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Review

The pathogenetic mechanisms of acute kidney injury and chronic kidney disease (a literature review)

T. M. Boychuk[1], A. I. Gozhenko[2], N. D. Filipets[1], V. M. Khodorovskyy[1]

[1]Higher State Educational Establishment of Ukraine "Bukovinian State Medical University", Chernivtsi, [2]State Enterprise "Ukrainian Research Institute for Medicine of Transport of the Ministry of Health of Ukraine", Odesa

Aim – compilation of scientific data on the pathogenetic mechanisms of acute kidney injury and chronic kidney disease.

Although the general pathophysiological picture and the main clinical and laboratory signs of renal damage or comorbid conditions causing CKD have been established, the research of the gradual nephron death mechanisms are still very actual. To date it is unknown why kidney injury initially causes reversible changes, but with the passing of time irreversible acute renal insufficiency occurs or chronic process develops. Broadening pathogenesis knowledge is an important step toward improving early diagnosis and treatment of acute and chronic kidney injury for the maximal postponement of end-stage renal disease. We have analyzed available scientific literature for the past 5 years that allows formulating the modern concept of the general pattern and the key links in the mechanisms of kidney dysfunction and loss of nephrons homeostatic functions. The results, shown in our own experiments, demonstrate the influence of ATP-dependent potassium (K_{ATP}) channel activator flocalin on renal. Defined nephroprotective effects of flocalin on tubular and glomerular parts indicate the pathogenetic role of K_{ATP} channels and importance of their pharmacological activation during acute and chronic kidney injury.

Conclusions. Regardless of its etiology acute injury of the nephrocytes proceeds through several mechanisms. The initial compensatory effects of these mechanisms can change to irreversible destructive influence that finally results in reduction in the number of the functioning nephrocytes, chronic kidney disease formation and terminal renal insufficiency. Despite intensive research of pathogenesis and continuous search for the new markers of acute and chronic kidney injury the causes of kidney pathology progression have not been fully disclosed yet. The important medical, social and economic aspects of renal diseases substantiate perspective of the key links further study that form a universal pathophysiological picture and facilitate the pathogenetic directions of pharmacological nephroprotection improvement.

Key words: acute kidney injury, chronic kidney disease, pathologic processes.

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E-mail: filipec.natalja@bsmu.edu.ua

Патогенетичні механізми гострого пошкодження та хронічної хвороби нирок (огляд літератури)

Т. М. Бойчук, А. І. Гоженко, Н. Д. Філіпець, В. М. Ходоровський

Мета роботи – узагальнення наукових даних щодо патогенетичних механізмів гострого пошкодження та хронічної хвороби нирок.

Попри визнання загальної патофізіологічної картини, основних клініко-лабораторних ознак пошкодження нирок чи коморбідних станів, що призводять до прогресування нефрологічної патології, не втрачають актуальності дослідження механізмів, котрі спрямовані на поступову загибель нефронів. Досі не з'ясованим залишається питання: чому при пошкодженні нирок спочатку викликають зворотні зміни, але надалі невідворотно виникає гостра ниркова недостатність або розвивається хронічний процес. Розширення уявлень про патогенез є важливим напрямом удосконалення ранньої діагностики, лікування гострого та хронічного пошкодження нирок для максимального відтермінування термінальної ниркової недостатності. Проаналізували доступну наукову літературу за останні 5 років, що дає змогу сформувати сучасні уявлення про загальні закономірності та ключові ланки механізмів розвитку дисфункції нирок і втрати гомеостатичної функції нефронів. Наведені результати власних досліджень впливу на нирки вітчизняного активатора АТФ-залежних калієвих ($К_{АТФ}$) каналів флокаліну. Виявлені нефропротекторні ефекти флокаліну в канальцевому та клубочковому відділах вказують на патогенетичну участь $К_{АТФ}$ каналів і на доцільність їхньої фармакологічної активації при гострому та хронічному пошкодженні нирок.

