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COMPARATIVE EFFICACY OF SULPHUR-CONTAINING AMINO ACIDS DERIVATIVES IN ACUTE KIDNEY INJUTY OF VARIOUS ETIOLOGY

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Abstract. This experimental study investigated the nephroprotective potential of sulfur-containing amino acids (SCAA) - ademetionine, taurine, and glutathione, under various models of acute kidney injury (AKI), including ischemia-reperfusion injury, rhabdomyolysis, and gentamicin-induced nephropathy. Functional and biochemical parameters were assessed to determine the effects of these agents on renal function, ion-regulatory activity, and oxidative stress markers. The results demonstrated that SCAA administration led to improved glomerular filtration rate, reduced proteinuria, normalized sodium and potassium ion transport, and decreased retention azotemia. Among the tested agents, glutathione showed the most pronounced nephroprotective effect under ischemia-reperfusion conditions, likely due to its antioxidant and detoxifying properties. The findings suggest that targeted application of SCAA compounds may serve as an effective strategy for the prevention and treatment of AKI through membrane stabilization and mitigation of oxidative damage in renal tissues.

Keywords: nephroprotective activity, ademetionine, ischemia-reperfusion kidney injury, gentamicin-induced nephropathy

Introduction.

Despite the fact that the concept of acute renal failure has existed in medicine for over 50 years, issues of screening, diagnosis, effective prevention, and treatment of this pathology remain unresolved because loss of kidney function is often accompanied by the development of multiple organ failure. This has led to the definition of a new syndrome—acute kidney injury (AKI)—with an expanded spectrum of diagnostic criteria, the main of which is an increase in plasma creatinine concentration, as even a slight rise may cause a sharp increase in patient mortality [1–3]. For the pharmaceutical community and medicine, the search for new and improvement of existing pharmacotherapy methods including etiological, pathogenetic, and symptomatic pathways of correction has become more urgent.

Protection of kidney tissue in such cases requires the use of nephroprotectors, but currently, they are not classified as a separate group of drugs, and information about nephroprotective properties of some agents is fragmentary and not always proven. A promising approach is the search for pleiotropic agents that can counteract hypoxia and mitigate the development of renal ischemia by affecting both renal blood flow and free radical oxidation processes [4, 5].

The hepatoprotective agents chosen for the study, sulfur-containing amino acids (SCAAs), are important components of antioxidant defense. For instance, ademetionine is the active form of methionine, due to the presence in its chemical structure of the -S^+-CH3 group, which is unstable but determines the high activity of the amino acid; moreover, ademetionine is a precursor of taurine and glutathione. Glutathione plays a crucial role in cell and organism viability as a key intracellular antioxidant [6], acts as a cysteine reserve in the cell, regulates protein synthesis, etc. Taurine, due to its physiological and pharmacological properties, is widely used in ophthalmology, cardiology, neurology, hepatobiliary system pathology, and corrects metabolic disorders [7].

Literature data confirm the multifaceted and complex use of the studied SCAAs (ademetionine, taurine, and glutathione) in various fields of medicine; however, experimentally justified reviews on their use in AKI are extremely rare, so the study of their effects on the course of AKI of different etiologies remains relevant.

The aim of the work. To investigate the effects of ademetionine, taurine, and glutathione on kidney functional status and the mechanisms of their renal effects in etiologically different models of AKI: gentamicin-induced and ischemia-reperfusion.

Materials and methods.

Gentamicin-induced nephropathy was reproduced by intramuscular administration to rats of a 4% gentamicin sulfate solution (gentamicin sulfate injection solution, 40 mg/ml, JSC "Halychpharm," Ukraine) at a dose of 80 mg/kg once daily for 6 days. The studied agents were administered prophylactically and therapeutically 40 minutes after each antibiotic injection. Animals were euthanized and materials collected on day 7 under conditions of water loading [8].

Ischemia-reperfusion AKI in rats was modeled by performing a midline laparotomy under barbiturate anesthesia (thiopental sodium, lyophilized powder for injection solution, 1 g, "Arterium," Ukraine). After laparotomy, each kidney was isolated and a clamp was applied to the renal pedicle for 60 minutes, followed by closure of the abdominal cavity. Animals were euthanized 24 hours after clamp removal under induced diuresis for functional kidney assessment. The studied agents were administered prophylactically for 3 days before ischemia/reperfusion induction [8].

