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Counteraction intoxication with heavy metals: the unique nephroprotective effects of plant peptides.

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ABSTRACT

The article discusses the main types of effects of heavy metals on the structure and functional state of the kidneys and focuses on the molecular mechanisms of the nephrotoxic effect of mercury. An experimental study of the nephroprotective properties of the immunotropic drug GA-40 was conducted. During the study, it was established that GA-40 reduces the content of mercury and tumor necrosis factor in the renal cortex at the polyuric stage of sublimated nephropathy, which positively affects the proximal nephron. Also, the experiment showed the anti-nephrosclerotic effect of GA-40 during the chronic period of Masugi nephritis - this helps prevent atrophy of the tubules and glomeruli of the nephron by suppressing apoptosis. Nephrotoxicity is not observed during the removal of heavy metals from the kidneys, since GA-40 suppresses inflammation and prevents fibrotic changes on the background of damaged tissue. The high safety profile of GA-40 provides the necessary conditions for the gradual restoration of the structure and function of the kidneys after poisoning with heavy metals, in particular mercury chloride, therefore the drug is considered as promising for the treatment of toxic nephropathy.

Key words: **heavy metals, mercury, nephropathy, plant peptides, GA-40, nephroprotector, nephron, NF-kB, p53, apoptosis, detoxification.**

Introduction. Kidneys is the main organ which excretes toxins that entered the body. The large number of nephrons arranges the wide surface endotheliocyte and epithelium tubules to contact them. The capillar endothelium`s surface succumbes the direct influence of toxins in the process of ultrafiltration. Another endotheliocyte glomerule`s characteristic, which can facilitate the kidneys affection, is the negative charge of filtration membrane. Positively charged ligands affected by the electrostatic force can accumulate on these membranes and change glomerule`s penetrance. [1,2,4,9].

To the highly nephrotoxic agents class belong plenty of metals, including cadmium, mercury, plumbum, chromium, arsenic, iron, boron. It related to the capacity of these agents to form repository in parenchymal organs with longstanding period of

semiejection. The influence of complex metals oftimes leads to the kidneys tela`s injury and the extension of progressive nephrism. [3,5,6,7,34].

The injury of glomerule`s epithelium, especially the paroxysmal, marked by plumbum and cadmium. The long-term low dose effect of plumbum on the body produces the enlargement breakdown the function of proximalis kidneys glomerules. The plumbum professional intoxications with the growth of plumbum nephropathy has been observed in individuals who work with alloys or colorants which contain plumbum: under the plumbum extraction, the galvanical cells production, the screen arrangement which are used in radiodiagnosis, mastication, fabricating recyclables, ceramic product burn-off, etc. [5,8, 11,33].

The physiologic processes of canalicular transportation facilitate the plumbum concentration in kidneys, specifically in proximalis evasive glomerules with further injury of glomerules. epithelium It triggers cell degeneration: mitochondria are swelling up, in the nucleus plumbum-rich eosinophilic fills are manifesting. Besides epithelium glomerules`s dystrophy and atrophy, the glomerular ischemia, fibrosis of kidneys arteriola`s adventitia and mediated cicatrisation of cortical substance are distinctive for the plumbum nephropathy. Proteinuria, cylindruria, erythrocyturia may be detected in urine examination, plumbum in urine may also be determined: more than 0.6 mg / day is a sign of plumbum poisoning. більше 0,6 мг / на добу - ознака свинцевого отруєння. Plumbum mainly affects tubules or interstitial structures, namely, the insult can be both acute and chronic. Therein the acute cells injuries, which are caused by plumbum basically are reversible and necrosis emerges infrequently.[12 – 16].

The earliest sign of cadmium nephropathy is low molecular weight proteinuria. Cadmium nephropathies are characterized by a predominant tubular lesion manifested by proteinuria with the release of low molecular weight proteins (beta-2-microglobulin) (бета-2-мікроглобуліну), that are not reabsorbed by damaged tubules. In the future, with the defeat of the glomerular apparatus, the development of a slowly progressing anemic syndrome is possible. Low molecular weight proteinuria probably reflects impaired tubular reabsorption, since its severity is closely correlated with other manifestations of tubular dysfunction.[5,9,35,44].