Висновки. Незалежно від етіології, слідом за гострим пошкодженням нефроцитів виникає низка механізмів, їхні початкові компенсаторні ефекти можуть змінюватися на незворотні руйнівні впливи, кінцевим результатом яких є зменшення кількості нефронів, що функціонують, формування хронічної хвороби нирок і термінальної ниркової недостатності. Незважаючи на інтенсивне вивчення патогенезу і безперервний пошук нових маркерів гострого та хронічного пошкодження нирок, причини закономірного прогресування нефрологічної патології ще остаточно не розкриті. Важливі медико-соціальні та економічні аспекти захворювань нирок обґрунтовують перспективність досліджень ключових ланок процесів, що формують універсальну патофізіологічну картину, сприяють удосконаленню патогенетичних напрямів медикаментозної нефропротекції.

Ключові слова: гостре пошкодження нирок, хронічна хвороба нирок, патологічні процеси.

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Патогенетические механизмы острого повреждения и хронической болезни почек (обзор литературы)

Т. Н. Бойчук, А. И. Гоженко, Н. Д. Филипец, В. Н. Ходоровский

Цель работы – обобщение научных данных, касающихся патогенетических механизмов острого повреждения и хронической болезни почек.

Ключевые слова: острое повреждение почек, хроническая болезнь почек патологические процессы.

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Несмотря на всеобщее признание патофизиологической картины, основных клинико-лабораторных признаков повреждения почек или коморбидных состояний, способствующих прогрессированию нефрологической патологии, актуальными являются исследования механизмов, направленных на постепенную гибель нефронов. До сих пор остается открытым вопрос: почему при повреждении почек изначально возникают обратимые изменения, но в дальнейшем формируется острая почечная недостаточность или хронический процесс. Расширение представлений о патогенезе – важное направление совершенствования ранней диагностики и лечения острого и хронического повреждения почек для максимальной отсрочки терминальной почечной недостаточности.Проанализирована доступная научная литература за последние 5 лет, позволяющая сформировать современные представления об общих закономерностях и ключевых звеньях механизмов развития дисфункции почек и потери гомеостатической функции нефронов. Приведены результаты собственных исследований влияния на почки отечественного активатора АТФ-зависимых калиевых ($К_{АТФ}$) каналов флокалина. Выявленные нефропротективные эффекты флокалина в канальцевом и клубочковом отделах указывают на патогенетическую роль $К_{АТФ}$ каналов и целесообразность их фармакологической активации при остром и хроническом повреждении почек.

Выводы. Независимо от этиологии, вслед за острым повреждением нефроцитов возникает ряд механизмов, начальные компенсаторные эффекты которых могут изменяться на необратимые разрушительные влияния, конечным исходом которых является уменьшение количества функционирующих нефронов, формирование хронической болезни почек и терминальной почечной недостаточности. Несмотря на интенсивное изучение патогенеза и непрерывный поиск новых маркеров острого и хронического повреждения почек, причины закономерного прогрессирования нефрологической патологии окончательно не раскрыты. Важные медико-социальные и экономические аспекты заболеваний почек обосновывают перспективность исследований ключевых звеньев процессов, которые формируют универсальную патофизиологическую картину и способствуют совершенствованию патогенетических подходов современной медикаментозной нефропротекции.

Unfavourable epidemiological indices and a limited arsenal of medicinal renal protection are the subject of great interest in scientific research; this in turn broadens the knowledge of pathogenetic mechanisms of renal injury. The urgency of the issue is largely due to the natural progression of nephrological pathology and, accordingly, the need for early suppression of new chains of damage involvement in the renal failure formation. In addition, analysis of available modern data supplements the primary mechanisms of kidneys homeostatic ability disturbance and outlines new directions of nephroprotection.

Aim: compilation of scientific data on the pathogenetic mechanisms of acute kidney injury and chronic kidney disease.

Acute kidney injury (AKI) is a frequent complication of critical conditions and chronic somatic diseases, which increases mortality and is a consequence of both direct nephrotoxic agents action and other secondary pathogenetic factors. Rapid progressive deterioration of kidney functions leads to various homeostatic disorders, primarily to water-electrolyte imbalance. AKI is clinically defined as an abrupt decline in renal function with a rapid (during 48 hours) absolute increase in serum creatinine level up to 0.3 mg/dL (26.4 μmol/L) and more, relative increase in serum creatinine level up to 50 % and more or oliguria less than 0.5 ml/kg/h during 6 hours and longer. These criteria are likely to be revised in the future because new genetic markers and biomarkers of tubular and glomerular injury have been identified, namely interleikin-18 (IL-18) of urine, neutrophilic gelatin-associated lipocalin (NGAL) of urine and plasma, cystatin C, kidney injury molecule-1 (KIM-1) [1,2].

