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COMPARATIVE ANALYSIS OF THE NEPHROPROTECTIVE ACTION OF ADEMETIONINE AND GLUTATHIONE IN ISCHEMIA-REPERFUSION ACUTE KIDNEY INJURY

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Зважаючи на значні досягнення у медикаментозному лікуванні та удосконалення методів нирковозамісної терапії, смертність від гострого пошкодження нирок (ГПН) залишається високою і становить близько 25-70 %. Не винятком є ішемічно-реперфузійна форма ГПН з його мультифакторним патогенетичним розвитком та швидким прогресуючим перебігом, причиною виникнення якого зазвичай стають травми, сепсис, трансплантація нирок, вплив токсичних речовин. Як засоби для патогенетичної корекції ішемічно-реперфузійної форми ГПН привернули увагу препарати з доведеною цитопротекторною та антиоксидантою активністю – адеметіонін та глутатіон.

Мета. *Порівняти вплив адеметіоніну та глутатіону на функціональну активність та прооксидантний-антиоксидантний баланс у нирках щурів при ішемічно-реперфузійному ГПН.*

Методи. *Досліди проведені на 28 статевозрілих нелінійних білих щурах масою 130–180 г, які були розділені на 4 групи (n=7): I група – контроль, II група – моделювання ішемії / реперфузії, III – група тварин, яким вводили внутрішньочеревно в профілактичному режимі адеметіонін в дозі 20 мг/кг (Гептрал, "Abbott SpA", Італія), IV – група тварин, яким вводили внутрішньочеревно глутатіон в дозі 30 мг/кг, (ТАД 600, Biomedica Foscama, Італія), V – група тварин, яким вводили внутрішньочеревно референс –препарат мексидол в дозі 100 мг/кг, (Мексидол, «Фармасофт», РФ). Функціональний стан нирок щурів оцінювали через 24 год за умов водного навантаження за показниками діурезу, ШКФ, концентрації та екскреції білка, показниками іонів натрію та калію з сечею. Стан пероксидації в нирках оцінювали за показниками МДА та продуктів ОМБ, та системи антиоксидантного захисту – за активністю КАТ, ГП.*

Результати. *Застосування досліджуваних препаратів при I/P призвело до відновлення видільної функції нирок, що реалізувалося збільшенням ШКФ, і відповідно, діурезу з одночасним зменшенням азотемії та протеїнурії, та іонорегулювальної функції, про що свідчить збільшення реабсорбції іонів натрію зі зменшенням концентрації іона в сечі та відновленням проксимального та дистального транспорту. Аналіз антиоксидантної системи захисту при застосуванні препаратів свідчить про зниження пероксидного окиснення ліпідів на тлі активації антиоксидантної системи, при чому достовірно кращі показники були зафіксовані у групі тварин, яким вводили препарат глутатіону, що підтверджується гістологічними дослідженнями.*

Висновки. *Встановлено, що адеметіонін та глутатіон виявляють нефропротекторну дію при ішемічно-реперфузійному гострому пошкодженні нирок. При цьому достовірно кращі показники були зафіксовані у групі тварин, яким вводили препарат глутатіону, як за відновленням функціонального стану нефронів, так і за впливом на прооксидантно - антиоксидантний баланс у тканині нирок, що підтверджується даними гістологічного дослідження. Отримані результати створюють підґрунтя для подальшого дослідження нефропротекторного потенціалу препаратів адеметіоніну та глутатіону за умов ГПН різної етіології*

Ключові слова: *нефропротекторна дія, адеметіонін, глутатіон, ішемія- реперфузія, гостре пошкодження нирок*

1. Introduction

Today, due to significant advances in drug treatment and the improvement of renal substitution therapy, the mortality rate from acute kidney injury (AKI) remains high and is about 25–70 % [1]. There is no exception for the ischemic-reperfusion form of the AKI with its multifactorial pathogenetic development and rapid progressive course, the cause of which is usually injury, sepsis, kidney transplantation, and the effects of toxic substances [2, 3].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