Cadmium is contained in fuel oil and diesel fuel, it is used as an additive to alloys, when applying galvanic coatings, to obtain the cadmium pigments required in the production of varnishes, enamels and ceramics, as stabilizers for plastics, in electric batteries, where the professional contact is possible. Prolonged contact with cadmium firstly leads to a change in the function of cells of the proximal nephron, and then to a decrease in glomerular filtration and the development of tubulointerstitial nephritis. Acute tubular damage by toxins can range from necrosis of tubular cells with the development of acute renal failure to weak subcellular damage with minor functional disorder. However, clinical observations indicate that in most cases, once occurring, cadmium proteinuria remains irreversible and the progression of renal dysfunction after cessation of cadmium continues, although very slowly.[17,20,21,37,38]

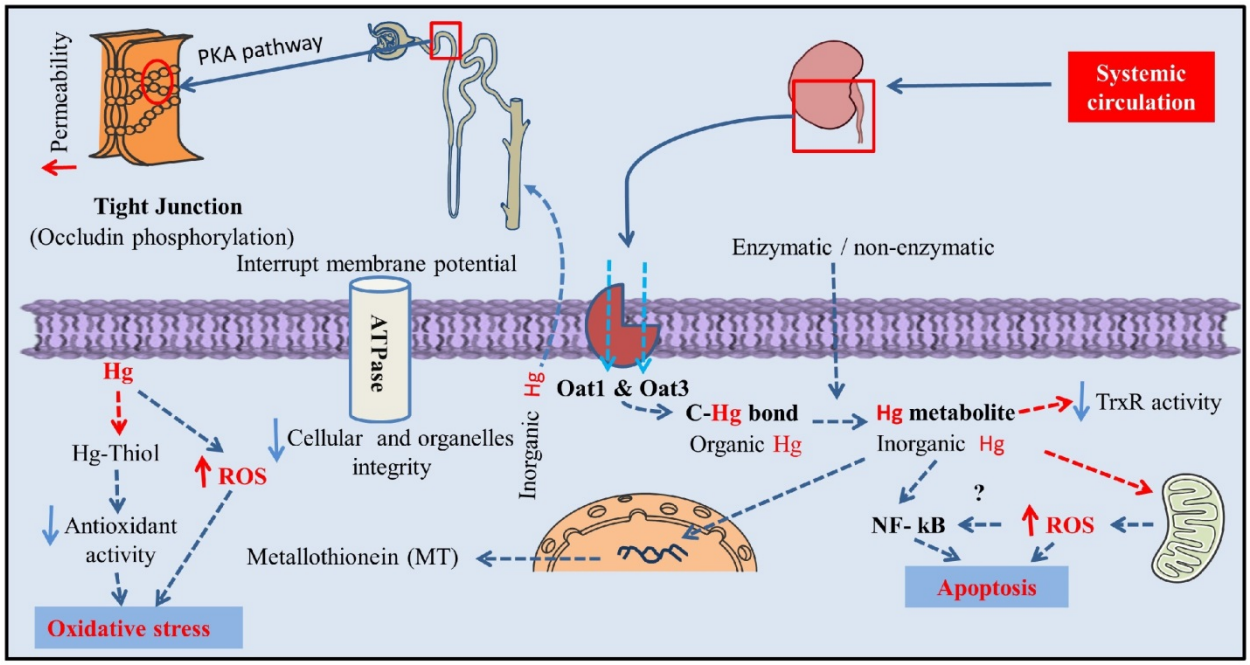
In acute arsenic poisoning, tubal necrosis can occur. Inorganic arsenic mainly damages organelles, and in the first place, mitochondria. Nephropathy in chronic arsenic intoxication is characterized by disorders of the proximal nephron, which in the future may also lead to the development of tubulointerstitial nephritis.[16,18,19,36].

The acute and chronic effects of chromium occurring mainly in the respiratory and skin organs are mainly related to the effects of hexavalent chromium. In animal experiments, acute toxic effects of chromium and dichromic acid salts on renal tubule cells were established. Renal tubular necrosis has also been described in people with acute chromium intoxication. Chronic exposure to chromium causes mild dysfunction of the kidney tubules. There is increased urinary excretion of β - glucuronidase, as well as such a sensitive marker of tubular damage as β 2 - microglobulin [22 ,23, 24,39,40].