According to pathophysiological mechanisms of development there are three categories of AKI: prerenal, renal and postrenal [3]. Prerenal injury is not associated with the pre-existing structural pathology in kidneys, but it's actually a functional response to renal hypoperfusion. The latter occurs in any diseases or pathologic conditions with hypovolemia, low cardiac output, systemic vasodilation and decrease of blood pressure (BP) or renal vasoconstriction, that further leads to hypoxic damage of renal parenchyma. The adequate therapeutic tactics in prerenal AKI aims to normalize renal blood flow with regard to the initial etiologic factor of hypoperfusion.

Postrenal kidney injury is a result of the mechanical obstruction of upper or lower urinary tract, which at the very beginning leads to the increase of pressure inside the tubules and reduction of glomerular filtration rate (GFR). In the structure of AKI its rate is less than 5 %.

Unlike pre- and postrenal AKI, renal injury occurs on the ground of pre-existing acute and mainly prolonged intrarenal pathology. In this connection, the removal of etiologic agents won't always lead to the renal functions normalization. So, renal AKI may be a consequence of various etiology glomerular apparatus damage, as well as tubular lesion resulting from continual renal ischemia or endogenous and exogenous toxicants, or acute pathology of interstitium (acute nephritis) in allergic, infectious, infiltrative processes etc. There are also vascular causes of renal injury like large vessels pathology (bilateral renal artery stenosis, renal vein thrombosis) and microcirculation disturbances (vasculitis, atheroembolic renal disease, thrombotic microangiopathies etc.).

Thus, about 90 % of renal AKI causes are ischemia, nephrotoxins or combined influence of both agents. Renal AKI rate is 2–5 % in the total number of hospitalized patients and 10–15 % among the intensive care unit patients. The in-hospital AKI is characterized by unfavorable prognosis and high case fatality rate – up to 50–70 % that hasn't changed significantly for the last decades. In the majority of patients who survive the renal functions improve, but they never normalize and more often transform into chronic kidney disease (CKD) [4].

In clinical practice the number of primary toxic renal injury makes 50 % of all AKI and CKD cases. The cells of the tubular part of nephron are extremely sensitive to the toxin mediated injury due to a long-lasting contact with circulating chemical compounds and their high concentration in the tubulocytes because of reabsorption and secretion processes. Renal blood flow intensity, hypersensitivity of renal vessels to imbalance between vasoconstrictors and

vasodepressors, high ability of toxicants to biotransformation in renal epithelium cells with the formation of active intracellular and circulating metabolites are also significant. There's a generally accepted opinion that the toxin (or its metabolite) initiates its own destructive action by linking with biologically important cellular macromolecules or by the active forms of oxygen production. In both cases the activity of macromolecules (plasmatic membrane proteins and lipids, nuclei, lysosomes, mitochondria) is disturbed that finally results in tubular cells injury [5,6].

Mitochondria, the key generators of cellular ATP often become toxins' critical target [7,8]. Violation of oxidative phosphorylation and ATP insufficiency results in the change of the cellular ion balance with lowering of intracellular K^+, rising of Na^+ content and membrane depolarization. At the same time there is an increase of free cytosol Ca^{2+} that can occur both at early and late stages of cellular damage and is a decisive factor for cellular destruction. The increased Ca^{2+} content activates calcium-dependent neutral proteases (calpains), which take part in intracellular proteolysis. The intensification of lipid peroxide oxidation processes and formation of its final products activate other enzymes responsible for cell destruction (phospholipase A2 etc.). These enzymes hydrolyze cellular membrane phospholipids and intracellular cysteine proteases (caspases), the key components of apoptosis [9]. Hydrolysis of the membrane substrate causes elevation of extracellular chlorine ions inflow that accelerates terminal swelling of cells.

