DOI 10.26724/2079-8334-2023-2-84-191-196
UDC 616.61-092.9: 616.831-005.4:612.08

N.I. Voloshchuk, A.P. Korol, O.M. Denysiuk, O.S. Pashinska, I.V. Taran, A.V. Sayenko, O.O. Nefodov[1]
National Pirogov Memorial Medical University, Vinnytsya
[1]Odesa I. I. Mechnikov National University, Odesa

MORPHOLOGICAL STRUCTURE AND CHANGES OF THE RENAL CELL CYCLE IN CHRONIC KIDNEY DISEASE AND ITS CORRECTION WITH HYDROGEN SULPHIDE AND GENISTEIN

e-mail: nefedov2406@gmail.com

The purpose of the study was to establish the effect of hydrogen sulfide and genistein on cell cycle indicators and histomorphological changes in kidneys under conditions of experimental chronic kidney disease. In sexually mature white non-linear rats, the pathology was modelled by unilateral nephrectomy and subtotal (5/6) resection of the contralateral kidney. Cytometric parameters and renal morphological changes were evaluated after 40 days by DNA flow cytometry and light microscopy, respectively. It was established that the use of the hydrogen sulfide donor NaHS, as well as genistein, showed a pronounced nephroprotective effect due to the antiapoptotic effect, the normalization of the number of mitoses and the activity of DNA synthesis, inhibition of the development of structural and degenerative-dystrophic changes in the kidneys, activation of compensatory-adaptive and regenerative processes and normalization of hemodynamics. This can become the basis for developing more effective pharmacotherapy for chronic kidney disease.

Key words: chronic kidney disease, hydrogen sulfide, nephroprotective action, plant polyphenols, genistein, rats, morphological structure, flow cytometry.

Н.І. Волощук, А.П. Король, О.М. Денисюк, О.С. Пашинська, І.В. Таран, А.В. Саєнко, О.О. Нефьодов

МОРФОЛОГІЧНА СТРУКТУРА ТА ЗМІНИ КЛІТИННОГО ЦИКЛУ В НИРКАХ ЗА ХРОНІЧНОЇ ХВОРОБИ НИРОК ТА ЇЇ КОРЕКЦІЇ ГІДРОГЕН СУЛЬФІДОМ І ГЕНІСТЕЇНОМ

Метою дослідження було вивчити вплив гідроген сульфіду та геністеїну на показники клітинного циклу та гістоморфологічні зміни в нирках за умови експериментальної хронічної хвороби нирок. Статевозрілим білим нелінійним щурам патологію моделювали шляхом однобічної нефректомії та субтотальної (5/6) резекції контрлатеральної нирки. Цитометричні показники і морфологічні зміни в нирках оцінювали через 40 діб методом проточної ДНК-цитометрії та світлової мікроскопії відповідно. Встановлено, що застосування донатора гідроген сульфіду NaHS, як і геністеїну, виявляло виразну нефропротекторну дію через антиапоптичну дію, нормалізацію кількості мітозів та активності синтезу ДНК, стримування розвитку структурних і дегенеративно-дистрофічних змін у нирках, активацію компенсаторно-пристосувальних і регенеративних процесів та нормалізацію гемодинаміки. Це може стати підґрунтям для розробки більш ефективної фармакотерапії хронічної хвороби нирок.

Ключові слова: хронічна хвороба нирок, гідроген сульфід, нефропротекторна дія, рослинні поліфеноли, геністеїн, щури, морфологічна структура, проточна цитометрія.

The study is a fragment of the research project "Search and study of biologically active substances among natural compounds and products of chemical synthesis", state registration No. 0118U001903.