Also there are well-known nephropathies caused by organic and inorganic mercury compounds. The influence of mercury is possible in professional conditions - at mercury mines and factories, in the production of measuring instruments, x-ray tubes, quartz and electric lamps, in the production of pharmaceuticals. The high concentrations of mercury cause a variety of kidney diseases - acute necrosis, rarely nephrotic syndrome. [10,41,43].

The study of the functional state of the kidneys in mild and moderate forms of chronic mercury poisoning revealed changes mainly in the tubular apparatus: the presence of protein, cylinders, erythrocytes in the urine. The tendency to decrease tubular reabsorption at normal glomerular filtration is revealed, in rare cases the development of chronic glomerulonephritis is possible. [42,45]

The mechanism of mercury`s effect on the kidneys is well understood, in particular at the molecular level: Hg is transported by the organic anion transport protein-1 (Oat1) and the organic anion transport protein-3 (Oat3) selectively into the proximal tubule. Further, cleavage of carbon-mercury bonds converts organic Hg into inorganic mercury as metabolites or by an enzymatic or non-enzymatic process. At the same time, Hg deposition is closely related to oxygen reactive compounds (ROS), metallothionein (MT) miRNA expression, apoptosis, and damage to the proximal tubules. Organic transport anion 1 (Oat1) and organic transport anion 3 (Oat3) are localized mainly in the lysosomes in the proximal tubules, absorbing Hg into the kidney. As far as Hg2 + has a greater affinity for binding to thiol-containing enzymes, it inactivates the enzymes with the thiol group by irreversible oxidation; this leads to a depletion of the total thiol content and oxidative stress. Inactivation of the sulfhydryl protein also affects cell integrity, interrupting the membrane potential and volume of cells, as well as cell organelles. At the same time, a deficiency of detoxifying proteins or reduced antioxidant activity of selenolthiol also contributes to the damage of the proximal tubules. It is interesting to note that the regulatory peptide NF-κB also plays a crucial role in kidney damage because it increases sensitivity to apoptosis. The ability of Hg to reduce transepithelial electrical resistance (TER) established and thereby promote phosphorylation of the protein of the tight junction - occludin, using mechanisms dependent on protein kinase A (PKA). (Pic.1).[46, 47].



Pic.1 Toxicodynamics of Hg-Induced Renal Toxicity.

Most heavy metals have a stimulating effect on the formation of toxic free oxygen radicals in organs and tissues, with further enhancement of lipid peroxidation processes. Not only do they potentiate the formation of free oxygen radicals in tissues, they also inhibit the oxidative metabolism of immune cells, leading to the development of damage and the inflammatory process in tissues, and in the kidneys in particular.[25,26, 48,49,50,52].

Adversely affecting the human body usually has not one metal, but their complex. The development of dysmetabolic nephropathy and interstitial nephritis or tubulo-interstitial syndrome is associated with the complex influence of adverse environmental factors.[27,28,51,53].

It should be noted that the increase in the frequency of urate, oxalate and other metabolic nephropathies is to some extent associated with the deterioration of the environmental situation, and in particular the influence of salts of heavy metals on the body. Of particular importance is the increased excretion of nephrotoxic and stone-forming substances with urine, which contributes not only to the formation of concretions in the urinary tract, but also to the development of chronic inflammatory process. In these conditions, the occurrence of acute or chronic abacterial inflammatory process in the intermediate kidney tissue is often a complication. Inflammation is accompanied by the involvement of tubules, blood vessels and lymphatic vessels of the renal stroma, which can lead to the formation of chronic interstitial nephritis.[29,31, 54,55,57].

Chronic tubulointerstitial nephritis is characterized by interstitial fibrosis and atrophy of the tubules. The enlargement of the extracellular matrix leads to an increase in the interstitial space. As the tubulointerstitial process progresses, inflammation and cellular infiltration decrease. In the later stages of intoxication with heavy metals, morphological features of focal-segmental glomerulosclerosis are noted.[30,32,56,58]. In our opinion, if a person is at risk of developing kidney disease due to the influence of heavy metals, and even more so when detecting any concentration of dangerous substances in the body,

even in the absence of clinical symptoms — it is important to take immediate measures to detoxify and prevent possible negative consequences.

