism of hypoxic development during nitrite methemoglobinemia", state registration No. 0117U006710.

The search for means to protect the body from toxic effects of antitumor chemotherapeutic drugs is an urgent scientific problem. Doxorubicin is one of the most effective drugs, which is often used in clinical practice [9]. Cytotoxic action is aimed to inhibit the synthesis of nucleic acids, to interact with cell membrane lipids, to change the physicochemical state of the phospholipid layer, membrane fluidity and ion transport disorder [4]. This mechanism of doxorubicin action contributes to high antimitotic activity, but low selectivity of action, accompanied by severe side effects – cardio-, nephro-, hepatotoxicity, etc. [14].

To reduce the toxic effects of doxorubicin, it is proposed to use various drugs with antioxidant, membrane-protective, antitoxic properties, to create combined drugs with doxorubicin [3, 6, 8].

The purpose of the work was to study the structural basis of doxorubicin toxic effects on the heart, liver and kidneys and under the influence of metabolic drugs.

Materials and methods. The experiment was performed on white outbred male rats weighing 220–260 g. Rats were kept under the standard vivarium conditions: granulated compound feed, free access to water, 24-hour lighting schedule (12 h day/12 h night).

Animals were divided into 4 groups:

Group 1 rats injected with doxorubicin solution (doxorubicin hydrochloride, "Sindan Pharma" SRL, Romania) (i.m., 5 mg/kg body weight, once a week for three weeks to simulate doxorubicin cardiomyopathy [3];

Group 2 - rats treated with doxorubicin complex of precursors and modulators of ubiquinone biosynthesis (EPM-Mg), which consisted of vitamin E (10 mg/kg), para-oxybenzoic acid (100 mg/kg), methionine (100 mg/kg) and magnesium ions (5 mg/kg);

Group 3 - rats treated with doxorubicin morpholinium salt of thiazotic acid (tiotriazoline drug, PAT "Halychpharm", Ukraine) at the dose of 150 mg/kg body weight;

Group 4 - rats treated with doxorubicin and ubiquinone-10 (kudesan Q10 drug, ubidecarenone, TOV "VneshtorgPharma", Russia) at the dose of 10 mg/kg body weight;

Group 5 - rats, which were injected with 0.9% NaCl solution at the appropriate terms (control group).

Thiotriazoline, kudesan and EPM-Mg complex were administered to animals orally, daily, for three weeks from the first administration of doxorubicin at the above doses. Animal experiments were performed in compliance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986).

Histological and morphometric examination was performed to assess the toxic effects of doxorubicin and the effect of the studied drugs. Animals were decapitated under brief ether anesthesia.

Samples of organs (heart, liver, kidneys) were fixed in 10% formalin solution (pH 7.4, with phosphate buffer, duration of fixation 24 h). After fixation and washing in running water, the samples were dehydrated in ascending concentrations of ethanol (70%, 80%, 90%, 96%), dioxane, xylol, paraffin xylol (1: 1; 37°C), and embedded in paraffin (after 2 paraffin changes, 56°C) (Leica Surgipath Paraplast Regular). Paraffin organ sections with the thickness of 4-6 μm were made using Thermo Microm HM 360 microtome. The sections were dewaxed, rehydrated and stained with hematoxylin and eosin according to standard methods [5].

For morphometric assessment of quantitative changes in organs, the following indices were selected: in the heart – the mean area of cardiomyocyte nuclei (μm^2), in the liver – the mean area of the hepatocyte nuclei (μm^2), the mean area of hepatocyte soma (μm^2), the diameter of sinusoidal hemocapillaries (μm), in the kidney – the mean area of the renal corpuscle capsule (μm^2), the diameter of the nephron's proximal convoluted tubules (μm), the diameter of the nephron's thin tubules (μm), the diameter of the ascending distal tubule (μm). To do this, by means of Olympus BX 51 microscope photomicrographs of microscopically examined organs were obtained (magnification×400). Measurements were performed in microphotographs using Carl Zeiss software (AxioVision SE64 Rel.4.9.1).

The data are presented as M±m. The intergroup difference was assessed using Student's t-test.

Results of the study and their discussion. According to the results of histological study, no obvious signs of necrosis or dystrophic changes of the myocardium in the studied heart samples were detected at the histological level. But there was some difference estabiuished. Thus, in the group of animals administered doxorubicin only, a probable decrease in the area of cardiomyocytes nuclei was found (table 1). In groups of animals that received EMP-Mg complex and thiotriazolini together with doxorubicin, significant changes or a tendency to recovery were found, which indicates a cytoprotective effect (table 1).

