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Nephroprotective properties of ATP-sensitive potassium channels agonist flocalin

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System of the ATP-dependent potassium channels (K_{ATP}) is an important endogenous mechanism of organism protection against ischemia and hypoxia, arousing an interest in search and study of the pharmacological activators of potassium current. Review is devoted to a generalized scientific literary data justifying a wide pharmacodynamical spectrum of flocalin – a potential drug from the class of K_{ATP}-channels activators with its features as a cardioprotector, myotropic spasmolytic, vasodilator and cerebroprotector. Results of own research showing the ability of flocalin to maintain homeostatic functions of kidneys under the conditions of water-salt loading are also represented. Taking into consideration cardiorenal continuum, pathogenetic connection between renal and cardiac pathology makes it possible to suggest an inhibitory influence of flocalin on the development of nephropathy. A prerequisite for a study of its renal effects is data concerning the mechanisms of correction the morphological, functional and biochemical pathological changes in myocardium by flocalin, which allows positioning this new activator of K_{ATP}-channels as a perspective cardioprotector and also may give rise to a new direction in nephroprotection.
Key words: activator of ATP-sensitive potassium channels flocalin; pharmacodynamics; cardioprotection; nephroprotection.

Flocalin is an original cardioprotector and myotropic spasmolytic with the specific ability to activate ATP-sensitive potassium channels (K_{ATP}) of the sarcolemma and mitochondrial cell membranes. Flocalin (N-(-4-difluoride-methoxiphenyl)-N′-1,2,2-trimethylpropyl-N′′-cyanoguanidine) is synthetized in the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. It contains a benzoic ring with a difluoridemethoxi-group. Due to the presence of fluoride ion the pharmacological properties of the domestic activator of K_{ATP}-channels are significantly improved comparing to its foreign analog – pinacidil [1, 2]. A dosage form of flocalin (tablets), produced according to a new technological scheme of synthesis on a base of JSC «Borshchagiv chemical pharmaceutical factory», doesn't differ significantly from its laboratory substance flocalin [3]. Numerous research results demonstrated the potent cardioprotective mechanisms of a new compound and served as a basis for the manufacturing of flocalin [4].

Taking into account a generally accepted cardiorenal continuum, common pathogenetic mechanisms of heart and kidney disturbances, a logical assumption that flocalin has renal effects may be made. In patients with cardiovascular pathology an impairment of kidney function is a common occurrence and is associated with the worse prognosis, while nephrological patients are at high risk of cardiovascular death [5-7]. Consequently, correction of vascular tone and structural-functional state of myocardium along with maintenance the adequate functional state of kidneys is at the top of both cardio- and nephroprotection strategy [8-10]. For this reason, the vasodilatory, membrane stabili-

zing, metabolic, and cardioprotective effects of flocalin became a background for the investigation of nephrotropic effects of flocalin [11, 12]. Moreover, a low toxicity of K_{ATP}-channels activators, particularly a low nephrotoxicity of a new representative flocalin draws the attention. As known, a central role of kidneys in a drugs and their metabolites excretion calls forth a high sensitivity of organ to undesirable effects of drugs. Kidney tissue is affected by drugs present in blood and also due to their transtubular transport. Concentration of substances in kidney tubules may be significantly higher than in blood and, consequently, more toxic. Nephrological patients require cautious approach to the prescription of even potentially non-toxic drugs. Pharmacokinetics parameters of flocalin aren't fully determined yet. Conducted toxicity studies of flocalin have shown that according to drugs toxicity classification flocalin belongs to the III class – low toxic substances. Median lethal dose (LD_{50}) of flocalin with the administration into stomach of white rats (on a starch gel) fluctuates between 1630-2180 mg/kg against 600 mg/kg for pinacidil. It is established that flocalin doesn't affect adversely the function indicators of the vitally important organs and systems: survival rate of experimental animals, body mass, body temperature, morphological composition and rheological properties of blood were within the normal physiological range; main functions of cardiovascular and nervous system weren't altered; liver and kidney function wasn't affected. Long-term (during 3 month) administration of flocalin to rats and dogs at doses exceeding the maximal daily dose for humans by 10-fold and 50-fold hasn't caused any significant adverse effects [13].