Chronic kidney disease (CKD) is an extremely urgent medical, social and economic problem worldwide. On the one hand, this is due to the widespread distribution of this pathology- in about 10- 15 % of the planet's population [4]. On the other hand, CKD disrupts not only the kidneys but also the body as a whole, resulting in disability and deterioration of the quality of life of patients. In addition, CKD is irreversible, difficult to treat, and requires the use of expensive methods of replacement therapy, such as dialysis and kidney transplantation. Therefore, there is an urgent need to search for biomarkers for early diagnosis and study the molecular mechanisms of kidney damage to develop new strategies for preventing the development of CKD and effective pharmacological treatment of this pathology. Recently, more and more attention has been paid to the role of hydrogen sulfide in the correction of renal pathology. It is known that it is constitutively synthesized in the kidneys and plays a vital role in regulating their main physiological processes (arterial blood flow, glomerular filtration, transport of water and electrolytes). Its expression is impaired in CKD [7]. Therefore, using hydrogen sulfide and agents that stimulate its formation in the body can become the basis for effective CKD pharmacotherapy. In this plan, phytocompounds with multi-organic cytoprotective action, the mechanisms of which include the induction of endogenous hydrogen sulfide, are being investigated.

In our previous studies, it was shown that plant polyphenol preparations are able to protect the kidneys in the condition of their chronic damage. Genistein showed the most pronounced nephroprotective effect [5].The obtained data indicate that the effect of polyphenols on the state of the hydrogen sulfide system in the kidneys in CKD was associated with a decrease in the activity of free radical oxidation of lipids and proteins against the background of restoring balance in the pro – and antioxidant systems. Genistein also caused an increase in the activity of the endothelial isoform of NO-synthase and decreased the activity of its inducible isoform in the kidneys. The obtained positive changes in the biochemical markers of the kidneys became the basis for evaluating changes in the structure of the excretory organs under the conditions of CKD and its correction.

The purpose of the study was to evaluate the effect of hydrogen sulfide and genistein on cell cycle indicators and morphological changes in kidneys in experimental chronic kidney disease.

Materials and methods. The study was performed on white male Wistar rats weighing 280- 330 g, which were obtained from the Institute of Pharmacology and Toxicology of the National Academy of Sciences of Ukraine and were kept in the standard conditions of the vivarium of the VNMU on a 12-hour day/night regime with access to water and food ad libitum by the general ethical principles of animal experiments European Convention for the protection of vertebrates used for experimental and other scientific purposes (Strasbourg, 1986) [3]. CKD was modelled by unilateral nephrectomy and subtotal (5/6) resection of the contralateral kidney [12]. Sham-operated animals of the control group underwent median dissection of the anterior abdominal wall followed by layer-by-layer suturing of the surgical wound without nephrectomy and resection.

Animals were divided into four groups: 1 – sham-operated animals and 2–4 – rats with simulated pathology. At the same time, the second group were the animals with CKD without treatment. Animals of the third and fourth groups, starting from the second day after modelling the pathology, were injected intragastrically once a day with NaHS (3 mg/kg) (Sigma, USA) and genistein (5 mg/kg) (Sigma-Aldrich, St. Louis, MO, USA). Animals of the first and second groups received an equal amount of solvent once a day. Cytometric parameters and morphological changes in the kidneys were evaluated after 40 days. Animals were euthanized under thiopental anesthesia (30 mg/kg of body weight intraperitoneally).

The DNA content in the nuclei of renal cortical epithelial cells in rats was determined by DNA flow cytometry. A kit for studying nuclear DNA CyStain DNA Step 1 (Partec, Germany) and disposable filters Cell Trics 50 μm (Partec, Germany) were used to obtain a suspension of nuclei from the renal cortical epithelial cells. It allows the extraction of nuclei and the labelling of nuclear DNA with diamidinophenylindole (DAPI). Flow analysis was performed on a multifunctional research flow cytometer, Partec PAS (Partec, Germany). UV radiation was used to excite DAPI fluorescence. Cyclic analysis was performed using FloMax software (Partec, Germany) in complete digital correspondence according to a mathematical model, which determined: G0G1 – percentage ratio of G0G1 phase cells to all cells of the cell cycle (DNA content=2 c); S is the percentage ratio of the DNA synthesis phase to all cells of the cell cycle (DNA content >2 c and <4 c); G2+M – percentage of G2+M phase to all cells of the cell cycle (DNA=4 c). Determination of DNA fragmentation (apoptosis) was performed by isolating the SUB-G0G1 area on DNA histograms – RN1 before the G0G1 peak, which indicates cell nuclei with DNA content<2 c.