Nephrotoxic agents can cause various clinical variants of renal injury, particularly acute tubular necrosis, acute or chronic interstitial nephritis, medullary (papillary) renal necrosis, glomerulonephritis, membranous nephropathy and further lead to arterial hypertension [10].

The mechanism of AKI development is complicated and in most cases combines toxic, immunoallergic renal parenchyma damage and obligatorily hemodynamic disturbance with kidney hypoxia. In medical practice this pathology can be caused by antibacterial drugs: antibiotics (aminoglycosides, cephalosporins, penicillins, polymyxins), sulphanilamides (sulfadimezine, sulfadimethoxine), fluoroquinolones (norfloxacin), cytostatics (doxorubicin, cisplatin, methotrexate, nitrosourea derivatives), radiocontrast substances (iohexol), immunosupressors (cyclosporine A), antiviral drugs (acyclovir, valacyclovir, foscarnet), nonsteroidal anti-inflammatory drugs (NSAIDs) (indometacin, diclofenac, ibuprofen, naproxen, acetylsalicylic acid, acetaminofen), angiotensin-convertive enzyme (ACE) inhibitors (captopril, enalapril, lisinopril), angiotensin II (Ang II) receptor blockers (losartan), and some other medical drugs – lovastatin, mannitol, penicillamine, thiazide diuretics [11,12]. The nephrotoxic effect is well known for different exogenous chemical agents, particularly salts of heavy metals (mercury, cadmium, cobalt), organic solvents (ethers, ketones, nitro compounds), and also endogenous compounds like myoglobin, hemoglobin, calcium ions, uric acid, oxalates, cystine, homocysteine [13,14]. Aminoglycoside antibiotics and radiocontrast agents are more often associated with nephrotoxic injury among hospitalized patients. Intravenous contrast agents can cause AKI not more than in 5 % of cases but this rate can rise to 50 % in risk factors presence which are CKD, diabetes mellitus, heart failure, usage of nephrotoxic drugs, hypovolemia [15].

Nephrotoxic substances are characterized by selectivity of different nephron parts or renal vessels damage. Thus, NSAIDs, ACE inhibitors, cyclosporine A and radiocontrast dye induce vasoconstriction, so they can cause hemodynamic-induced AKI. Interferon-alpha and penicillamine cause glomerular damage. Aminoglycosides, cadmium chloride and potassium dichromate damage S1 and S2 segments of the proximal tubules, and cisplatin and mercuric chloride destruct S3 segment. Cephalosporins, cadmium chloride and NSAIDs initiate inflammatory reaction in the interstitium while acetaminofen leads to renal papillary necrosis.

Nephrotoxins can decrease GFR by one or several mechanisms which are renal vasoconstriction; obstruction as a consequence of drug precipitation or endogenous substance inside of the renal medullary collecting ducts; a direct obstruction and dysfunction of tubules that leads to the increase of intratubular pressure and reverse glomerular filtrate flow; imbalance between vasoactive mediators which results in decrease of renal perfusion pressure, lowering of afferent arteriolar tone, increasing of efferent arteriolar tone, decrease in glomerular capillaries hydrostatic pressure.

AKI to a certain extent is a reversible process that depends on the degree of nephron damage. In the sublethally injured cells there can be restoration and adaptation processes or on the contrary, cell death. In the uninjured cells there is dedifferentiation which is a temporary loss of structure specialization signs, as well as proliferation, migration, differentiation and compensatory hypertrophy [16]. In the reversibly damaged tubular cells there are changes in cytoskeleton and normal distribution of membrane proteins, such as Na^+/K^+-ATPase and β1 integrins [17]. The latter are connected with the components of cytoskeleton and provide a signal transmission in the cell. These changes lead to polarity loss in the cell membrane, decrease of integrity of tight junctions and disorders of cell-substrate adhesion. The lethally damaged cells die by one of the mechanisms, either apoptosis, or necrosis.

Despite intensive study of AKI pathogenesis and continuous search of early diagnostics new markers many of its mechanisms remain unidentified. That is why today there is no effective specific pathogenetic treatment of this condition and the existing treatment strategies require further investigation. The key question is why the persistent kidney injury or repeated exacerbations of the existing disease are the first cause of reversible changes which further inevitably lead to kidney failure or chronic process development.