A low toxicity of flocalin enabled the identification of its dose-dependent properties and determination of an optimal dose range for the treatment of cardiovascular diseases. Following the intravenous administration of flocalin, dissolved in dimethylacetamide, a degree of a systemic arterial blood pressure reduction as well as dilation of coronary vessels was correlating explicitly with the administered doses from 0.05 to 1.5 mg/kg. Vasodilatory response was rapid and reached its maximum 2-4 min after flocalin administration [14]. These vasodilatory effects of a fluoride-containing K_{ATP}-channels activator are of a significant value in pathologies like hypertension or diabetes mellitus, accompanied with increased arterial pressure and, consequently, high risk of nephropathy development. Another valuable flocalin characteristic is the absence of hyperglycemic response after the opening of K_{ATP}-channels [15]. Given effect is especially important in diabetic nephropathy, considering a blockage of potassium channels by oral hypoglycemic drugs. The potent vasodilatory effects of flocalin were demonstrated in experiments on rats with genetically determined arterial hypertension, whereas less significant effects were observed on a model of streptosocine-induced diabetes [16-18]. It should be mentioned that reduction of a vascular pressure in hypertensive patients preventively inhibits development of chronic kidney disease independently of its etiology [19].

Flocalin demonstrated its cardioprotective effect in a wide dose range – from 0.1 mg/kg with intravenous administration to 3.3 mg/kg with oral use. An intragastric administration of flocalin tablets in a dose of 2.2 mg/kg prevented a significant decrease of a minute volume of blood as well as an increase of peripheral vascular resistance, reducing a cardiac preload of ischemic heart; maintained the indices of myocardial contractility – force of contraction and relaxation of the left ventricle; significantly diminished the reperfusion rhythm disturbances in ischemic heart. In addition, a coronary arteries vasoconstriction during the reperfusion of ischemic heart wasn't observed on the condition of prophylactic flocalin administration. A coronary perfusion pressure was slightly decreased yet, reaching the control values by the end of ischemia/reperfusion. A size of necrotic area and, therefore, myocardial infarction zone was restricted against the background of flocalin use [20]. A significant reduction of heart necrotic area in rats with myocardial infarction was ob-

served in the *in vivo* experiments, when flocalin was used as a reference drug [21].

Thus, taking into account common risk factors and mechanisms of the feedback, which forms a continuum between the heart, vessels and kidney [22-25], suggestion was made that pharmacological activation of K_{ATP}-channels by flocalin will give to the whole cardio-renal system a pathogenetic resistance and postpone the development of the integral disturbances on the part of homeostatic organs.

Correction of disturbed biochemical processes is an important area of organoprotection. In the experiments conducted on dogs with ischemia/reperfusion injury the biochemical indices of the various zones of heart (intact, risk and necrosis) were studied following the intravenous flocalin administration at a dose of 2.2 mg/kg [26]. Analysis of results has provided an opportunity to designate some possible cardioprotective mechanisms, running due to opening of K_{ATP} channels in sarcolemma and mitochondrial membranes. Flocalin produced a remarkable antioxidant effect by the inhibition of lipid peroxidation, causing a reduction of the amount of hydrogen peroxide and superoxide anion (O_2^-) by inhibition of its triggers such as xanthine oxidase, lipooxigenase, cyclooxygenase 2 (there was a decrease in uric acid, leukotriene C_4 (LTC_4), thromboxane B_2 (TxB_2) levels). At low doses uric acid is a potential water soluble antioxidant; at high doses it is toxic [26]. Eicosanoids LTC_4, TxB_2 take part in a numerous processes, including the regulation of water and sodium secretion by kidneys, influence a formation of thrombi, inflammation and proliferation. As a result, mentioned above effects of flocalin probably result in the changes of a functional state of kidneys.