Table 1

Results of cardiomyocyte nuclei morphometric assessment

Index	Group				
	Control	Dox.	Dox.+ EPM-Mg	Dox.+ thiotriazolini	Dox.+ ubiquinone-10
Mean area of cardiomyocytes nuclei, μm^2	116.2±7.09	90.4±5.04 ^	99.7±5.66 ^*@	108.5±6.25	94.3±6.13 ^

Note: Henceforward: ^ – reliable for control (p <0.05); * – authentic to the Dox group. (p <0.05); # – significantly to the group Dox. + EPM-Mg (p <0.05); @ – significantly to the group Dox. + thiotriazoline (p <0.05).

In the myocardium of animals treated with doxorubicin, ubiquinone-10 and thiotriazolini, cross striation of cardiomyocytes was found, whereas in the group without pharmacorrection striation was absent in most cardiomyocytes. However, karyopyknosis, i.e. death of cardiomyocytes, was not registered. Loss of cross striation was assessed as a morphological evidence of dystrophic changes in cardiomyocytes under the action of doxorubicin. Additional changes were found in myocardial vessels: abrupt stasis, dilatation and blood supply of hemocapillaries, venules and arterioles. This indicates a blood flow disorder, perfusion in the myocardium. The absence of vascular stasis was observed in the group of animals treated with EPM-Mg and ubiquinone-10. The conclusion about cytoprotective (cardioprotective) action of thiotriazolini and EPM-Mg complex at doxorubicin intoxication was made.

According to the results of histological study, obvious signs of structural damage (hemorrhage, necrosis of lobules or hepatocytes, inflammation) in the studied liver samples of animals that received doxorubicin only, were not detected. Structural changes were only observed at the level of sinusoidal capillaries and hepatocytes. In the group receiving doxorubicin only, there was a sharp blood filling of the central veins in the liver lobules and increased lumen of the sinusoidal capillaries, hepatocytes were characterized by the increased nucleus size (table 2). In groups with pharmacocorrection, the histological structure of hepatic lobules did not differ significantly from the control group, but the action of EPM-Mg and ubiquinone-10 caused a probable increase in the mean cross-sectional area of hepatocytes (table 2), and in the group of animals receiving ubiquinone-10, cytoplasm was granular, indicating initial dystrophic changes at the cellular level. In the group of animals treated with ubiquinone-10, a sharp increase in the lumen of sinusoidal capillaries was additionally found, which also indicates structural and functional changes in the liver lobules and explains the cytological changes of hepatocytes in this group. According to histological and morphometric

data, the most pronounced effect was found for thiotriazolini and EPM-Mg. No probable changes were found between these drugs action.

Table 2

Results of the liver morphometric study

Index	Group				
	Control	Dox.	Dox.+ EPM-Mg	Dox.+ thiotriazolini	Dox.+ ubiquinone-10
Mean area of the hepatocyte nucleus, μm^2	112.2±5.62	129.9±4.20 ^	100.1±5.52 *^	96.8±5.04 *	154.7±5.44 *#@^
Mean area of hepatocyte soma, μm^2	367.2±16.2	393.9±11.9	415.0±13.3 ^	317.4±14.0 *#^	537.0±15.7 *#@^
Diameter of sinusoidal hemocapillaries, μm	8.64±0.32	10.1±0.33 ^	10.2±0.47 ^	13.7±0.92 *#^	19.1±1.25 *#@^

Increased lumen of sinusoidal hemocapillaries and their blood supply is a morphological manifestation of impaired microcirculation of liver lobules with the administration of doxorubicin. No hepatocyte necrosis was detected, but an increase in the area of hepatocytes was found in animals treated with ubiquinone-10 and thiotriazolini, and nuclei were decreased in the group of animals treated with thiotriazolini (table 2). Increase in the hepatocytes' size can be assessed as a result of two independent processes, such as activation of synthetic processes with the preserved cell cytology (as in the group of animals receiving EPM-Mg complex and thiotriazolini together with doxorubicin) or with the initial stage of dystrophic changes (as in the group of animals receiving ubiquinone-10 together with doxorubicin).