The ischemic injury primarily affects the structure and function of the tubular epithelium cells, which is accompanied by dysfunction of the microcirculation, the development of hypoxia, oxidative stress and inflammatory reactions, which further leads to necrosis and apoptosis of the nephrocytes. A critical factor in the development of this renal cell injury is the generation of a large number of free oxygen radicals and endothelial damage [4], since ischemia results in a rapid degradation of ATP, ADP and AMP, which leads to the depletion of the energy supply of the cell. AMP is metabolized in two ways:

1) the formation of nucleotides, the loss of which leads to a decrease in the formation of ATP and an increase in the intracellular level of calcium ions, which in turn activates proteinases and phospholipases – enzymes that violate cell cytoskeleton;

2) by the formation of hypoxanthine, the accumulation of which promotes the generation of active forms

of oxygen, and its subsequent biotransformation leads to the formation of hydrogen peroxide and superoxide, which, along with free iron ions and nitric oxide, which is formed in parallel with renal tubules by means of NO synthase, contribute to the formation peroxinitrate, which in turn leads to cellular damage through nitrosylation of cellular proteins, activation of peroxide lipid oxidation, damage to the DNA of nephrocytes and induction of apoptosis [5].

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

Our attention as a means for pathogenetic correction of ischemic-reperfusion form of AKI attracted drugs with cytoprotective and antioxidant activity - ademetionine and glutathione.

Ademetionine is a natural amino acid found in all body tissues. It participates in reactions of transmethylation, acting as a donor of a methyl group during the construction of a phospholipid cell membrane, providing membrane protective effect [6]. In the reactions of transfusion, ademetionine acts as a precursor in the formation of sulfurous compounds (cysteine, taurine and glutathione). With oxidative stress, it replenishes precisely the mitochondrial glutathione, providing the flow of the internal mitochondrial membrane. [7]. Affects the metabolism of catecholamines (dopamine, adrenaline, noradrenaline), indolamines (serotonin, melatonin) and histamine [8, 9]. As a medicinal product exhibits a powerful hepatoprotective effect, and also has anti-inflammatory, anti-depressant properties [10].

Glutathione – an endogenous tripeptide, is the most powerful antioxidant and detoxicant due to the reactivity of the SH group, which as a strong nucleophile binds electrophiles [11]. In addition, the available in its composition are involved in the metabolic processes of the body. Thus, glutamic acid is involved in protein and hydrocarbon metabolism, stimulates oxidation processes, prevents reduction of oxidation-reducing potential, affects processes of glycolysis in tissues, exhibits hepatoprotective effect, etc. As a medicinal product used to prevent nephrotoxicity and hepatotoxicity in chemotherapy with cisplatin, as a hepatoprotector in acute and chronic hepatitis, cirrhosis and other liver pathologies [12].

4. The field of research considering the general problem, which is described in the article

The issue of rational treatment and prophylaxis of I/R AKI remains unresolved today, and effective methods of treatment and prevention of this syndrome have not yet been developed. Therefore, the search for new drugs with nephroprotective activity is an important aspect of intensive therapy of modern nephrology.

5. Formulation of goals (tasks) of article

Considering the role of antioxidant defense in the pathogenesis of AKI, the aim of our study was to compare the effects of ademetionine and glutathione on functional activity and the antioxidant-prooxidant balance in rat kidneys in ischemic-reperfusion AKI.

6. Presentation of the main research material (methods and objects) with the justification of the results

Experiments were conducted on 28 sexually active non-linear white rats weighing 130–180 g. Animals were divided into 4 groups (n=7): group I – control (pseudo-operated animals), group II – Ischemia/Reperfusion modeling (I/P), group III animals received intramuscular injection of ademetionine 20 mg/kg (Heptral, "Abbott SpA", Italy) intradermally during the three days prior to I/P simulation, animals of the IV group received glutathione 30 mg/kg (TAD 600, "Biomedica Foscama", Italy). Doses of drugs are determined by reverse extrapolation [13]. As a reference drug was used Mexidol ("Farmasoft", RF) as an antihypoxant with expressive antioxidant and proven nephroprotective properties [14]. The drug was administered intraperitoneally at a dose of 100 mg/kg.