Histomorphological examination of rat kidney tissue was carried out by the standard light microscopy method [1]. The removed kidneys were fixed in a 10 % neutral formalin solution, followed by dehydration in ethyl alcohol solutions and paraffin embedding. Sections were made through the entire organ with a 5–6 μm thickness, stained with hematoxylin-eosin. The material was analyzed at x4-x10 magnification on an Axioskop microscope (Zeiss, Germany) and using an 8-bit COHU-4922 CCD camera (COHU Inc., USA) was entered into the VIDAS-386 computer image analysis system (Kontron Elektronik, Germany). The state of the glomerular apparatus and the tubulointerstitial zone was evaluated.

Statistical processing of the obtained results was performed in the "STATISTICA 6.1" program. The data were presented as mean (M) and mean square deviation (σ). The reliability of the difference between parameters was evaluated using the Mann-Whitney nonparametric U-test. Differences were considered probable if $p<0.05$. The non-parametric Spearman Rank Correlation Coefficient determined the correlation between two independent parameters.

Results of the study and their discussion. At the first stage of the study, the effect of hydrogen sulfide and genistein on renal cytometric parameters in experimental CKD was determined. It was found that the first higher peak (G0G1 phase) on DNA histograms corresponded to the nuclei of renal cortical epithelial cells with DNA content=2c. The percentage of these nuclei of renal cortical epithelial cells in rats with simulated CKD was 93.75±0.81 %, which practically did not differ from that in shame-operated rats

(91.31±1.0 %) (Table 1, Fig. 1a, b). Administration of NaHS and genistein also did not change the number of events in this phase.- The percentage of cells was, on average, 90.48±1.72 % and 92.31±1.24 %, respectively, which was not statistically different from the indicators of the first two groups (Fig. 1c, d).

Table 1

The influence of the hydrogen sulfide donor on the cell cycle parameters of the renal cortical epithelial cells in rats with experimental CKD (41st day, M±σ)

Experimental groups (n=5)	Cell cycle phases, m±σ			
	G0G1	S	G2+M	SUB-G0G1
Sham-operated animals	91.31±1.0	1.66±0.67	7.02±0.73	2.1±0.33
CKD without treatment	93.75±0.81	0.37±0.16*	5.88±0.73	3.79±0.69*
CKD+NaHS	90.48±1.72	1.71±0.37#	7.8±1.79	2.47±0.18#
CKD+genistein	92.31±1.24	1.37±0.65#	6.32±0.68	3.16±0.61*

Notes: 1. * - statistically significant differences ($p<0.05$) relative to sham-operated rats (Mann-Whitney test); 2. # - statistically significant differences ($p<0.05$) relative to animals with CKD without treatment (Mann-Whitney test).

The second peak, which reflects the percentage of cells in the G2+M phase (DNA content=4c), was lower in animals from the “CKD without treatment" group compared to sham-operated animals and averaged 5.88±0.73 % vs 7.02±0.73 %, respectively. Still, this difference did not reach statistically likely values (see Fig. 1b). In the group of animals "CKD+NaHS", this indicator was the same as in control. Between these two peaks in the DNA histograms of proliferating cells, there were objects with DNA content>2c and <4c, those in the so-called phase of DNA synthesis (S-phase). According to the obtained results, the percentage of cells in this phase in animals with CKD without treatment is statistically significantly lower ($p<0.05$) compared to the rate of sham-operated rats. At the same time, administering a hydrogen sulfide donor contributed to restoring the synthetic phase, and the studied indicator in the "CKD+NaHS" group practically did not differ from the control (Fig. 1).