Statistical analysis was performed using SPSS Statistics 17.0. Significance of differences between parameters was assessed using the parametric Student's t-test (for normal distribution) and nonparametric Mann-Whitney U-test (for non-normal distribution). Survival effects were evaluated with Fisher's angular transformation. Multigroup differences were analyzed with the Kruskal-Wallis H-test. Correlation was assessed by Spearman's coefficient. The critical significance level was set at $p < 0.05$.

Results. The problem of nephrotoxicity caused by aminoglycoside antibiotics remains relevant. Studying the effect of the tested SCAAs (ademetionine, taurine, and glutathione) on gentamicin nephropathy allows assessment of their effectiveness in toxic injury. Antibiotic administration was accompanied by deterioration of kidney functional parameters: model group animals showed significant decreases in glomerular filtration rate (GFR) and diuresis, reduced water reabsorption, and increased plasma creatinine concentration, indicating retention azotemia compared to controls. Since gentamicin mainly affects the proximal tubules by damaging epithelial cells and causing mitochondrial energy depletion, impaired sodium reabsorption (both absolute and fractional) with increased sodium excretion was observed [9, 10]. Damage along the nephron was evidenced by decreased proximal and distal transport. Potassium ion content decreased with increased excretion, typical for gentamicin nephropathy hypokalemia due to tubular cell necrosis and disrupted reabsorption [11].

Urine pH significantly decreased due to reduced ammoniagenesis and increased ammonia secretion, which binds fewer hydrogen ions in the nephron lumen. The

pathology was accompanied by pronounced proteinuria, demonstrating kidney tissue damage severity. (Tab. 1).

Table 1 – Effectiveness of Ademetionine, Taurine, and Glutathione in Gentamicin Nephropathy

Parameter	Intact Control	Gentamicin Nephropathy (GN)	GN + Ademetionine (20 mg/kg)	GN + Taurine (100 mg/kg)	GN + Glutathione (30 mg/kg)
Diuresis, ml	4,63±0,19	2,47±0,10##	4,34±0,11**	4,40±0,09**	3,96±0,21**
Plasma Creatinine (PCr), µmol/l	43,49±1,01	121,88±3,40##	64,06±3,95**˚	53,94±1,62**˚	69,96±2,01**˚
GFR, µl/min·100 g	645,39±27,52	201,09±6,76##	524,01±51,46**	574,17±23,80**˚	490,49±31,33**
Protein Excretion Rate (Epr), mg/2 hr	0,079±0,01	0,188±0,02##	0,123±0,01**	0,093±0,01**˚	0,117±0,01**
Fractional Excretion of Sodium (FENa+), %	0,14±0,01	3,80±0,26##	0,45±0,03**˚	0,34±0,02**˚	0,77±0,02**
Total Sodium Reabsorption (TpNa+), mmol/2 hr	13,06±0,77	4,30±0,24##	10,86±1,21**	11,57±0,47**˚	10,22±0,81**
Total Sodium Excretion (TdNa+), µmol/2 hr	679,29±33,73	390,01±21,87##	654,86±37,17**	645,46±10,89**	601,82±42,95**
Plasma Potassium (PK+), mmol/l	5,14±0,25	4,24±0,26#	5,21±0,49*	5,11±0,18*	5,32±0,44**

*Notes: * $p < 0.05$, ** $p < 0.01$ vs. Intact Control; ˚ $p < 0.05$ vs. Gentamicin Nephropathy without treatment.*

Administration of ademetionine, taurine, and glutathione in prophylactic-therapeutic mode during gentamicin nephropathy reduced antibiotic toxicity. Taurine showed the most pronounced effect, although the others also contributed to restoration of renal morphofunctional state [325, 326]. Taurine treatment led to increased GFR ($N=8.2$, $p < 0.01$), enhanced diuresis by about 1.7 times, and improved ion-regulatory function, preventing sodium transport disturbances. Treated animals showed significant reductions in sodium ion excretion due to restored absolute reabsorption (ademetionine—2.4 times, taurine—2.6 times, glutathione—2.3 times) and decreased

fractional sodium excretion (8.4, 11.1, and 4.9 times, respectively) with increased proximal and distal transport (2.5 and 1.6 times). Cytoprotective effects on nephrocytes were evidenced by a 2.9-fold decrease in proteinuria, with taurine showing significant superiority (N=7.78, $p < 0.01$) (Table 2).