Ischemia was modeled according to aseptic conditions under general anesthesia (aethaminalum sodium, 40 mg/kg): they performed mid-laparotomy, isolated each kidney, impositioning on the renal leg of the clamp for the purpose of crossing the artery, veins and ureter for 60 minutes, followed by sealing the abdominal cavity. After removing the clamp, the abdominal cavity was stained with subsequent 24-hour reperfusion and a grading of the kidneys [15].

Functional state of kidney of rats was evaluated after 24 h under the conditions of water loading (intragastric injection of warm drinking water (37 °C) in the volume of 5 % of body weight) according to the parameters of the excretory and ionregulatory function of the kidneys. Excretory kidney function was evaluated for diuresis, glomerular filtration rate (GFR), plasma creatinine, water reabsorption, protein concentration and excretion. The ionoregulatory function is based on Na^+ concentration in urine, fractional excretion of Na^+, absolute and relative Na^+ reabsorption, Na^+ proximal and distal transport, K^+ concentration in blood plasma and its excretion. The content of Na^+ and K^+ ions in the urine was measured on the device "FPL-1" (Ukraine) by the method of photometry of the flame [16, 17]. The standardization of the indicators was carried out by converting to 100 g of animal body weight or 100 μl of glomerular filtrate. Based on the obtained data, the indicators of kidney function were calculated [18].

The state of peroxidation in the kidneys was evaluated by the indicators: malone dialdehyde (MDA) by the reaction between MDA and thiobarbituric acid [19] and products of oxide-modified proteins (OMB), which was determined by the amount of 2,4-dinitrophenylhydrazones obtained by the interaction of 2,4-dinitrophenylhydrazine with carbonyl groups formed during the process of oxidative modification of proteins [20]. Antioxidant protection systems - by activity of catalase (KAT), which was determined by the principle of destruction of the catalase of a substrate of H_2O_2 and measuring the proportion of undiluted hydrogen peroxide interacting with ammonium with molybdate to form a stable colored complex [21], and glutathione peroxidase (GP) by the amount of oxidized glutathione, which was formed from reduced glutathione in the disinfection of hydrogen peroxide in an enzymatic reaction [22].

The kidney tissue that was taken for microscopic examination was fixed for 48 hours in a solution of neutral buffered formalin (10 %), followed by an ethanol dehydration procedure and paraffin emulsion at a temperature of 58 °C. For morphological evaluation of histological sections, histologic sections of 5 μm thick, captured with hematoxylin and eosin were obtained. Documentation of pathological processes was carried out by computer morphometry of objects in histological preparations. Digital copies of the optical image of microscopic sites were obtained using an Olympus digital camera (model C740UZ) and a microscope LUMAM-P8 with the creation of a bank of digital microphotographs and then analyzed in the medium of the computer program "VideoTest - Size 5.0" (TOV "VIDEOTEST", RF) All studies were conducted in accordance with the European Union Directive 2010/63 / EU on the protection of animals used for scientific purposes [23].

Statistical processing of the results was performed using SPSS Statistics 17.0. The reliability of the difference between the scores was evaluated using the parametric t-criterion of Student (in normal distribution) and non-parametric Mann-Whitney U-criterion (in case of mismatch with normal distribution). The critical value level was adopted for $p<0.05$.

7. Results and their discussion

In animals, after the pathology modelling were significant changes in the excretory function of the kidneys, which manifested in a decrease of diuresis by 84 %, a decrease in GFR in 3.1 times, and a significant reduction in water reabsorption, indicating the development of renal hypophiltration, and, accordingly, the oliguric stage of the AKI (Table 1). Significant decrease in glomerular filtration led to the development of retention azotemia: the concentration of creatinine in the blood plasma increased by 2.6 times, compared with the group of pseudo-controlled animals. Instead, the administration of the investigational drugs led to increased urinary excretion in the treated animals, preventing the development of oliguria: when using ademetionine, diuresis increased by 53.8 %, glutathione – by 81.1 %, compared with those of the animals in the group of pathology. Accordingly, there was a resumption of glomerular filtration (with the use of ademetionine GFR increased 1.7 times, glutathione - 2.7 times) with a significant restoration of water retention and reduction of retention azotemia: the concentration of creatinine in blood plasma decreased by 1.4 times and in 2 , 1 time in comparison with animals of the group of pathology (Table 1).