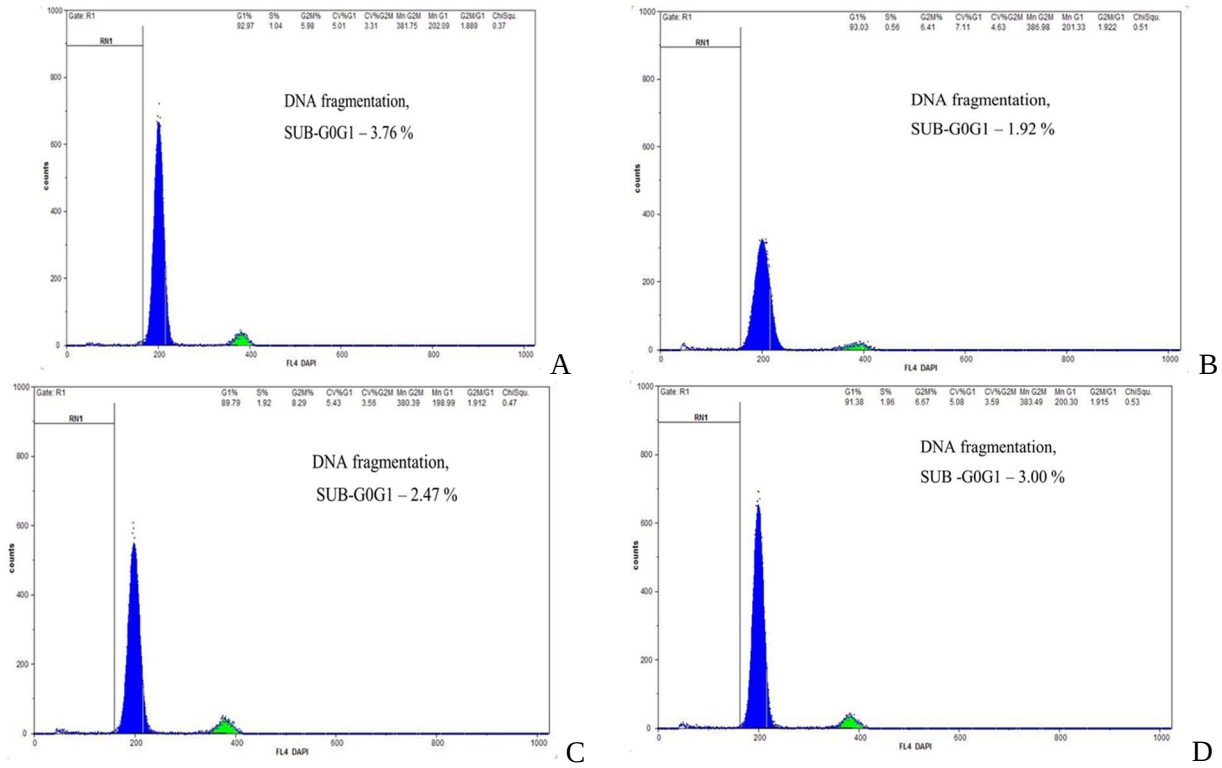

Fig. 1. DNA histogram of the nuclear suspension of renal cortical epithelial cells in the sham-operated animals (A), in the “CKD without treatment” group (B), "CKD+NaHS" group (C), and the “CKD+genistein” group (D). The number of events – 20,000.

DNA fragmentation is known to be an integrative indicator of apoptosis processes. On DNA graphs, this indicator corresponded to the SUB-G0G1 phase of the cell cycle. In the study, the rate of DNA fragmentation in the nuclei of renal cortical epithelial cells in rats with CKD was 3.79±0.69 %, which was 1.80 times ($p<0.05$) higher than the rate of DNA fragmentation in sham-operated animals. This indicated the activation of apoptosis processes. At the same time, in the group of CKD rats treated with NaHS, the percentage of renal cortical epithelial cells in the SUB-G0G1 phase was, on average, 2.47±0.18, which was 34.8 % less than that of untreated animals and slightly different from sham-operated animals ($p >0.05$).

In the group of rats treated with genistein, the percentage of cells in the SUB-G0G1 phase was 16.6 % lower and was 3.16±0.61, but this difference did not reach statistically significant values ($p>0.05$), so it can be considered a trend. At the same time, in animals injected with genistein, in comparison with untreated animals with CKD, a probable (3.7 times) increase in the percentage of renal cortical epithelial cells with DNA content >2c and <4c, that is, those in the phase of DNA synthesis (S- phase). This practically corresponded to the results of sham-operated animals and testified to the normalization of this cell cycle phase. At the same time, there were no significant changes in the number of cells with a DNA content=4c, i.e., those in the G2+M phase and the G0G1 phase, between the studied groups (Fig. 1).

Correlation analysis showed that there is a significant inverse relationship ($r=-0.81$; $p<0.05$) between the H_2S content in the kidneys and the number of cells in the SUB-G0G1 phase on the background of treatment, while with the number of cells in the S phase had a direct correlation ($r=0.78$; $p<0.05$).