Among the various effects of flocalin there is a reduction of non-enzymatic lipid peroxidation products (conjugated dienes, malonic dialdehyde). It was shown in the experiment that production of the pathogenic oxidized metabolites of the arachidonic acid was decreased not only due to suppression of its lipoxygenase and cyclooxygenase metabolic pathways, but also as a result of depletion of its endogenous pools within the risk and necrotic zones of ischemic heart. Suggestion was made, than reduction of the free arachidonic acid levels following the activation of K_{ATP}-channels occurs due to blockage of L-type calcium channels of the cytoplasmic membrane [27]. An ability of flocalin to inhibit the high-threshold calcium channels was justified experimentally [28]. An increase in intracellular concentration of calcium channels plays an important role in pathogenesis of nephropathies as hemodynamic and proliferative effects of most cytokines, including angiotensin II, are mediated by this cation [29]. Direct inhibition of inward calcium flow by flocalin more effectively, comparing to other K_{ATP}-channels activators, inhibits pathological processes caused by high level of calcium ions in injured nephrocytes. It should be mentioned a position of pharmacological blockers of slow calcium channels of L-type in a clinical nephroprotection is practically defined [30-32].

Following flocalin administration there was a significant reduction of the purine nucleotides degradation products levels in myocardium of animals with ischemia/reperfusion injury: ATP and guanosine triphosphate (GTP) – xanthine, hypoxanthine and inosine. At the same time flocalin intensified heme degradation, as evidenced by an increase of bilirubin production by the hemoxygenase pathway in the myocardium [33, 34]. It is known that products of the hemoxygenase reaction such as bilirubin and carbon oxide possess a considerable neuro- and cardioprotective activity. An inhibition of ATP (apoptosis pathway) and GTP degradation (necrosis pathway) in cardiomyocytes and, on the contrary, stimulation of the hemoxygenase reaction markedly potentiate a protective spectrum of flocalin. Another important effect is the prevention of activation of the inducible nitric oxide synthase in blood plasma along with the activation of endothelial nitric oxide synthase and reduction of L-arginine degradation by arginase, which provides the preservation of sub-

strate for a constitutive synthesis of nitric oxide (NO). It stimulates the vasodilatory reaction of blood vessels and prevents thrombogenic reactions [33, 34]. Similarly, the NO system defect is one of the risk factors of chronic kidney disease progression, which justifies the pathogenetic approaches to prophylaxis and treatment of kidney pathology with the correctors of vasoregulatory function of endothelium by means of balanced influence on the interrelations between vasoconstrictory and vasodilatory mechanisms of endothelium, particularly through NO production [35, 36].

One more protective mechanism is a membrane stabilizing effect of flocalin on mitochondria, which increases the resistance of organelles to Ca^{2+}-inductor of mitochondrial pore (MP). Mitochondria are among the main sources of reactive oxygen species and play an important role in maintenance of cellular energy balance [37]. Overload of the mitochondrial matrix with calcium ions leads to opening of MP – a principal regulator of their function and swelling of organelles. In experiments with calcium-induced swelling of mitochondria it was shown that activation of calcium-selective permeability of inner mitochondrial membrane leads to dose-dependent inhibition of MP opening in heart, indicating the anti-ischemic, anti-apoptotic effects of flocalin as well as its efficacy against mitochondrial dysfunction [38].

Ultrastructure of nephron is characterized by the highest mitochondrial concentration in the cells of proximal and distal convoluted tubules of the cortical layer of kidney as well as in the ascending part of the loop of Henle in the outer layer of medulla. In case of kidney mitochondrial dysfunction the active processes in these nephron structures are affected firstly: active reabsorption of glucose, amino acids, inorganic phosphates in the proximal tubules; concentration of plasma ultrafiltrate, its conversion into urine within loop of Henle and distal convoluted tubules [39]. Thus, correction of the mitochondrial functional state by flocalin provides an energy support of the main kidney processes in case of kidney injury.