Table 1

Functional state of kidney of rats at application of ademetionine and glutathione on the background of development of ischemic-reperfusion (I/R) AKI, M±m (n=7)

Indicator	Control	I/R	I/R+ademetionine	I/R+glutathione	I/R+mexidol
Diuresis, ml	4.38±0.19	2.38±0.11$^{\#\#}$	3.66±0.13**	4.31±0.14**	3.91±0.14**
GFR, μl/min	532.7±47.3	173.1±9.9$^{\#\#}$	296.7±8.3$^{**\circ\circ}$	463.7±24.2$^{*\circ\circ}$	342.47±12.7**
Plasma creatinine, μmol/L	63.21±6.05	165.4±9.23$^{\#\#}$	117.83±4.93$^{**\circ}$	78.39±2.37$^{**\circ\circ}$	101.65±4.35**
H_2O reabsorption, %	99.14±0.08	98.61±0.07$^{\#\#}$	98.76±0.05	99.06±0.04$^{**\circ}$	98.85±0.04**
Concentration of protein in urine, g/l	0.016±0.002	0.049±0.003$^{\#\#}$	0.033±0.004**	0.022±0.002**	0.030±0.004**
Excretion of the protein, mg/100 ml	0.014±0.001	0.068±0.004$^{\#\#}$	0.040±0.002**	0.021±0.002$^{**\circ}$	0.034±0.005**
Concentration of Na^+ in urine, mmol/l	0.52±0.03	2.57±0.07$^{\#\#}$	1.29±0.06$^{**\circ\circ}$	0.75±0.04$^{**\circ\circ}$	1.06±0.03**
Concentration of Na^+ in blood, mmol / l	121.07±6.77	146.76±7.96	136.07±2.88	120.00±4.50*	131.79±3.85
Fractional excretion of Na^+, μmol/min	0.38±0.05	2.46±0.13$^{\#\#}$	1.19±0.10**	0.57±0.05$^{**\circ\circ}$	0.93±0.05**
Absolute reabsorption of Na^+, μmol/min	63.78±5.17	25.35±1.88$^{\#\#}$	40.38±1.60**	55.73±3.80**	45.28±2.68**
Relative reabsorption of Na^+, %	98.08±0.17	94.86±0.36$^{\#\#}$	96.06±0.24*	97.40±0.18$^{**\circ\circ}$	96.54±0.11**
Proximal transport of Na^+, mmol/2 h	7.13±0.61	2.70±0.20$^{\#\#}$	4.35±0.17**	6.17±0.43$^{**\circ}$	4.92±0.29**
Distal transport Na^+, μmol/2 h	527.6±34.5	346.1±29.3$^{\#\#}$	494.2±25.4**	514.7±25.6**	512.84±29.9**
Concentration of K^+ in plasma, mmol/l	5.18±0.49	4.46±0.10$^{\#}$	4.93±0.23	5.25±0.13**	5.07±0.29
Excretion of K^+, μmol/100 μl	4.37±0.47	16.92±4.27$^{\#}$	12.11±0.74	6.51±0.52$^{*\circ\circ}$	10.55±0.84

*Note: Statistically significant differences with the data of the group: control - $^{\#}$ ($p<0.05$), $^{\#\#}$ ($p<0.01$); Model Pathology (AKI) - * ($p<0.05$), ** ($p<0.01$); of experimental preparations with a reference preparation - $^{\circ}$ ($p<0.05$), $^{\circ\circ}$ ($p<0.01$)*

Due to the injury of the filtration apparatus of the nephron in animals of the model pathology group, there was a significant proteinuria: the concentration of protein in the urine increased 3.1 times, and its excretion – 4.8 times, compared with the group of intact animals. The use of the investigational drugs led to a significant reduction in proteinuria: ademetionine reduced the concentration of protein in urine by 1.5 times, glutathione – by 2.2 times, with excretion decreasing 1.7 times in the group of ademetionine and 3.2 times in the glutathione group, which indicates a decrease in the degree of damage to the nephrocytes (Table 1).