At the next stage, we investigated the effect of hydrogen sulfide and genistein on the morphological structure of the kidneys under experimental CKD. Macro-and microscopic examination of the kidneys of sham-operated animals showed their typical structural and morphological organization (fig. 2.a). The kidney mass ratio averaged 0.71±0.09.

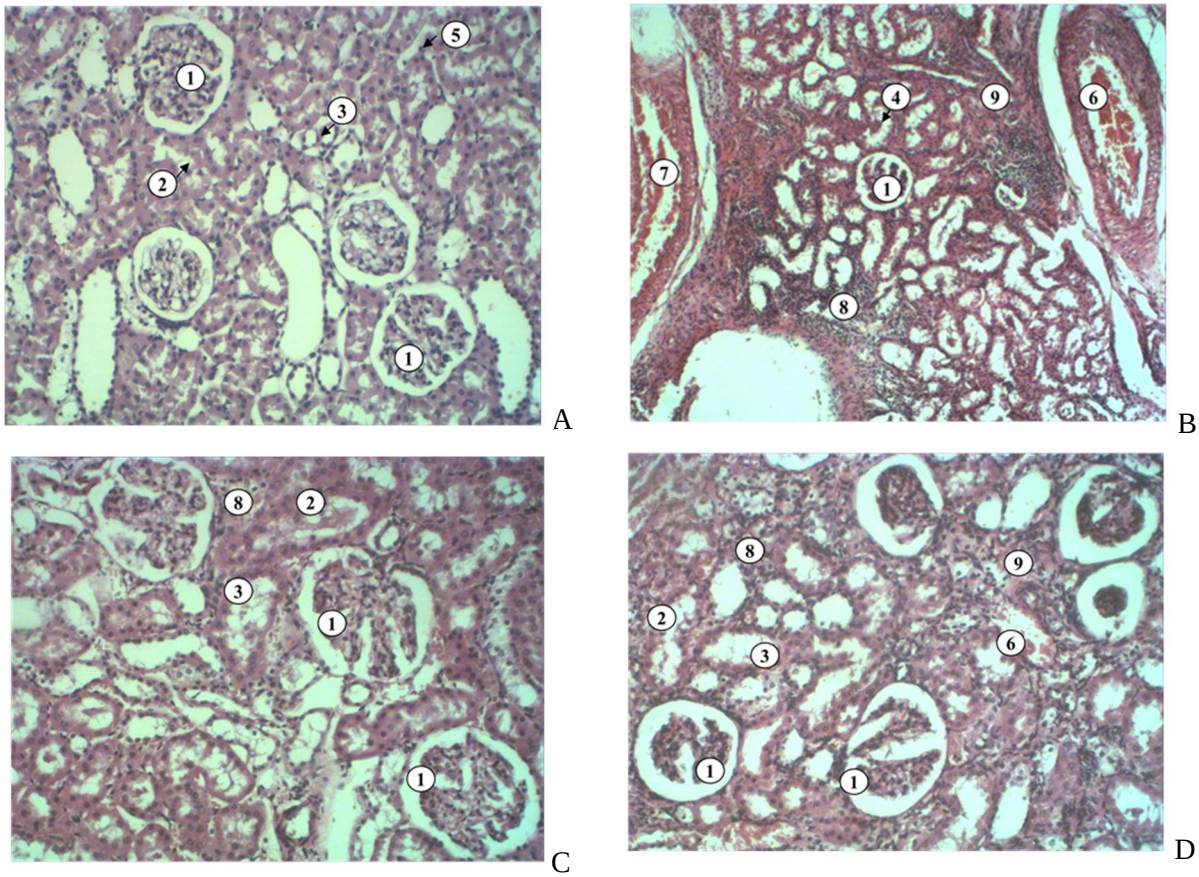

Fig. 2. Fragment of the rat's renal cortical epithelium on the 41st day. A. Sham-operated rats. B. The stump of a single rat kidney left after 5/6 nephrectomy in experimental CKD. C. The stump of a single rat kidney in experimental CKD using NaHS. D. The stump of a single rat kidney in experimental CKD under the conditions of genistein use. Hematoxylin-eosin staining. Lens x10. Eyepiece x10. Designation: 1 – renal corpuscles, 2 – proximal tubules, 3 – distal convoluted tubules, 4 – cellular detritus and granular cylinders in the lumens of proximal tubules, 5 – peritubular blood vessels, 6 – thrombus in arterioles, 7 – thrombus in the venule lumen, 8 – thrombus in the venule lumen, 9 – interstitial sclerosis.