Recently, many substances of natural origin that have nephroprotective effects after exposure to the kidneys of various toxic substances, in particular heavy metals, have been studied. Among them are ginger extracts, flaxseed oil, curcumin, ginkgo biloba, astxanthin, resveratrol, etc. [46]. Our study is devoted to the study of nephroprotective effects of exogenous peptides of plant origin after modeling of tubulo-interstitial syndrome and Masugi nephritis [59] in animals.

Objective: To investigate the protective effect of GA-40, a complex of regulatory peptides of plant origin, on the course of Sulemic nephropathy and chronic Mazugi nephritis in rats, using histological examinations and autonomic resonance test capabilities of “IMEDIS TEST+”.

Materials and methods. In the early 1990s, Professor Georgii Alexidze identified several groups of plant regulatory peptides from the Solomon's Seal (Polygonatum verticillatum) plant. These peptides have been found to have a molecular weight of 15 to 98 kilodaltons. Due to their relatively small size, such peptides can affect not only membrane receptors but also penetrate cells through membrane pores. This gives them the ability to react with intracellular structures: regulatory peptides and genes, ligands and enzymes. Subsequently, owing to numerous experiments, the first ever immunocorrector based on plant regulatory peptides, GA-40, was obtained.

The drug GA-40 interacts with membrane formations: lectin receptors, T-cell receptors, phospholipids, glycoproteins. Intracellular peptides GA-40 alter the microstructure and active potential of participants in the regulatory cascades: proteins associated with miRNAs, caspases, proteins, kinases, prointerleukins, interleukins, etc. The uniqueness of GA-40 consist in the fact that in conditions of reduced antitumor immunity due to aggressive activity of tumors, or after antitumor chemotherapy, exogenous peptides restore immune surveillance and promote apoptosis of onco-cells and vice versa - in terms of hyperproducts, , plant peptides are able to reduce the intensity of peptide-peptide interactions and prevent unwanted damage and apoptosis of nephrocytes.

The history of inventing and studying the immunotropic and gene-protective properties of GA-40 is set out in Professor Georgii Alexidze's monograph “GA-40. New Immunotherapy and Anticancer Drug ", which was released in 2014 in the United States/*G.Alexidze. GA-40 A New Immunotherapeutic & Anti-Cancer Drug. Lambert Academic Publishing. Feb 12, 2014)/.*

In order to study the nephroprotective effect of GA-40, we isolated 2 groups of experimental animals - rats with sulphal nephropathy, which were modeled by the introduction of 0.1% sulemas at a dose of 5 mg / kg with a study in the acute period of early polyuric stage of acute renal failure (3 days) and the period of formation of tubulo-interstitial syndrome (on the 30th day) and Masugi jade, which was modeled by 2-fold intraperitoneal injection of rabbit nephrotoxic serum with a titer of anti-renal antibodies in the binding reaction to plementu not less than 1: 1024. The study was performed for 45

days, which corresponded to the development of chronic Masugi jade with the formed tubulo-interstitial syndrome.

The drug Ga-40 was administered to animals daily at a dose of 2 μg / kg per day.

Determined creatinine, thromboxane, mercury, the preparation of GA-40 after 72 h after administration of sulemia using a vegetative resonance test, which was carried out using the “IMEDIS BRT PC” using software.

Histological examination was performed by the method of staining of deparaffin sections with hematoxylin-eosin and Slinchenko using a Levenhuk 870T microscope, magnification x400.

Histological examinations were performed for 45 days of chronic Masugi nephriti.

The resonance study was performed on days 3 and 30 of Sulemic nephropathy and 45 days of chronic Masugi nephritis.

Markers of connective tissue and apoptosis were determined: oxyproline and p53 protein using the “IMEDIS-TEST+“ vegetative resonance test.

The content of amorphous and crystalline substance was performed by means of correlation-optical study of the kidneys.

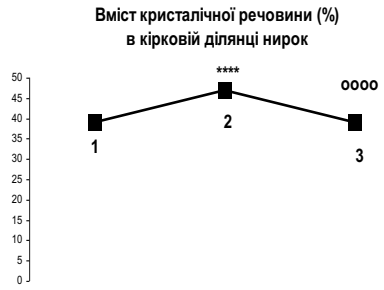
Results.