The condition of the tubal duct system of the kidneys of animals was evaluated according to the indicators of the ion-regulating function of the kidneys. Thus, in animals of the model of pathology, there was a marked increase in sodium content in urine (4.9 times), with a decrease in the fractional excretion of this ion by

6.5 times compared to pseudo-controlled animals. With the decrease in the activity of tubular transport, the absolute reabsorption of sodium ions decreased by 2.5 times, relative – by 3.3 %, which indicates a significant damage and death of tubular cell.

Investigated drugs prevented the transport of sodium ions by restoring the reabsorption process. Thus, the concentration of sodium ions in urine was significantly lowered when glutathione was used 3.4 times, fractional excretion – 4.3 times. When ademetionine was administered, the indices decreased by 2 times and by 2.1 times, respectively. Indicators of absolute and relative reabsorption of sodium ions also tended to improve, indicating that the functional capacity of nephrons was maintained under the influence of drugs. Thus, absolute reabsorption of sodium ions under the influence of ademetionine increased 1.6 times, glutathione – 2.2 times, relative reabsorption increased by 1.3 % and 2.7 % respectively (Table 1)

Significant ischemic injury to the proximal nephron in the model of the AKI is confirmed by a decrease in the corresponding index of transport of sodium ions, which is accompanied by a decrease in the transport of these ions in the distal nephron. In the group of treated animals, the protective effect on tubular cells was manifested by an increase in the index of proximal transport of sodium ions in the application of ademetionine in 1.6 times, glutathione - in 2.3 times. In this case, the activation of distal transport of these ions by the mechanism of the canal-canal balance: 1.4 times using ademetionine and 1.5 times - in the group of glutathione, respectively (Table 1).

The study of potassium ion content showed that in the group of model pathology animals the concentration of potassium ions in plasma decreased by 15.6 % due to an increase in excretion of this ion by 3.9 times, and the use of glutathione prevented the development of hypokalemia.

Simultaneously, in the kidneys of animals in the group of model pathology, the activation of peroxide oxidation of lipids was observed, which was shown by an increase in the content of MDA by 1.7 times in the kidney tissue. The content of OMB products increased by 1.5 times compared to pseudo-operated animals. Instead, in the treated animals, these rates were lower: the content of MDA in the kidneys decreased slightly by 1.2 times with the use of ademetionine and 1.5 times - with the application of glutathione. A similar trend was observed in the processes of oxidation of proteins: the content of OMB products in the kidney tissue decreased by 1.2 times with the use of ademetionine, and by 1.4 times, with the introduction of glutathione (Table 2).

From the antioxidant system at I/R model of the AKI, a decrease in CAT activity in the kidney tissue was detected by 23.2 % compared to pseudo-operated animals. Glutathione more effectively increased the activity of the enzyme (by 27.6 %), which slightly exceeded the pseudo-controlled animals. Under the influence of ademetionine, the activity of KAT in renal tissue increased by 10.1 % compared to the animals in the group of pathology.

The development of ischemic-reperfusion GPN was accompanied by a decrease in 1.9 times the activity of GP in the renal tissue compared with the control group animal. In the use of drugs noted an increase in the activity of GP, compared with the indicators of the group of pathology: 1.7 times with the introduction of glutathione and 1.3 times – with the use of ademetionine (Table 2).