Microscopic and macroscopic studies of kidney stumps of animals with simulated pathology revealed destructive changes in all structural elements. The most pronounced changes were in the group of CKD animals without treatment and were significantly different from the kidneys of sham-operated animals. So, the stump of the kidney had a soft consistency of greyish-brown colour, had a bumpy surface. Numerous hemorrhages were found under the fibrous capsule. The connective tissue membrane is fused with the organ's parenchyma and thickened. The border between the cortical and cerebral layers is clear on the incision. Signs of fatty dystrophy were determined in the cortex, and sclerosis in the medulla. The renal pelvis was significantly dilated. The mass coefficient of the renal stump averaged 0.54±0.06, which was 23.9 % less than in control.

Microscopically, significant dystrophic-destructive changes in the histological structure were also detected (Fig. 2c).

Both hypertrophied and atrophied renal corpuscles were present. In the preserved corpuscles, the lumens of the glomerular capillaries were widened, some were empty, and erythrocytes were found in the form of rouleaux. There is mesangial proliferation, granular and hydropic dystrophy of mesangial cells and podocytes. Part of the glomeruli is destroyed and disorganized. Foci of sclerosing of the glomeruli or the entire renal corpuscle was detected. Various changes were found in the epithelium of the renal body capsule (granular dystrophy, hypertrophy, hyperplasia) and the proximal and distal tubes - . Cells were enlarged in volume, perinuclear spaces were expanded, and the cytoplasm was enlightened with numerous vacuoles. Part of the epithelial cells was atrophically and necrotically altered in the tubular apparatus. Most nephrons have significantly expanded urinary spaces, but corpuscles with normal or reduced capsule lumen were visualized, which was accompanied by corresponding changes in the tubular apparatus: expansion of proximal and distal convoluted tubules in nephrons with enlarged urinary spaces in renal corpuscles, and vice versa, narrowing of tubules in nephrons with sclerosed glomeruli. There was the destruction of tubules with the growth of fibrous connective tissue, which may indicate the development of fibroblastic changes. Sometimes there are microcysts. Protein detritus was found in the lumen of the tubules, in some – red blood cells, which indicates damage to the glomerular capillary wall and basement membrane. Interstitium with signs of edema, dilated lymphatic vessels, significant foci of sclerosis and infiltration by lymphocytes, monocytes and macrophages, which indicated focal interstitial lymphocytic nephritis. Part of the arterioles is narrowed, the walls are thickened, and parietal blood clots were found in the lumen. The veins are full of blood, the walls are swollen, and erythrocyte sludge is in the lumens. The endothelium of the vascular wall of veins and arteries is discontinuous in places with areas of cell desquamation and endothelial cells protruding into the vessel lumen. Myocytes had signs of granular dystrophy. In some places, the vascular wall was swollen with signs of hyperelastosis. There were areas of arteriolar wall sclerosis.

Macro- and microscopic changes in renal stumps in the third ("CKD+ NaHS") and fourth ("CKD+genistein") groups of animals differed significantly from the previous group and were similar to each other (Fig. 2 C–D).

As in the second group, the kidney stump of rats had a soft consistency and was bumpy, greyish-brown in color, but the connective tissue membrane was not fused with the parenchyma and was less thickened. Hemorrhages under the capsule were isolated. The mass coefficient of the kidney in the third group is 0.61±0.01, in the fourth - 0.59±0.02. On the cross-section, the pattern of the kidney layers and the border between them were clear; the renal pelvis was moderately dilated.