The advantage of taurine's efficacy in gentamicin nephropathy is explained by its ability to influence cellular membranes, retaining potassium and magnesium ions intracellularly and sodium ions extracellularly, thus producing a diuretic effect. This was supported by observed reductions in urinary sodium concentrations and normalization of plasma sodium.

Table 2 – Effectiveness of ademetionine, taurine and glutathione in acute kidney injury of various etiologies

Types of AKI	Gentamicin Nephropathy (GN)			Ischemia-reperfusion AKI		
	Ad	Tau	GL	Ad	Tau	GL
Збільшення діурезу, %	86,5	89,3	68,9	64,0	88,5	96,5
Відновлення ШКФ, %	72,7	83,9*	65,1	34,4	55,3	80,8*
Зниження креатинемії, %	73,7	86,6*	53,9	46,5	67,3	85,1*
Зниження протеїнурії, %	86,4	93,2*	77,9	48,5	72,7	81,8
Відновлення реабсорбції іонів натрію, %	75,4	83,2*	67,7	39,1	57,7	86,8*
Зменшення фракційної екскреції іонів натрію, %	91,5	94,5*	82,7	61,0	81,2	90,8

*Notes: * - normalization of the indicator; Ad - ademetionine, Tau - taurine, Gl - glutathione; AKI - acute kidney injury, GP - gentamicin nephropathy, I/R AKI - ischemic-reperfusion acute kidney injury, GFR - glomerular filtration rate.*

Ischemia-reperfusion AKI accounts for 20–30% of cases in the general AKI population and is accompanied by acute tubular necrosis often requiring hemodialysis

[12]. Therefore, studying ademetionine, taurine, and glutathione efficacy in ischemia-reperfusion AKI is logical. Ischemic injury is usually initiated by increased reactive oxygen species generation by endothelial cells, causing methylation and oxidative deamination disruptions, resulting in toxic products like peroxides, ketones, aldehydes, and decreased cellular antioxidant defenses [3]. These free radicals induce lipid peroxidation of membranes, altering protein structures and permeability. Excess NO production under hypoxia also damages endothelium, disrupts microcirculation, and causes endothelial swelling. Reduced microcirculation and increased arteriovenous shunting activate compensatory mechanisms in reperfusion injury [2]. Leukocytes further exacerbate injury by releasing radicals and proteolytic enzymes, promoting endothelial dysfunction and thrombosis.

Ischemic AKI modeling showed impaired tubular-glomerular balance, 3.1-fold GFR reduction, oliguria development, increased plasma creatinine indicating retention azotemia, and marked proteinuria with a 4.8-fold increase in urine protein excretion compared to sham-operated animals. (see Table 3).

Evidence of damage to the epithelial cells of the renal tubules—not only the proximal segments, where sodium ion reabsorption predominantly occurs, but also the distal segments - is indicated by impaired ion-regulatory function. This manifested as a decrease in both absolute and relative sodium ion reabsorption, accompanied by increased sodium excretion. The study of potassium ion content revealed a decrease in plasma potassium concentration, which was due to enhanced excretion of the ion. Additionally, a significant 20.7-fold increase in γ-glutamyl transpeptidase (GGT) activity in operated animals pointed to the severity of the acute kidney injury (AKI), potentially further exacerbated by the surgical intervention used to model the pathology.

The use of sulfur-containing amino acids (SCAA) in a therapeutic-prophylactic regimen allowed for partial mitigation of post-ischemic reperfusion manifestations. This was accompanied by improved renal function, including a 2.3-fold increase in glomerular filtration rate (GFR), a 1.7-fold increase in diuresis, and a 1.7-fold reduction in retention azotemia compared to untreated model animals (see Table 1). Treatment

Table 3 – Effect of ademetionine, taurine and glutathione kidney function of rats with ischemia-reperfusion kidney injury