Table 2

Prooxidant-antioxidant balance in renal kidneys of rats with ischemic-reperfusion acute kidney damage (AKI) (M±m, n=7)

Indicator	Control	I/R	I/R+ademetionine	I/R+glutathione	I/R+mexidol
Content of MDA, μmol/g	40.36±2.83	70.18±2.16$^{\#\#}$	58.83±0.96$^{**\circ\circ}$	46.48±2.44**	49.01±1.39**
Content of OMB, o.o.g./g	8.43±0.43	12.56±0.76$^{\#}$	10.40±0.72	8.94±0.42**	9.23±0.19**
CAT activity, μmol/min×mg	7.13±0.35	5.29±0.23$^{\#\#}$	5.83±0.77	7.42±0.20**	7.04±0.37**
GP activity, nmol/min×mg	217.7±9.8	114.4±9.5$^{\#\#}$	144.6±11.9°	196.3±4.4**	188.07±9.46**

*Note: Statistically significant differences with the data of the group: control – $^{\#}$ ($p<0.05$), $^{\#\#}$ ($p<0.01$); model pathology (AKI) – * ($p<0.05$), ** ($p<0.01$); experimental drugs with a reference preparation ($p<0.05$); MDA – malonic dialdehyde, OMB - oxide-modified proteins, GP - glutathione peroxidase, CAT – catalase*

Thus, the use of ademetionine and glutathione in the conditions of I/R led to a decrease in peroxide oxidation of lipids on the background of activation of the antioxidant system. At the same time, the antioxidant effect of ademetionine was slightly inferior, and the glutathione effect corresponded to the activity of the referent drug.

Nephroprotective activity of ademetionine, glutathione and mexidol was verified by histological data. Analysis of histopreparations of kidney of rats in the pathology group allowed to establish significant pathological changes in the histostructure of the kidneys in the form of necrosis and dystrophy.

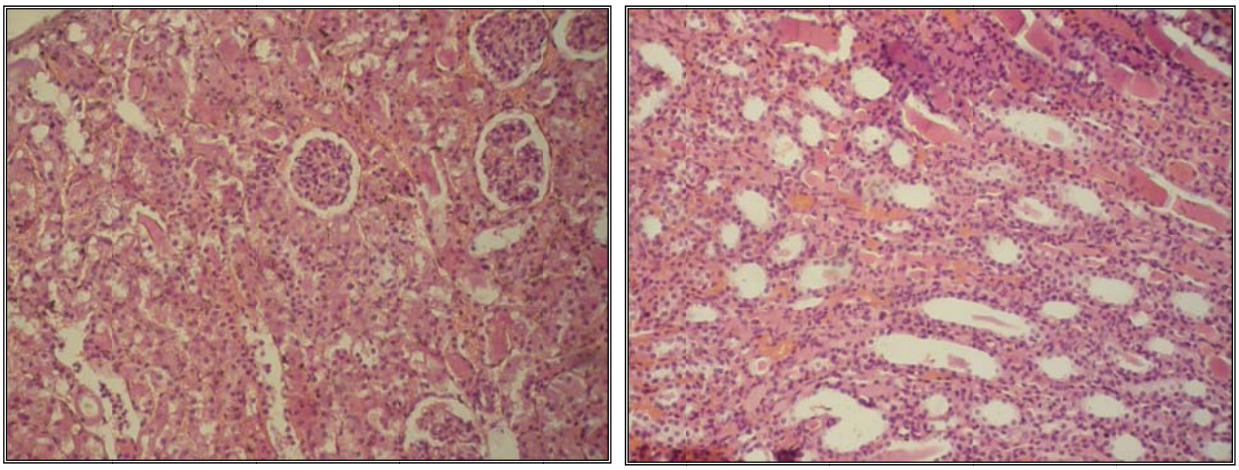
In the kidneys of the animals, changes in the model of the pathology of the disease cover 89.1 % of the tubular epithelium cells, of which 10.4 % are in the state of coagulation necrosis, the remaining nephrocytes with signs of degenerative changes of varying degrees of defeat. Thus, for 75 % of epithelial cells characterized by

dystrophy as a hydropic swelling, 3.7 % cells – with signs of hydropic vacuolisation. The expressed changes are also present in the brain substance, where the expansion of the lumen of the collecting tubes has been revealed, with 6.7 % filled with hyaline cylinders. Areas are different with haemorrhage (Fig. 1).

In the application of ademetionine, the prevalence of pathological changes in the epithelial cells of the tubule cells of the cortical substance was 84.1 % of cells, however, virtually no necrosis was observed. In 77.9 % of cells there was a hydropic swelling, in 4.2 % of cells - a dystrophic process in the form of hydropic vacuolisation. In the cerebrospinal fluid, the tubules are enlarged, and the collection tubes are 2 % filled with hyaline cylinders (Fig. 2).