Microscopically, the pathological changes were also less pronounced than in the untreated CKD group. The glomeruli in the renal corpuscles are homogeneous. Glomerular capillaries were somewhat dilated and moderately full-blooded, with no sludge syndrome. In some renal glomeruli, capillaries were compactly arranged, extracapillary spaces were absent, and in some, extracapillary spaces were dilated, and the number of small capillary loops was reduced. There are no signs of necrobiotic changes in endothelial cells in the capillary walls. The number of mesangial cells in the glomeruli is increased, but granular and hydropic dystrophy was not detected in them, as in podocytes. Segmental sclerosis was observed in isolated renal corpuscles. The thickness of the parietal epithelium of the renal capsule was uniform without signs of hypertrophy and hyperplasia of simple squamous epithelial cells. The urinary spaces were slightly dilated and filled with exudate without red blood cells, indicating the filtration barrier's integrity. Some of the nephrons' proximal and distal convoluted tubules were moderately dilated. Pathological changes in the epithelium of the tubules were insignificant. The number of endothelial cells with hyperchromic nuclei was lower than in the "CKD without treatment" group. There was also a smaller number of large tubular cysts. Protein masses, granular and hyaline cylinders in the lumens were rarely detected. Foci of the proliferation of histiocytes and lymphocytes, as well as hyperplasia of fibroblasts and collagen fibers of connective tissue around vessels of the blood microcirculatory channel and renal tubules in the renal cortex, were less pronounced than in rats with CKD without treatment, foci of hyalinized and necrotic fibers were not detected. In isolated cases, signs of dysplasia of varying degrees were detected, as well as inflammatory and sclerotic processes. Interstitial edema was insignificant and evenly expressed in all parts of the kidney. Diapedesic hemorrhages, areas of lymphohistiocytic infiltration and foci of sclerosis were isolated. Signs of dysangiogenesis were also less pronounced in the renal vascular bed. The vessel walls were not thickened, and the endothelial lining showed no dystrophic-destructive changes. Mural thrombi in the lumens of renal and arch arteries and interlobular arterioles were rarely detected. The veins were dilated and moderately full-blooded.

Therefore, the obtained results indicate that CKD induces apoptosis, slows down the processes of DNA synthesis, and reduces the number of mitoses in the renal cortical epithelial cells. The use of NaHS, like genistein, contributed to the normalization of the number of mitoses and the activation of DNA synthesis and also reduced the intensity of apoptosis of the renal cortical epithelial cells. According to the literature data, the anti-apoptotic effect of H_2S can be realized through the hydrogenation of NF-kβ. This

causes its translocation into the nucleus and is accompanied by a decrease in the synthesis of the pro-apoptotic protein BAX, an increase in the synthesis of the anti-apoptotic protein Bcl-2 and inhibitory proteins that block apoptosis mediated by receptors TNFR 1 and Apo 3 [9], as well as by hydrogenation of ATP-sensitive K^+ channels, which leads to the phosphorylation of protein kinase C. It activates the Ca^{2+}-ATP phase of the endoplasmic reticulum, which, in turn, leads to a decrease in the cytoplasmic concentration of Ca^{2+} and stabilization of the mitochondrial permeability transition pore [11].

Also, for chronic kidney damage, violations of their histological structure were recorded: hypo- and atrophy of renal corpuscles, mesangial proliferation (is a sign of chronic endotoxemia), destruction of podocytes (indicates a violation of the filtration barrier), foci of glomerular sclerosis or the entire renal corpuscle, focal interstitial lymphocytic nephritis, vascular endothelial dysfunction and thrombosis. The use of NaHS, like genistein, contributed to the reduction of inflammation, degenerative-dystrophic and fibroblastic processes, and hemodynamic disorders and showed endothelial and epithelioprotective effects, which, in our opinion, is associated with an increase in the level of hydrogen sulfide. The antifibrotic effect of hydrogen sulfide is associated with its ability to increase the expression of TGF-β, which is accompanied by the activation of the SMAD proteins family, which inhibit the proliferation of fibroblasts and their transformation into myofibroblasts. Anti-inflammatory properties are associated with the ability to block signalling mediated by NF-κB (nuclear factor kappa-B) and MAPK (mitogen-activated protein kinase), which is accompanied by a decrease in the synthesis of pro-inflammatory cytokines TNF-a, IL-1b, etc. Endothelial protective effects are associated with its antioxidant properties and ability to influence the production of nitrogen monoxide. The antioxidant effect of this gas transmitter is realized by affecting the activity of transcription factors such as Nrf2, which activates about 200 protein genes involved in antioxidant protection [6]. The effect on vascular tone and platelet aggregation is realised through stimulation of K^+ATP channels of vascular smooth muscles and activation of the endothelial isoform of NO synthase and NO production [2, 8, 10].

