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Organ-protective effects of the alternative renin-angiotensin system and prospects for therapeutic treatment. Review

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The article is devoted to review the data regarding the identification of biochemical and functional features of the components of the renin-angiotensin system using the tools of bibliometric analysis of scientific literature. A modern interpretation by the dividing of the multifunctional complex into two systems, namely the classical renin-angiotensin system and alternative renin-angiotensin system, in accordance with the definition of biological effects, is given. The enzymatic cascade involved in the production and metabolism of peptides in both classical and non-classical pathways of renin-angiotensin systems is shown from the point of view of the evolution of scientific concepts. The triggering role of components of the classical renin-angiotensin system in pathophysiological processes with transformation into cardiovascular diseases and metabolic dysfunction has been proven. The history of the creation of pharmacological drugs for the correction of the classic renin-angiotensin system is presented. In view of the achievement of recent years, the revision of the alternative renin-angiotensin system is emphasized due to the discovery of the counter-regulatory action of the angiotensin-converting enzyme 2, angiotensin-(1—7), the Mas receptor in relation to their correction of metabolic processes, regulation of blood pressure, and the presence of anti-fibrotic, anti-inflammatory and antioxidant properties. The positive effect of the components of the non-classical renin-angiotensin system on the protection of the cardiovascular system and kidney is presented based on the results of experimental studies on animals. Pharmacokinetic and pharmacodynamics characteristics of recombinant angiotensin-converting enzyme 2 in experiments on healthy volunteers are highlighted. The potential protective effects of angiotensin-converting enzyme 2 and angiotensin-(1—7) concerning cardiometabolic risk are presented. The available data indicate the need for further comprehensive scientific investigations of the components of alternative renin-angiotensin system to create a new class of pharmacological agents with their implementation in medical practice.

Keywords:
renin-angiotensin system, angiotensin-(1—7), angiotensin-converting enzyme 2, Mas receptor.

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It has been more than a century since the discovery of the first component of the complex pathway of the renin-angiotensin system (RAS). Scientists and practitioners continue to carefully evaluate this multifunctional mechanism and its involvement in physiological and pathophysiological processes. The classical concept of the RAS was formed and gradually supplemented with knowledge about enzymes, peptides, and receptors, which participate in maintaining the body's homeostasis and play a triggering role in the development of pathological conditions. These studies correspond to the current trend in pharmacotherapy, focusing on the development of targeted agents with inhibitory properties. These drugs have significantly contributed to therapeutic strategies and are considered a major advancement in treating arterial hypertension, heart failure, and diabetic nephropathy. Studying the RAS has progressed to the discovery of its new components. Beyond the border of classical RAS, the concept of

non-classical RAS has been formed, encompassing molecules such as angiotensin-converting enzyme 2 (ACE 2), angiotensin-(1—7), and Mas receptor. Alternative RAS is known to counteract certain components of classical RAS. Experimental studies have demonstrated the beneficial effects of ACE 2 and angiotensin-(1—7) on pathological disorders associated with the RAS when using specific agonists and antagonists of angiotensin peptides. This review aims to examine the historical progression of research in several areas of the RAS and propose future options for clinical implementation.

Biological effects of the renin-angiotensin system

Classical RAS. In modern terms, the classical RAS axis includes the following components: angiotensinogen, renin, angiotensin I, angiotensin-converting enzyme (ACE), angiotensin II, as well as angiotensin type 1 (AT1R) and type 2 (AT2R) receptors. Angiotensin II is the main player in the RAS. It exerts its negative effects via AT1R by increasing the tension of the sympathetic nervous system, exerting renal sodium reabsorption and potassium excretion, causing vasoconstriction, increasing blood pressure, and promoting inflammation and oxidative stress. Angiotensin II contributes to endothelial dysfunction and atherogenesis, as it regulates the expression of adhesion molecules. The proliferative properties of angiotensin II lead to mesangial hypertrophy and contribute to the development and progression of chronic kidney disease.

AT2R are considered the functional antagonists of AT1R and generally induce the opposite effects, including vasodilation, natriuresis, cellular differentiation, growth inhibition, and improving insulin resistance. AT2R serve as a potential therapeutic target for protecting against hypertension, metabolic dysfunction, and organ remodeling [23].

Non-classical RAS. In 1968, scientists H. Y. Yang et al. discovered a new enzymatic mechanism for the inactivation of different peptides found in pig and human urine. This discovery subsequently led to the identification of a previously unknown RAS pathway [44]. The end product of enzymatic hydrolysis of the H-terminal angiotensin heptapeptide was named angiotensin-(1—7). Later on, this was determined to be an ACE-independent pathway for the formation of angiotensin-(1—7) [21]. Angiotensin-(1—7) is an endogenous ligand for the G protein-coupled Mas receptor [32]. The discovery of the human ACE homologue in 2000, which was found to be a carboxypeptidase insensitive to captopril upon cloning and functional expression, might be regarded as an outstanding achievement. Consequently, it was called ACE 2 [38]. ACE 2 plays a crucial role in converting angiotensin I to angiotensin-(1—9) and angiotensin II to angiotensin-(1—7), making it the primary mediator of this biological process [8,39]. The investigation uncovered the essential role of alternative RAS in regulating blood pressure and mediating cardiometabolic consequences, considering the reception and expression of these peptides in different tissues and cells.