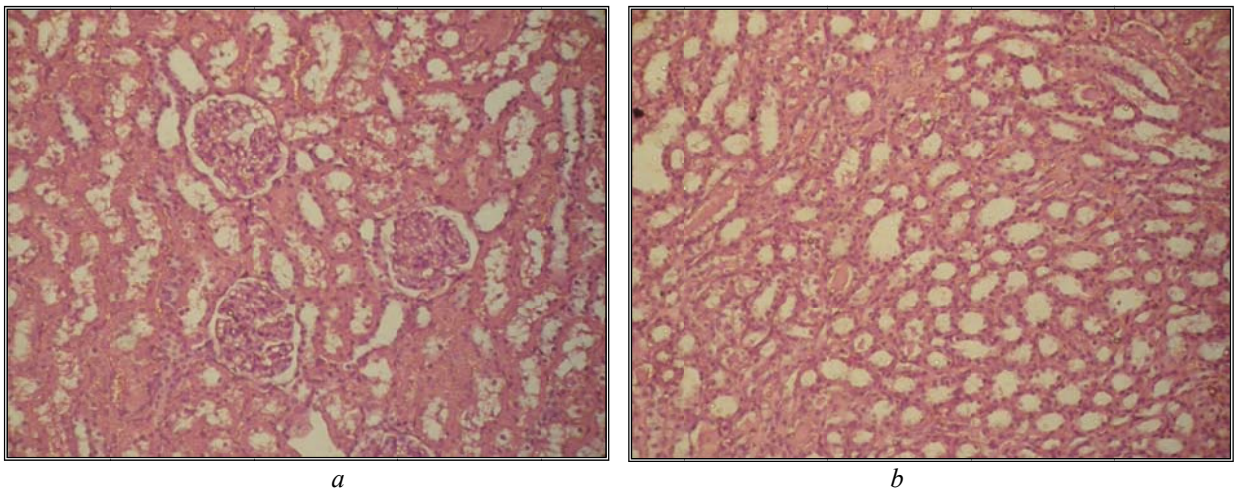
In the glutathione group, the histostructure of the kidneys approached the control group. Practically no necrotized epithelial cells were observed; the number of affected nephrocytes was 64.2 %, among which 60.3 % of the cells were in a state of hydropic swelling, and 3.9 % – with signs of hydropic vacuolization. Collective tubes of the cerebrospinal fluid are somewhat expanded, and there are isolated hyaline cylinders (Fig. 3).

In histopreparations of kidney animals, which were injected with mexidol there was no observed coagulation necrosis. The defeat of the epithelial cells of the proximal tubules of the cortical substance was 83.4 %, of which 72.8 % of the nephrocytes revealed dystrophic processes in the form of hydropic swelling, 10.6 % – hydropic vacuolization. Composite tubes of cerebrospinal fluid are filled with hyaline cylinders by 0.5 % (Fig. 4).