Conclusion

The use of the hydrogen sulfide donor NaHS, as well as genistein, under the conditions of experimental chronic kidney disease in rats showed a normalizing effect on the cell cycle and morphological structure of the kidneys. The nephroprotective effect was manifested through an anti-apoptotic effect, normalization of the number of mitoses and the activity of DNA synthesis, inhibition of the development of structural and degenerative-dystrophic changes in the kidneys, activation of compensatory-adaptive and regenerative processes and normalization of hemodynamics. Regarding the nephroprotective effect, genistein was not inferior to sodium hydrogen sulfide. Further in-depth study of agents that are inducers of endogenous hydrogen sulfide can create conditions for developing more effective pharmacotherapy of CKD.

References

1. Varenyuk IM, Dzerzhynskyy ME. Metody tsyto-gistologichnoyi diagnostyky: navchalnyy posibnyk.– Kyiv: Interservis.2019:256 s. [in Ukrainian]
2. Askari H, Seifi B, Kadkhodaee M, Sanadgol N, Elshiekh M, Ranjbaran M, et al. Protective effects of hydrogen sulfide on chronic kidney disease by reducing oxidative stress, inflammation and apoptosis. EXCLI J. 2018;17:14–23. https://doi.org/10.17179/excli2017-711
3. European convention for the protection of vertebrate animals used for experimental and other scientific purposes. Strasbourg:Council of Europe;1986. 53 p.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):1–127. https://doi.org/10.1016/j.kint.2022.06.008
5. Koniukh S, Voloshchuk N, Melnyk A, Domin I. Hydrogen sulfide metabolism and its role in kidney function in a rat model of chronic kidney disease. Health Problems of Civilization. 2020;14(4):289–297. https://doi.org/10.5114/hpc.2020.96571
6. Mykytenko AO, Akimov OYe, Yeroshenko GA, Neporada KS. Influence of transcription factor κB on remodeling of extracellular matrix of rat liver under conditions of chronic alcohol intoxication. World of medicine and biology . 2022;2(80):214–217.
7. Peleli M, Zampas P, Papapetropoulos A. Hydrogen Sulfide and the Kidney: Physiological Roles, Contribution to Pathophysiology, and Therapeutic Potential. Antioxid Redox Signal. 2022;36(4-6):220–243. https://doi.org/10.1089/ars.2021.0014
8. Peng Q, Li Y, Shang J, Huang H, Zhang Y, Ding Y, et al. Effects of Genistein on Common Kidney Diseases. Nutrients. 2022;14(18):3768. https://doi.org/10.3390/nu14183768
9. Sen N, Paul BD, Gadalla MM, Mustafa AK, Sen T, Xu R, et al. Hydrogen sulfide-linked sulfhydration of NF-κB mediates its antiapoptotic actions. Mol Cell. 2012;45(1):13–24. https://doi.org/10.1016/j.molcel.2011.10.021
10. Shirazi MK, Azarnezhad A, Abazari MF, Poorebrahim M, Ghoraeian P, Sanadgol N, et al. The role of nitric oxide signaling in renoprotective effects of hydrogen sulfide against chronic kidney disease in rats: Involvement of oxidative stress, autophagy and apoptosis. J Cell Physiol. 2019;234(7):11411–11423. https://doi.org/10.1002/jcp.27797
11. Varfolomeev E, Goncharov T, Vucic D. Roles of c-IAP proteins in TNF receptor family activation of NF-κB signaling. Methods Mol Biol. 2015;1280:269–282. https://doi.org/10.1007/978-1-4939-2422-6_15
12. Wang D, Chen J, Liu X, Zheng P, Song G, Yi T, et al. A Chinese herbal formula, Jian-Pi-Yi-Shen decoction, improves muscle atrophy via regulating mitochondrial quality control process in 5/6 nephrectomised rats [retracted in: Sci Rep. 2021 Jun 14;11(1):12831]. Sci Rep. 2017;7(1):9253. https://doi.org/10.1038/s41598-017-10027-4

Стаття надійшла 27.04.2022 р.