The effectiveness of K_{ATP}-channels activation in anthracycline antibiotics-induced cardiomyopathy were evidenced by the conclusions about the appropriateness of amlodipine and dimeodipine (representatives of calcium channel blockers) and guanidine derivative PF-5 (flocalin) use. Potassium current activator PF-5 at a dose of 1.5 mg/kg, in contrast to dihydropyridine-type blockers of calcium current, contributed to decrease of the white rats mortality rate during 14 days after the formation of doxorubicin-induced cardiomyopathy [40]. Antibiotics of the rubomycin group, included in the protocols of anticancer therapy, exert not only a cardiotoxic effect. Doxorubicin causes kidney injury, induced by oxidative stress, what is confirmed by the increased levels of protein carbonyl groups and malonic dialdehyde, and decreased concentration of reduced glutathione in rats' kidneys [41]. From the practical position, correction of the antioxidant status by flocalin resulted in an improvement of the functional state of kidneys and, consequently, increased the survival rate of animals.

Taking into consideration the common mechanisms of the pathological processes, which develop simultaneously to cardio-renal continuum in the cerebrovascular system [42, 43], data concerning the cerebroprotective effects of flocalin are quite valuable. It was estimated, that administration of flocalin (5 mg/kg, intraperitoneally, for 5 days) to rats with acute disorder of cerebral circulation resulted in a normalization of indices of the bioenergetics processes in brain. Thus, there was an amelioration of the adenylyl nucleotides imbalance through the increasing of ATP, adenosine diphosphate (ADP) and creatinine phosphate levels, as well as a restoration of the brain energetic potential. Moreover, under the influence of flocalin there was a reduction of metabolic lactate acidosis signs, demonstrated by the decrease of lactate acid level and an increase of pyruvate level in the ischemic cerebral hemisphere. By the extent of a normalizing influence on the biochemi-

cal processes in ischemic brain flocalin didn't concede the effect of a neuroprotector mexidol [44]. It was also established, that in cats with experimental cerebral embolism flocalin (1 mg/kg, intravenously) caused an increase of cerebral blood flow rate, exceeding the effect of cerebroprotector cavinton by 2.5 times. What is more, flocalin stimulatory influence on a cerebral blood circulation lasted longer than action of cavinton [44].

Research results concerning the influence of flocalin on the urinary system, specifically its detrusor-selective spasmolytic properties and its myorelaxant influence on the smooth muscles of ureter, illustrate the substantial interest of scientists to drug's effects. Obtained in vitro data give an experimental rationale for the usefulness of flocalin administration for the correction of urinary bladder hyperactivity, pharmacotherapy of renal colic caused by nephrolithiasis as well as during the uretropyeloscopy [45-48]. Furthermore, wide spectrum of the pharmacological activity indicates the considerable potential of this K_{ATP}-channels opener as a kidney protecting agent. As a result of stimulation of the sarcolemma K_{ATP}-channels of smooth muscles cells and endothelial cells flocalin produces a significant spasmolytic and vasodilatory effect. In this way blood circulation is regulated and improved, validating the prospects of flocalin use for the correction of renal endothelial dysfunction with the predominant activity of vasoconstrictory factors, arterial hypertension and imbalance of angiogenesis. Under the influence of flocalin a decline in increased blood pressure is accompanied with the maintenance and even a slight increase of the heart pumping function [49]. Therefore, there is a less possibility of renal hypoxia following the failure of circulatory system. At the same time maintenance of systemic arterial pressure in normotensive experimental animals preclude the possibility of hypotensive hypoperfusion, disturbances of glomerular processes and progression of kidney dysfunction. In any case, activation of K_{ATP}-channels promotes a pharmacological preconditioning, providing a compensatory functioning and reducing injury of cells under the conditions of oxygen deprivation.