Parameter	Intact Control	I/R AKI	I/R AKI + Ademetionine (20 mg/kg)	I/R AKI + Taurine (100 mg/kg)	I/R AKI + Glutathione
Diuresis, ml	4,38±0,19	2,38±0,11□□	3,66±0,13**	4,15±0,16**	4,31±0,14**
Plasma Creatinine (PCr), µmol/l	63,21±6,05	165,37±9,23##	117,83±4,93**	96,59±2,41**	78,39±2,37**○ϕ
GFR, µl/min·100 g	532,71±47,29	173,08±9,90##	296,74±8,32**	372,08±24,99**	463,69±24,19**○ϕ
Protein Excretion Rate (Epr), mg/2 hr	0,014±0,001	0,068±0,004##	0,040±0,002**	0,028±0,003**	0,021±0,002**○
Fractional Excretion of Sodium (FENa+), %	0,38±0,05	2,46±0,13##	1,19±0,10**	0,77±0,05**	0,57±0,05**
Total Sodium Reabsorption (TpNa+), mmol/2 hr	7,13±0,61	2,70±0,20□□	4,35±0,17**	5,18±0,51**	6,17±0,43**○
Total Sodium Excretion (TdNa+), µmol/2 hr	527,56±34,45	346,14±29,29##	494,23±25,40**	525,66±38,43**	514,66±25,58**
Plasma Potassium (PK+), mmol/l	5,18±0,49	4,46±0,10#	4,93±0,23**	5,04±0,35**	5,25±0,13**

*Notes: * $p < 0.05$, ** $p < 0.01$ vs. Intact Control; ˚ $p < 0.05$ vs. Gentamicin Nephropathy without treatment.*

with the investigated compounds contributed to the restoration of nephron filtration structures, as evidenced by a 1.8-fold reduction in proteinuria. Compared to untreated animals, SCAA treatment prevented sodium ion transport disorders by restoring both absolute (1.9-fold) and standardized (4.3-fold) proximal sodium transport, due to the recovery of reabsorption and excretion processes. The effect of the compounds on acid-base regulation was reflected in increased urine pH, indicating enhanced ammoniagenesis over acidogenesis, thereby preventing urinary acidification.

Among the compounds tested, glutathione demonstrated the most pronounced nephroprotective effect in ischemia/reperfusion (I/R) injury. This may be attributed to its antioxidant and pharmacokinetic properties. The kidneys are the primary site for glutathione catabolism, where oxidized glutathione—formed from its reduced form - undergoes degradation after fulfilling its biological functions. Within the cell, oxidized

glutathione freely diffuses across the membrane and is transported via the bloodstream to the kidneys. In the proximal tubules, enzymatic hydrolysis occurs through enzymes located on the brush border of the tubular epithelium, including cysteinylglycine dipeptidase, γ-glutamyl transpeptidase, and cystine reductase, completing the inter-organ glutathione metabolism.

When administered prophylactically, glutathione prevented the progression of ischemia, likely due to its capacity to neutralize peroxidation products through conjugation reactions with cytotoxic lipid peroxidation products and their active metabolites generated during oxidative stress. Consequently, the compound significantly improved I/R injury outcomes: renal excretory function recovered as shown by GFR values ($H = 9.63$, $p < 0.01$), leading to a 1.8-fold increase in diuresis, significant restoration of water reabsorption, and a reduction in retention azotemia. Plasma creatinine concentration decreased 2.1-fold compared to the untreated pathology group and was 17.9% lower than in the taurine group and 33.4% lower than in the ademetionine group ($H = 7.22$, $p < 0.05$).

A decrease in urinary protein excretion and normalization of ion-excretory function alongside increased GFR support the protective effect of the drug, suggesting glomerular filtration barrier stabilization. Notably, among the tested compounds, the glutathione group demonstrated the greatest increase in absolute sodium ion reabsorption ($H = 8.1$, $p < 0.05$), which led to nearly a twofold reduction in sodium ion excretion and a significant decrease in natriuresis, approaching levels observed in sham-operated animals [339].

Conclusion.

The presented experimental data demonstrate the nephroprotective activity of the investigated hepatoprotective agents—SCAA compounds ademetionine, taurine, and glutathione—through their influence on key pathogenetic mechanisms of AKI. These effects were evidenced by improved renal functional state and the restoration of the prooxidant-antioxidant balance in both blood and kidney tissues of treated animals. It should be noted that the compounds differed in nephroprotective efficacy depending on the experimental AKI model. In rhabdomyolysis-induced AKI, ademetionine

showed the most significant activity across several parameters; in gentamicin-induced nephropathy, taurine was the most effective in the therapeutic-prophylactic regimen; and glutathione most effectively mitigated ischemia-reperfusion injury in experimental animals. These findings provide a foundation for further experimental studies aimed at optimizing the prevention and correction of kidney pathology using selected SCAA compounds.

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