During the study, we found that the GA-40 drug reduced the level of azotemia during the polyuric stage of sulemic nephropathy, which can be judged by the decrease in creatinine in the blood plasma, as well as a decrease in the content of mercury, angiotensin 2, thromboxane A2, factor 1 necroxin, necroxin factor.

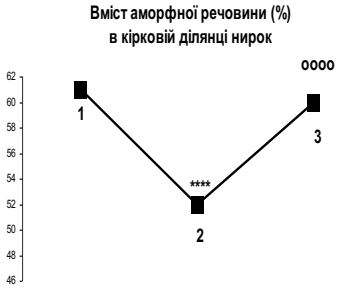
(Table 1.) Influence of GA preparation - 40 on the degree of retention azotemia, mercury content, angiotensin 2, thromboxane A2, TNF in the cortical substance of the kidneys at the polyuric stage of sulphal nephropathy in the study of rats using vegetative resonance test "IMEDIS TEST +" (x ± Sx)

Indexes	**Sulemian nephropathy - 72 hours**	**Sulemian nephropathy - 72 h + GA-40**
Blood plasma creatinine, um.	17,66±0,333	4,83±0,307
Mercury content in cortical substance, um.Okreatinin of blood plasma, um.Od.d	10,33±0,421	3,83±0,307 p< 0,001
Angiotensin 2 content in cortical substance, um.Od.	17,16±0,307	8,50±0,223 p< 0,001
Thromboxane A2 content in cortical substance, um.Od.	15,83±0,401	8,83±0,307 p< 0,001
The content of TNF-alpha in the cortical substance, um.Od.	15,00±0,365	5,16±0,307 p< 0,001

On the 30th day of Sulemic nephropathy in the cortical, medullary substance and papillary kidneys, the formation of tubulo-interstitial syndrome was observed, as evidenced by the increase of crystalline substance (as a collagen marker) and the decrease in amorphous (as a reflection of atrophy of nephron segments). Under these conditions, the drug GA - 40 showed antinephrosclerotic effect at the level of all renal layers, the latter was accompanied by normalization of the level of amorphous, crystalline substance and their relationship. (Pic. 2) [60].



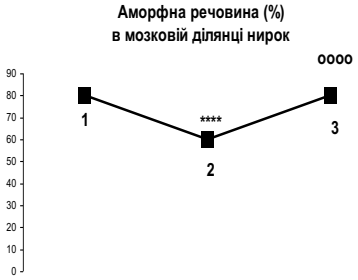
The content of the crystalline substance (%) in the cortical area of the kidney



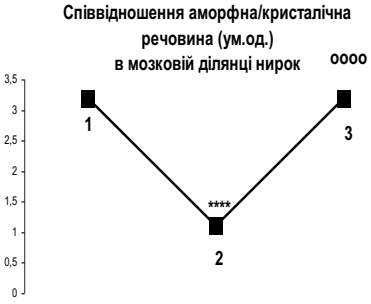
The content of amorphous substance (%) in the cortical area of the kidney

The ratio of amorphous/ crystalline substance (ppm) in the cortical region of the kidney

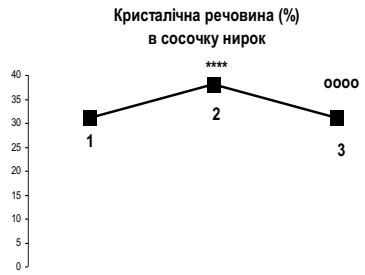
The crystalline substance (%) in the renal medulla



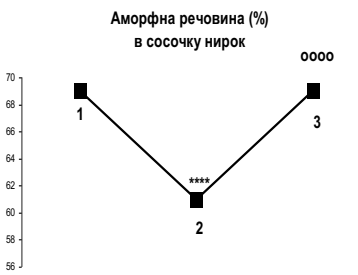
The amorphous substance (%) in the renal medulla



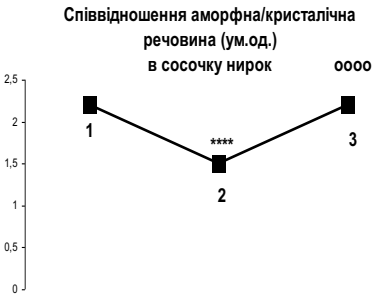
The ratio of amorphous/ crystalline substance (ppm) in the renal medulla