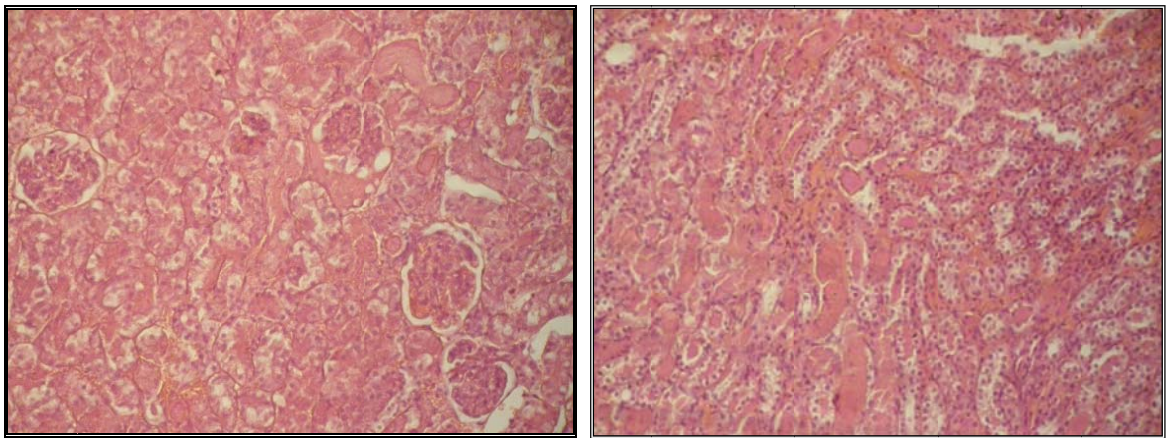
a *b*

Fig. 1. Microslide of kidney of rat with ischemic-reperfusion acute kidney injury: *a* – cortical substance; *b* – brain substance. Coloring with haematoxylin and eosin. Objective magnification ×100



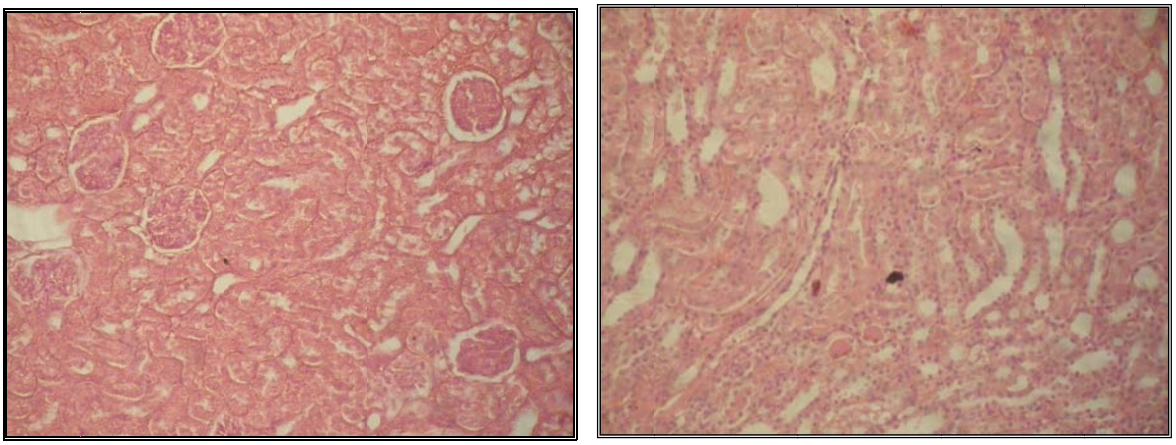
a *b*

Fig. 2. Microslide of rat kidneys with ischemic-reperfusion acute kidney injury in the use of ademetionine: *a* – cortical substance; *b* – brain substance. Coloring with haematoxylin and eosin. Objective magnification ×100



a *b*

Fig. 3. Microslide of rat kidneys with ischemic-reperfusion acute kidney injury in the application of glutathione: *a* – cortical substance; *b* – brain substance. Coloring with haematoxylin and eosin. Objective magnification ×100



a *b*

Fig. 4. Microslide of rat kidneys with ischemic-reperfusion acute kidney damage in the use of mexidol: *a* – cortical substance; *b* – brain substance. Coloring with haematoxylin and eosin. Objective magnification × 100

8. Conclusions from the conducted research and prospects for further development of this field

1. Thus, according to the functional study of the kidneys, ademetionine, glutathione and mexidol exhibited nephroprotective effect in ischemic-reperfusion AKI, promoting the protection of the renal cells in the development of renal ischemia with reperfusion, manifested in increasing GFR and diuresis, decreased proteinuria, limitation of ion losses with urine, with the predominance of glutathione in a number of indices.

2. The results of the study indicate that the most reliable indicators were recorded in the group of animals administered glutathione as both the restoration of the functional state of the nephrocytes and the effect on the prooxidant-antioxidant balance in the renal tissue, which is confirmed by the data of the histological study.

3. The established effectiveness of the drugs creates the basis for further study of their nephroprotective potential for different models of AKI.

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