Numerous renal disorders can cause CKD. The concept of CKD comprises a group of pathologic conditions that are characterized by stable decrease of renal excretory function and usually structural renal changes. The National Kidney Foundation (NKF) has classified CKD into 5 stages according to severity of kidney dysfunction and injury, as well as symptoms and required therapy [18]. CKD definition is based on measured or estimated GFR <60 ml/min normalized to an average surface area of 1.73 m^2 which persists for at least 3 months or higher levels of GFR with the evidence of kidney injury, like hypercreatininemia, hyperuricemia, proteinuria or by visual methods of analysis.

The overwhelming majority of CKD forms are irreversible and progressive and they finally result in the loss of nephrons and require substitution therapy like dialysis or

kidney transplantation. The pathological process can start as tubular-interstitial, glomerular or renovascular disease and may arise due to systemic diseases (diabetes mellitus, arterial hypertension), autoimmune processes and kidney transplant rejection; influence of drugs, toxins and metals; infectious processes; mechanical damage; ischemia; obstruction of urinary tract; primary genetic anomalies; unidentified (idiopathic) causes. Most of these diseases have both specific and general pathophysiological features which enable to outline the general mechanisms of CKD progression [19]. Regardless of the etiology CKD is characterized by gradual loss of renal functions and excessive accumulation of extracellular matrix in glomeruli and tubular interstitium. CKD progression is associated with the appearance of a general fibrotic phenotype when the cause of the disease can be determined only by characteristic morphological signs. This is due to the fact that tubular-interstitial disease leads to the damage of glomeruli which results in the lesion of interstitium. In both cases there is loss of the nephrons and replacement of kidney cells with scar-like tissue, as well as progressive GFR decrease and deterioration of excretory renal function. It is important to note that the severity of functional and morphological changes strongly correlates with the severity of tubular-interstitial fibrosis without reference to its etiology [20]. So it is possible that the damaged tubules have a greater impact on the excretory function than the damaged and sclerotized glomeruli at least at the initial stages. Owing to the renal functional reserve (RFR) the filtration process is maintained and this generally positively affects the activity of the kidneys. Nevertheless, moderate disorder of tubular reabsorption by the reverse tubular-glomerular connection mechanism may induce GFR decline, sometimes to the catastrophic level to keep water-electrolyte balance [21]. The decrease or significant reduction of filtration can also be caused by the destruction of tubular epithelium and complete obstruction of the tubules by tissue detritus with the further disorder of renal hemodynamics.

Tubules are a main structural and functional component of renal parenchyma. In case of tubulopathy tubular cells produce profibrotic and proinflammatory factors (complement factors 3 and 4, asymmetric dimethylarginin, TGF-β (transforming growth factor β), Ang II, endothelin, factors of platelets activation and growth, IL-6, prostaglandin (PG) E2 etc.), which at first play a regenerating role but further turn into paracrine mechanisms of glomerular lesion. The final process is fibrosis development when the inflammation phase is substituted by fibrogenesis in glomeruli and in renal interstitium [22]. A number of cytokines, growth factors and proteins of complement system potentiate mesangial cells to release chemotactic factors by the ways connected with nuclear factor NF-kB [23].

One of the main effectors involved in resident cells activation in nephropathies, particularly in hypoxic one is Ang II. For a short period of time Ang II affects mesangial cells, induces the elevation of calcium ions and inositol phosphate in cytosol, synthesis of PG and contraction of cells. In the distant period Ang II induces proliferation and hypertrophy processes and intensifies the production of intercellular matrix. Ang II causes vasoconstriction and further potentiates the decrease of renal blood flow and, apart from GFR reduction, generates even greater oxygen deficiency and hypoxia. Hypoxia gives rise to cell destruction and activates hypoxia-induced factor (HIF) that contributes to fibrosis [24]. Besides, hypoxia decreases intracellular ATP reserve and in this way induces cell necrosis.