An absence of organ-specific influence of hypoxia due to the common pathogenetic pathways provides the realization of the flocalin multiple mechanisms of metabolic defense of kidneys during the development of energy deficiency. Therefore, an ability of flocalin to open mitochondrial potassium channels of heart and liver cells in various functional states deserves particular attention [50]. Activation of the potassium-selective penetration of the inner membrane of mitochondria, which play a significant role in a maintenance of cellular energetic balance and also represent the main source of generation of the reactive oxygen species, enables a prevention of oxidative stress and protection of rich in mitochondria nephrocytes. Identification of flocalin as a pharmacological opener of mitochondrial K_{ATP}-channels confirms its role as a cytoprotector with anti-ischemic and anti-apoptotic effect.

It must be pointed out that flocalin meets the most of requirements for medications. It produces fast effect, while an optimal range of therapeutic doses allows the modification of effect in a dose-dependent manner with a possibility to stabilize dose depending on clinical reaction. Its low toxicity limits a risk of side and adverse effects development during a monotherapy with flocalin or its combination with other drugs. An absence of nephrotoxic effects is a highly important characteristic of flocalin and enables its use for the cytoprotection in conditions of kidney dysfunction. Thus, the above-stated convincing experimental data about the potent cardioprotective properties as well as evidence of its protective effect on brain similar to commonly accepted cerebroprotectors encouraged us to study the influence of flocalin on kidney processes and function.

Analysis conducted under the conditions of water-salt physiological loading has shown that following intragastric administration of flocalin at a dose of 5 and 10 mg/kg the indices of the functional state of kidneys of white non-linear

rats have the same tendency of changing, mostly without dose-dependent effects. Use of higher doses than to study cardiovascular effects is caused by administration of starch substance into stomach, which affects pharmacokinetics on absorption stage, as well as by method for the kidney function determination 2.5 hours after flocalin administration. A single activation of K_{ATP}-channels on the background of 5% water loading resulted in an increase of sodium and creatinine excretion and reduction of potassium excretion. Stability of a proximal and distal transport of sodium ions evidenced a balance of tubular processes. The increase of sodium and decrease of potassium excretion excluded the activation of renin-angiotensin-aldosterone system (RAAS) [51]. A 7-day administration of flocalin resulted in an increase of glomerular filtration rate (GFR) and creatinine excretion, maintenance of glomerular-tubular balance [52].

Apparently, more significant vasodilatory effect of flocalin at a dose 10 mg/kg has caused a decrease in GFR after a single administration in conditions of 3% salt loading induced by 0.45% NaCl solution. It was accompanied by a decrease of proximal sodium transport by 4.4%. Stability of diuresis and decrease of natriuresis served as reactions directed on the preservation of the water compartments of the organism and characterize flocalin as an agent maintaining a homeostatic kidney function in conditions of a salt loading. On the 7th day of flocalin administration at a dose of 5 mg/kg on a background of salt loading an increase of diuresis and creatinine excretion was observed, confirming the conclusion about more pronounced effects of the lower experimental doses of flocalin. Otherwise, an increased ammonium coefficient after flocalin administration at a dose of 10 mg/kg indicated on a potential efficacy of flocalin administration at a higher dose for the correction of metabolic acidosis [53, 54].

It should be mentioned that stimulated by water-salt loading diuresis reflects a natural influx of osmotic active ions and water into the body, inducing the activation of general and highly sensitive renal neurohumoral regulatory reactions directed on the maintenance of water-salt homeostasis. It allows a rapid investigation of the nephrotropic properties of studied drugs, determination of their mechanism of action, estimation of regulatory potential and functional reserve of kidneys against a background hyperhydration of the organism. Under the influence of flocalin the changes of the functional state of kidneys had an adaptive character, providing a homeostatic function of nephron as well as water-salt balance, mostly in the use at a lower dose, justifying the selection of a dose of 5 mg/kg for the following investigation of nephroprotective effects.