Histological studies showed nephrotoxic effect of doxorubicin. In the renal cortex there was a urinary space increase in the renal corpuscles (cross-sectional area increase of the Shumlyansky-Bowman capsule, free space appeared between the capsule and the vascular glomerulus), a tendency to decrease the size of the vascular glomerulus. The blood capillaries of the glomerulus and microvessels of the renal cortex are blood-filled, in the state of stasis. The capsule's integrity remained structurally intact. A probable decrease in the diameter of the thin tubules in the nephrons was found in the medulla, and edema and dystrophic changes of epitheliocytes were registered in the thick tubules (proximal and distal convoluted tubules). Structural changes were assessed as initial structural and functional disorders (table 3).

In the group of animals that received the EPM-Mg complex together with doxorubicin, a sharp increase of the urinary space in the renal corpuscles and an increase in the lumen of the nephrons' thin tubules were found. Acidophilic gelatinous content was detected in the lumen of the nephron tubules in the cortex and medulla. The authors [13] describe this as a structural manifestation of sclerosis. Inclusions similar to hemosiderin or hemoglobin pigment were found in some tubules (table 3). These changes are evidence of dystrophic changes in the kidney under the action of doxorubicin.

In the group of animals treated with thiotriazolini together with doxorubicin, relative preservation of nephron structure was observed. The structural organization and morphometric data of the renal corpuscles did not differ from the control ones, but a slight decrease in the lumen of thin tubules in the nephrons was found. In capillaries of cortex and medulla increase in blood filling is observed (table 3).

In the group of animals treated with ubiquinone-10 together with doxorubicin, polymorphic changes were observed at the level of various nephrons. The structural organization of some nephrons was preserved, while in others sharp dystrophic changes of epitheliocytes were noted. A separate structural manifestation of functional changes in the tubular epithelium nephrons was the occurrence of inclusions similar to hemosiderin (table 3). These changes may be associated with hemolysis, filtration of hemolysis products through glomerular microvessels, reabsorption and lysosomal digestion of epitheliocytes' tubules [15]. In the medulla, 1/2-2/3 tubules were filled with acidophilic content, as observed in the group of animals that received the EPM-Mg complex, which also indicates increased filtration and changes in reabsorption. Similar structural changes of nephrons are described concerning the model of doxorubicin nephropathy in the publication [12].

It is known from the literature that doxorubicin causes myocardial damage, which consists in the vacuolar decay of cardiomyocytes and the replacement of damaged areas with interstitial fibrosis. But fibrosis occurs less frequently than focal fibroblast proliferation and histiocyte infiltration [7]. The primary sign of cardiotoxicity is disruption of myofibrils and disorganization of the nucleus, which further progresses up to vacuolation of cells. In our study, only the loss of striation and reduction in the size of cardiomyocytes' nuclei was found, which can be assessed as a cytological manifestation of the early development of doxorubicin toxicity.

Table 3

Results of renal nephrons morphometric study

Index	Group				
	Control	Dox.	Dox.+ EPM-Mg	Dox.+ thiotriazolini	Dox.+ ubiquinone-10
Mean area of the renal corpuscle capsule, μm^2	25564.7± 1583.3	19794.5± 3267.8	33261.3± 3004.2 *^	24966.9± 5157.1	24481.6± 2905.8
Mean cross-sectional area of renal corpuscle's vascular glomerulus, μm^2	19775.3± 1296.9	13323.6± 2839.0	21760.2± 884.9 *	18120.2± 3609.5	19141.5± 2667.9
Diameter of the proximal nephron convoluted tubules, μm	65.9±1.62	57.1±1.38 ^	61.0±2.85	54.3±1.51 #^	57.4±2.35 ^
Diameter of the nephron thin tubules, μm	25.6±1.31	24.4±1.53	44.4±2.06 *^	19.7±1.41 *#^	27.25±2.14 #@

The increase in the nuclei area may be a manifestation of the synthesis activation and of cardiomyocytes' compensation. Changes in the microcirculatory system of the myocardium can be explained by the release of vasoactive compounds by damaged cells. Thus, there was a sharp increase in the level of venous histamine, catecholamines, E and F prostaglandins after the administration of doxorubicin [11]. The importance of preserving the capillaries' endothelium is pointed out by other authors [10]. Martinel Lamas, et al. showed that the administration of histamine before doxorubicin reduced the cardio- and hepatotoxic effects of the latter, which probably improves vascular perfusion [11].