The crystalline substance (%) in the kidney papilla



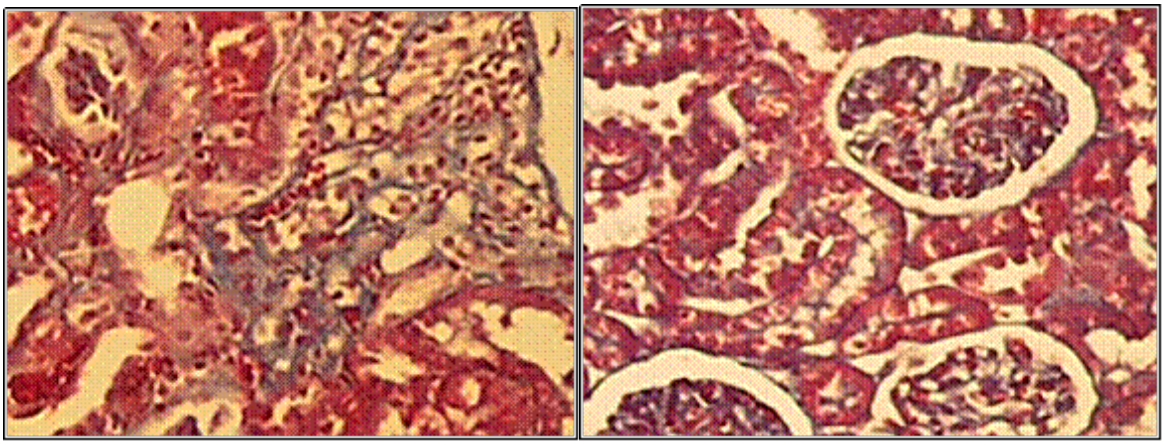
The amorphous substance (%) in the kidney papilla



The ratio of amorphous/ crystalline substance (ppm) in the kidney papilla

Pic. 2 Protective effect of GA-40 on the development of tubulo-interstitial syndrome on the 30th day of sulemic nephropathy based on the data of correlation-optical study of the kidneys. 1 - control findings (intact animals), 2 - tubulo-interstitial syndrome on the background of the drug GA-40. Significance of differences: **** - p <0,001 compared to control; ^{oooo} - p <0.001 compared with tubulo-interstitial syndrome on day 30 of sulphamous nephropathy.

Tubulo-interstitial syndrome is also diagnosed on the 45th day of chronic Masugi nephritis (Pic. 3a), manifested by interstitial fibrosis, atrophy of the nephron tubules. Under these conditions, the drug GA-40 showed antinephrosclerotic prophylactic effect (Pic. 3b)