In most variants of CKD the selectivity and permeability of glomerular filtration barrier change. It is believed that in conditions of glomerular damage the main mechanism of tubular-interstitial area involvement into pathological process is increased protein reabsorption in the proximal tubules resulting from glomerular hyperfiltration. It leads to activation of cytokines synthesis in the tubules that supports infiltration of the interstitium with the immune cells and activation of immunoinflammatory response [25]. Abnormal hyperfiltration provokes interaction of bioactive macromolecules with the epithelial cells of the proximal tubules and activates the signal ways including NF-kB type. The megalin-cubilin complex mediates the capture of proteins, including albumin and participates in the interaction of albuminuria with proinflammatory and profibrotic signals. The neonatal Fc-receptor (the receptor Fc of IgG fragment, human gene's FCGRT product) and CD36 (membrane protein) of gene mutation are likely to play a certain role. Moreover, the addition of albumin or transferrin to the tubular cells decreases their ability to bind factor H and counteract the activation of complement system. Albumin can also be a source of potential antigenic peptides in kidney injury. Proteinuria isn't simply a marker but an effector of nephropathy as well. It is confirmed by the facts which indicate a direct interrelation between protein excretion level and the disease development, and also of pharmacologic antiproteinuric effect with the reversal of renal pathology [26].

The possible result of the kidney vessels damage is CKD. Renovascular diseases can directly change renal structure and function at the expense of oxidative stress initiated by atherosclerosis, as well as endothelial dysfunction and inflammation which progressively leads to fibrosis and reduced filtration. It also facilitates hypoperfusion, ischemia of the glomeruli and tubules and development of arterial hypertension. Sclerosis nuclei initially come from the confluence sites between capillaries and Bowman's capsule of the glomerulus in the area of basal membrane with insufficient podocytes number that finally results in the formation of paraglomerular space. The content of the paraglomerular space which is the ectopic filtrate and capillary loops detritus is suggested to play a significant role in the damage initiation and is the key link between glomerular and tubular lesions. There's growing evidence that even in case of such traditional glomerulopathies as diabetic nephropathy certain tubular damage can be found before the first signs of glomerular pathology are revealed [27]. These facts encourage efforts to revise the concept of glomerular and tubular diseases differentiation into favor of more integrative ideas of nephropathy.

Regardless of renal dysfunction etiology, the compensatory mechanisms activate and also participate in the formation of a vicious circle in the nephropathies pathogenesis. Among such reactions are arterial hypertension and hyperactivity of peripheral or renal sympathetic nervous system that is usually observed in patients with CKD. The increased tone of the renin-angiotensin-aldosterone system (RAAS) initiates vasoconstriction and reduction of mesangium, as well as collagenosis which leads to diminution of ultrafiltration coefficient and GFR and also to cell death and loss of the nephrons [28].

CKD progression creates an universal pathophysiological picture with inflammation, fibrosis, loss of the nephrons, and scarring of the parenchyma. In the majority of cases modern methods of drug therapy are effective enough only for postponing the terms of renal replacement therapy. It should be mentioned that clear pathological signs of CKD, in particular creatinine elevation in blood plasma manifest only when the function of more than 50 % of nephrons is lost. It hampers significantly timely diagnosis of the disease. At the same time, not only the search of early diagnostic biomarkers for renal pathology is the subject of active research. Of great importance is the problem of improving the therapeutic approaches in nephroprotection based on new scientific knowledge of adaptive, compensatory and pathophysiological mechanisms pharmacological modulation in kidneys for renal diseases or their regression prevention.

Kidneys are characterized by high intensity of blood circulation and oxygen consumption. Hypoxia is the pathogenetic ground for various pathological processes and in conditions of the natural supportive reactions insufficiency it leads to the suppression of energy generation systems in renal tubules mitochondria. The development of acute and chronic kidney pathology is currently being considered through the prism of the main energy-dependent process violation which is proximal reabsorption of sodium ions. The most important sensors of energy metabolism are ATP-dependent potassium (K_{ATP}) channels that open in case of intracellular ATP decrease and provide the adaptation of the organism to hypoxia and ischemia. The pathogenetic role of this type of channels in the mechanism of AKI and CKD is confirmed by the nephroprotective effects of K_{ATP} channels activator (opener) flocalin which we have revealed in experimental nephropathies.