The nephrotoxic effect of doxorubicin is also damage to the renal corpuscles' vascular glomeruli, which is accompanied by an increase in urinary space and is a manifestation of impaired, increased filtration. Increased urinary space was recorded in all groups of animals administered with doxorubicin, and in the group of animals that were additionally administered EPM-Mg and ubiquinone-10, additionally acidophilic content in individual tubules was found, which is also evidence of damage to nephrons' epithelial cells, of increased and impaired reabsorption. Proximal tubules of the nephrons underwent minor structural changes compared to the thin tubules and the distal segment of the nephron. Reduced lumen of the thin tubules is also a consequence of epithelial cell dystrophy under the action of doxorubicin. However, the action of thiotriazolini had a positive effect on the nephrons' structure preservation in the kidney (renal rings, thick and thin tubules).

Our previous studies [1, 2] can explain this by the fact that under the influence of the complex of EPM-Mg, thiotriazolini and kudesan drugs, there was a restoration of the disturbed oxidant-antioxidant balance in the body under the action of doxorubicin. In the heart, liver and kidneys, the content of free radical oxidation products of lipids and proteins decreased together with the activation of antioxidant protection enzymes, which may further confirm the protective properties of these compounds under the action of doxorubicin.

Conclusion

The results of histological and morphometric studies indicate the potential cytoprotective properties of the studied drugs of metabolic action in the experimental doxorubicin cardiomyopathy and can serve as an experimental justification for their use as protective agents in clinical practice.

Prospects for further research: to develop and substantiate the efficacy of using metabolic drugs in clinical practice, in particular, complexes that activate endogenous synthesis of ubiquinone, to reduce the toxicity of doxorubicin and prevent the development of cardio-, nephro- and hepatopathies.

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PROTEINASE-INHIBITORY POTENTIAL IN RAT PANCREAS AT THE BURN SHOCK AND TOXEMIA STAGES OF BURN DISEASE

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The increase in general antitryptic activity was by 1.4 times higher for 1 day (at the stage of burn shock), while the total proteolytic activity decreased, compared to the respective parameters of the pancreas in the control group of rats under the conditions of burn disease. Then both indices decrease and remain reduced for 7 days. At the next stage of toxemia (on day 7), with a burn, the total antitryptic activity in the pancreas decreases by 1.6 times compared to the control animals. On the 7-th day, the total antitryptic activity in the pancreas decreases by 2. 2 times, compared to the 1-st day. Changes in proteolytic and antitryptic activity in the rat pancreas cause changes in proteinase-inhibitory potential at the stage of burn shock and the stage of toxemia in experimental burn disease. The proteinase-inhibitory potential of the rat pancreas on the 1-st day after the burn differs from this index value on the 7-th day.

Key words: burn disease, pancreas, antitryptic activity, proteolytic activity.

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ПРОТЕЇНАЗНО-ІНГІБІТОРНИЙ ПОТЕНЦІАЛ У ПІДШЛУНКОВІЙ ЗАЛОЗІ ЩУРІВ НА СТАДІЇ ОПІКОВОГО ШОКУ І СТАДІЇ ТОКСЕМІЇ ПРИ ОПІКОВІЙ ХВОРОБІ

Зростання загальної антитріптичної активності в 1,4 рази відзначено на 1 добу (на стадії опікового шоку), при цьому загальна протеолітична активність падає, в порівнянні з відповідними показниками підшлункової залози контрольної групи щурів в умовах опікової хвороби. Потім обидва показники зменшуються і залишаються зниженими на 7 добу. На наступній стадії токсемії (на 7 добу) при опіку загальна антитріптична активність в підшлунковій залозі знижується в 1,6 рази, в порівнянні з контрольними тваринами. На 7 добу загальна антитріптична активність в підшлунковій залозі знижується в 2, 2 рази, в порівнянні з 1-ю добою. Зміни протеолітичної і антитріптичної активності в підшлунковій залозі щурів викликають зміни протеїназно-інгібіторного потенціалу на стадії опікового шоку і стадії токсемії за експериментальної опікової хвороби. Протеїназно-інгібіторний потенціал в підшлунковій залозі щурів в 1-у добу після опіку відрізняється від даного показника на сьомий день.

Ключові слова: опікова хвороба, підшлункова залоза, антитріптична активність, протеолітична активність.

The work is a fragment of the research project "General patterns of pathological changes in experimental burn disease and development of methods for its correction", state registration No. 0119U102850.

From our previous studies in rats, changes in the inhibitory potential of the blood serum as well as in the pancreas in acute stress are known. The total proteolytic activity both in the blood serum and in parallel in the pancreas, increases against the background of total antitryptic activity declining [1].

The literature highlights the results of proteinase-inhibitory potential studies in stress under the burn disease conditions [2].