Therefore, common mechanisms of development and progression of cardiovascular pathology, including cerebrovascular disorders, and kidney pathology determine the relevance of study the renal effects of flocalin – a prospective medicine with a wide spectrum of protective properties. A prerequisite for a study of its renal effects is, at the first place, its ability to correct functional, morphological and biochemical state of myocardium under the pathological conditions. From the standpoint of cardiorenal syndrome pathogenesis, the various mechanisms of vascular tone and heart work regulation simultaneously define a wide range of extrarenal effects of flocalin, which have the great potential to serve as a background for a new direction in nephroprotection.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co authors of the article.

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НЕФРОПРОТЕКТОРНІ ВЛАСТИВОСТІ АКТИВАТОРА АТФ-ЗАЛЕЖНИХ КАЛІЄВИХ КАНАЛІВ ФЛОКАЛІНУ

Система АТФ-залежних калієвих ($K_{АТФ}$) каналів є важливішим ендогенним механізмом захисту організму при ішемії та гіпоксії, що зумовлює інтерес до пошуку та

вивчення фармакологічних активаторів калієвого струму. В огляді представлені узагальнені дані наукової літератури, які засвідчують широкий фармакодинамічний спектр флокаліну – потенційного представника класу активаторів $К_{АТФ}$-каналів із властивостями кардіопротектора, міоспазмолітика, вазодилататора, церебропротектора. Наведені результати власних досліджень, які вказують на здатність флокаліну підтримувати гомеостатичні функції нирок за умов водно-сольових навантажень організму. Беручи до уваги кардіоренальний континуум, патогенетичний взаємозв'язок ниркової та серцевої патології, можливим є припущення про пригнічувальні впливи флокаліну на розвиток нефропатій. Передумовою для дослідження ренальних ефектів є відомості щодо механізмів корекції флокаліном морфофункціональних та біохімічних змін міокарда за умов патології, які дають змогу позиціонувати новий активатор $К_{АТФ}$-каналів як перспективний кардіопротектор і значною мірою можуть слугувати підгрунтям нового напряму нефропротекції.

Ключові слова: активатор АТФ-залежних калієвих каналів флокалін; фармакодинаміка; кардіопротекція; нефропротекція.

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НЕФРОПРОТЕКТОРНЫЕ СВОЙСТВА АКТИВАТОРА АТФ-ЗАВИСИМЫХ КАЛИЕВЫХ КАНАЛОВ ФЛОКАЛИНА

Система АТФ-зависимых калиевых ($К_{АТФ}$) каналов является важнейшим эндогенным механизмом защиты организма при ишемии и гипоксии, что обуславливает интерес к поиску и изучению фармакологических активаторов калиевого тока. В обзоре представлены обобщенные данные научной литературы, свидетельствующие о широком фармакодинамическом спектре флокалина – потенциального представителя класса активаторов $К_{АТФ}$-каналов со свойствами кардиопротектора, миоспазмолитика, вазодилататора, церебропротектора. Наведены результаты собственных исследований, указывающие на способность флокалина поддерживать гомеостатические функции почек в условиях водно-солевых нагрузок организма. Принимая во внимание кардиоренальный континуум, патогенетическую взаимосвязь почечной и сердечной патологии, можно предположить угнетающее влияние флокалина на развитие нефропатий. Поводом для исследования почечных эффектов являются сведения про механизмы коррекции флокалином морфо-функциональных и биохимических патологических изменений миокарда, которые позволяют позиционировать флокалин как перспективный кардиопротектор и в значительной степени могут служить основой нового направления нефропротекции.

Ключевые слова: активатор АТФ-зависимых калиевых каналов флокалин; фармакодинамика; кардиопротекция; нефропротекция.

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