A single flocalin prescription in acute sublimate rat kidney injury increased diuresis, GFR and creatinine excretion; decreased the elevated indexes of creatininemia and proteinuria [29]. The 7-day use of flocalin led to antiproteinuric effect and reduction of retentional azotemia. We also observed the normalization of natremia level which was increased in the rats with acute sublimate nephropathy [30]. Flocalin using in rats on the day of acute hypoxic histohemic nephropathy (HHHN) modeling contributed to activation of volume regulating, ion regulating and excretory renal functions at the expense of tubular and mainly glomerular processes modification. The GFR increased, energy-dependent distal sodium reabsorption restored, natriuresis and proteinuria decreased [31]. After 7-day flocalin usage the acid regulating kidney function in the rats with HHHN was characterized by the reduction of acidogenesis, maintenance of the electrolyte balance due to the decrease in sodium and potassium ions excretion, decrease in proteinuria index calculated per 100 μl of glomerular filtrate. It has given evidence of K_{ATP} channels pathogenetic role in the kidney damage development [32].

Conclusions

1. Although the general pathophysiological picture and the main clinical and laboratory signs of renal damage or comorbid conditions causing CKD have been established, the research of the gradual nephron death mechanisms are still very actual. Homeostatic renal function loss is the result of the pathological process in tubules, interstitium, glomeruli, and renal vessels. The rate of kidney diseases progression is mainly dependent on their etiology. Regardless of the specific cause, the initial nephrocyte damage is followed by a chain of adaptation mechanisms. Their compensatory effects can turn into irreversible destructive influence which finally results in the reduction in the number of the functioning nephrons, CKD and terminal renal insufficiency formation.

2. A deeper understanding of CKD development and progression mechanisms is a key to pathogenetic substantiation of the basic nephroprotection principles for maximal postponement of renal replacement therapy that proves the perspective of the further research in this scientific direction.

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Information about authors:
Boychuk T. M., MD, PhD, DSc, Professor, Rector, Higher State Educational Institution of Ukraine "Bukovinian State Medical University", Chernivtsi.
Gozhenko A. I., MD, PhD, DSc, Professor, Director of the State Enterprise "Ukrainian Research Institute of Transport Medicine of the Ministry of Health of Ukraine", Odesa, Honored Worker of Science and Technology of Ukraine.
Filipets N. D., MD, PhD, DSc, Associate Professor, Department of Pharmacology, Higher State Educational Institution of Ukraine "Bukovinian State Medical University", Chernivtsi.
Khodorovskyy V. M., MD, PhD, Associate Professor, Department of Pathologic Physiology, Higher State Educational Institution of Ukraine "Bukovinian State Medical University", Chernivtsi.

Відомості про авторів:
Бойчук Т. М., д-р мед. наук, професор, ректор ВДНЗ «Буковинський державний медичний університет», м. Чернівці, Україна.
Гоженко А. І., д-р мед. наук, професор, директор ДП «Український НДІ медицини транспорту МОЗ України», м. Одеса, заслужений діяч науки і техніки України.
Філіпець Н. Д., д-р мед. наук, доцент каф. фармакології ВДНЗ «Буковинський державний медичний університет», м. Чернівці, Україна.
Ходоровський В. М., канд. мед. наук, доцент каф. патологічної фізіології ВДНЗ «Буковинський державний медичний університет», м. Чернівці, Україна.

Сведения об авторах:
Бойчук Т. Н., д-р мед. наук, профессор, ректор ВГУЗ «Буковинский государственный медицинский университет», г. Черновцы, Украина.
Гоженко А. И., д-р мед. наук, профессор, директор ГП «Украинский НИИ медицины транспорта МЗ Украины», г. Одесса, заслуженный деятель науки и техники Украины.
Филипец Н. Д., д-р мед. наук, доцент кафедры фармакологии ВГУЗ «Буковинский государственный медицинский университет», г. Черновцы, Украина.
Ходоровский В. М., канд. мед. наук, доцент каф. патологической физиологии ВГУЗ «Буковинский государственный медицинский университет», г. Черновцы, Украина.

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