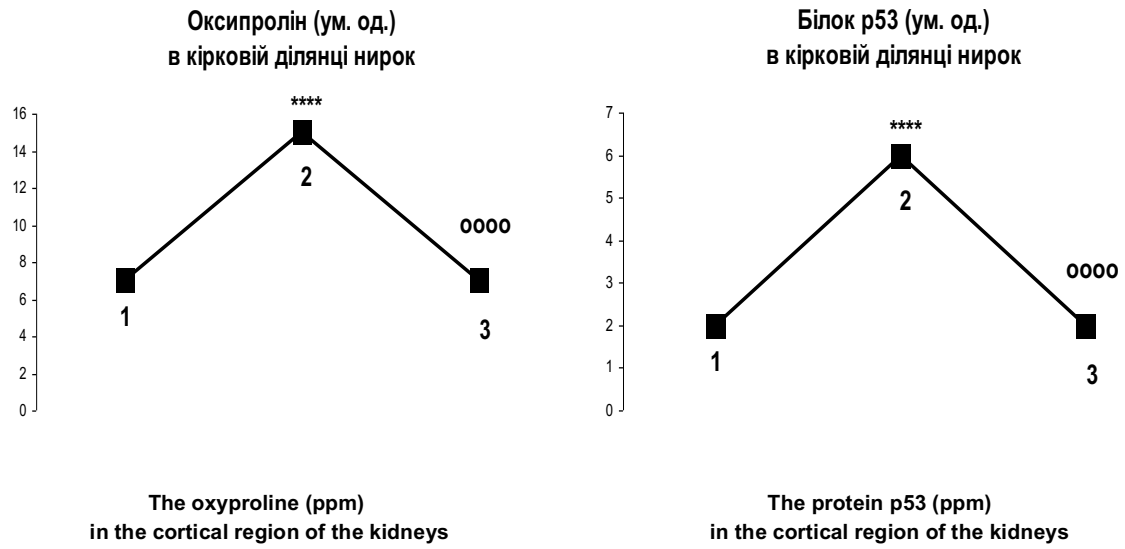


a b

TIS TIS + GA – 40

Pic. 3. Antinephrosclerotic effect of the drug GA-40 in the development of tubulo-interstitial syndrome (TIS). Histologically determined: interstitial fibrosis, atrophy of the glomeruli and damage to the tubules. Unlike the control group, the study group does not show growth of connective tissue in the interstitium, improves the condition of the glomeruli and tubules of the kidneys.

On the 45th day of chronic Masugi nephritis in the renal substance, an increase of the collagen marker - oxyproline and the proapoptotic p53 protein - was diagnosed (Pic. 4). In these conditions, the drug GA - 40 showed antinephrosclerotic prophylactic effect.



Pic. 4. Protective effect of GA-40 on the development of tubulo-interstitial syndrome on the 45th day of chronic Masugi jade according to the results of testing by the method of vegetative resonance test "IMEDIS TEST +". 1 - control (intact animals), 2 - tubulo-interstitial syndrome, 3 - tubulo-interstitial syndrome against the background of the drug GA-40. Significance of differences is noted: **** - p <0,001 compared to control; ^{oooo} - p <0.001 compared with tubulo-interstitial syndrome on day 45 of chronic Masugi's nephritis.

Discussion.

The study found that the nephroprotective effect of GA-40 is due to the following mechanisms. Firstly, GA-40 reduces the content of mercury and tumor necrosis factor in the renal cortex during the polyuric stage of sulphal nephropathy, which has a positive effect on the proximal portion of the nephron. This is accompanied by a decrease in the reactivity of the tubulo-glomerular feedback with a decrease in the level of vasoconstrictors of angiotensin 2 and thromboxane A2 in the cortical substance of the kidneys, and also correlates with a decrease in the content of azotemia - according to the analysis of plasma creatinine.

Secondly, the lowering of the cardiovascular, collagen-stimulating potency of angiotensin 2 and thromboxane A2 with a potent GA-40 drug is a real anti-nephrosclerotic period of time for chronic nephritis and isn't excreted by the club. This effect can also be verified by the results of the potential of hydroxyproline and p53 in the course of the experiment. The regulatory action of the GA-40 can be explained by the evolution of the European authorities on the low molecular weight of the exogenous harmonious processes in the process and the implementation of the latest ones. Even for its molecularly growing, long-standing peptides that are identical to those of animals and people, have not the only same parameters of molecular mass and biological activity, but the same way in the trivial expanses of the vital microenvironment.

Thirdly, the capacity of GA-40's to inhibit the inflammation at the expense of the lack of control over the cascades of the deregulation, including participation for the part of the caspase system and the regulatory peptide NF-kB, and as a result, prevent the occurrence of fibrotic changes on the background of damaged tissue, creates the necessary conditions for the gradual restoration of the structure and function of the nephron. In this sense, the safety profile of the drug comes to the fore. After all, the strategy of treatment of nephritis is not enough to simply neutralize or purposely remove nephrotoxic substances. This removal and excretion should be carried out safely for the renal tissue. And in this sense also manifests the nephroprotective effect of GA-40, which we can conditionally call "secondary nephroprotection". Unlike other peptide preparations, in particular animal origin, GA-40 has an unsurpassed safety profile because it does not contain large mass polypeptides with pronounced antigenic properties. This is extremely important when the body is weakened and there are no additional reserves to counteract allergic reactions.

Conclusions.

1. The drug GA-40 realizes clear nephroprotective effects in sulemic nephropathy and Masugi jade in experimental animals.

2. GA-40 drug has a high safety profile and creates conditions for restoration of the structure and functions of damaged nephrocytes.

3.The data obtained allow us to reasonably recommend GA-40 as a potentially promising means of preventing the negative nephrotoxic effects of heavy metal poisoning, in particular mercury chloride. The study of GA-40 in nephrological pathology should be continued.

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