The hypotensive effect of the components of the non-classical renin-angiotensin axis has been proven in experimental animal studies. Thus, chronic administration of angiotensin-(1—7) into the lateral ventricles of the brain reduced blood pressure in genetically hypertensive rats [12]. Angiotensin-(1—7) interacting with the Mas receptor is considered to promote vasodilation by increasing the release of nitric oxide via Akt-dependent pathways and post-translational regulation of nitric oxide synthase [35]. An investigation of the mRNA of the Mas receptor revealed an imbalance between nitric oxide and reactive oxygen species production in the endothelium of mice. Therefore, an overexpression of ACE 2 in blood vessels was observed in genetically modified hypertensive rats, resulting in a reduction in blood pressure and improvement of endothelial function [2]. Angiotensin-(1—7) effects include dilatation of microcirculation induced by nitric oxide release and increased telomerase activity of the endothelial cells [9]. The authors came to the conclusion about the significant contribution of non-classical RAS to the regulation of vascular tone and blood pressure control.

ACE and ACE 2 play opposite roles in the metabolism of peptides belonging to the angiotensin family. The alternative renin-angiotensin axis acts as a physiological antagonist to the classical components of the RAS by counterbalancing the effects of angiotensin II. A high level of ACE 2 is transformed into an increased amount of angiotensin-(1—7) and angiotensin-(1—9), forming protective phenotypes for cardiovascular diseases, including hypertension. At the same time, a decreased level of ACE 2 results in the activation of the classical branch of the RAS and the progression of cardiovascular pathology. Angiotensin-(1—7) as an antagonist of angiotensin II enhances the beneficial effects of the RAS due to vasodilation, blunting of inflammation, improvement of endothelial function, and contribution to antifibrotic pathways [33].

The cardioprotective properties of ACE 2 and angiotensin-(1—7) include the prevention of fibrosis, suppression of myocyte growth and pathological hypertrophy, and inhibition of myocardial remodeling in patients with hypertensive heart and post-infarction conditions caused by angiotensin II activity [3, 18, 37]. The experimental studies have conclusively shown that the non-classical

components of the RAS have antifibrotic activities that effectively guard against the development of myocardial dysfunction and heart failure [27, 41].

The alternative axis of the RAS is involved in the correction of metabolic disorders. The obtained data shows the positive impact of the angiotensin-(1—7)/Mas receptor system on glucose metabolism. Chronic infusion of angiotensin-(1—7) improves insulin resistance and hypertension caused by a high-fructose diet in rats [47]. In an *in vivo* experiment, it was established that angiotensin-(1—7) increases glucose uptake by skeletal muscles and improves insulin sensitivity in rats [10]. The metabolic effects of the renin-angiotensin alternative axis are also involved in the pathogenesis of diabetic nephropathy, exerting a confirmed protective effect by experimental studies. ACE 2 knockout in mice with streptozotocin-induced diabetes demonstrated accelerated glomerulosclerosis, tubular damage, interstitial fibrosis, podocyte apoptosis, and elevated serum creatinine [25]. In contrast, podocyte-specific overexpression of ACE 2 in streptozotocin-induced diabetic mice resulted in reduced levels of mesangial expansion and hypertrophy of glomeruli, confirming the attenuation of diabetic nephropathy [31].

The protective features of the compounds of non-classical RAS in patients with cardiac disease, diabetic nephropathy, and severe viral infections can be attributed to the anti-inflammatory and antioxidant capabilities of ACE 2 and angiotensin-(1—7) [30]. ACE 2 participates in the ACE/angiotensin II/AT1R signaling cascade and counteracts the damaging effects of this system, making it a potential marker of cardiac and renal pathology [5].

Pharmacological correction of the classical renin-angiotensin system

Scientific evidence suggests that traditional RAS has a dominant role in the pathogenesis of arterial hypertension. Therefore, the researcher's efforts were focused towards the creation of pharmacological agents that primarily function by inhibiting the adverse effects of the components of this system (Fig. 1). [13].

The starting point was the observation that the bite of the Brazilian snake, Bothrops jararaka, led to a robust decrease in blood pressure [11]. The research conducted by H. Y. Yan et al. revealed that a component found in snake venom, identified as dipeptidyl carboxypeptidase, was discovered to be ACE. This molecule is responsible for converting angiotensin I and deactivating bradykinin [45]. The first ACE inhibitor, captopril, was created in 1977 and received clinical approval in 1980 [6]. Also, in 1980, a new class of ACE inhibitors, known as carboxyl dipeptide enalapril, was developed [26]. Currently, there is a huge number of ACE inhibitors with different pharmacokinetic and pharmacodynamic characteristics that have specific clinical effects and indications. AT1R antagonists became the next class of antihypertensive drugs based on the RAS blockage. The first representative of this pharmacological class, losartan, was advocated for clinical use in 1994. Nowadays, RAS blockers are routinely prescribed as a basic medication to manage hypertension, myocardial infarction, heart failure, and renal complications of diabetes at all stages of cardiovascular disease.

Scientific studies have investigated the antihypertensive, cardioprotective, and renoprotective effects resulting from the direct stimulation of the AT2R. Compound 21 (C21) was introduced in 2004 as the first nonpeptide highly selective AT2R agonist due to its proven *in vivo* actions, which include anti-inflammatory, anti-fibrotic, and anti-apoptotic properties [14] (see Fig. 1).

Chronic AT2R stimulation resulted in a decrease in blood pressure in an experimental hypertension induced by angiotensin II [16]. The findings of this study encourage to evaluate acute and chronic AT2R activation in the control of sodium excretion and blood pressure, with or without concomitant AT1R blockade. C21 increases plasma and adipose levels of adiponectin and improves insulin signaling in the liver. Chronic C21 infusion has positive metabolic effects in female diabetic db/db mice, alleviating type 2 diabetes complications through

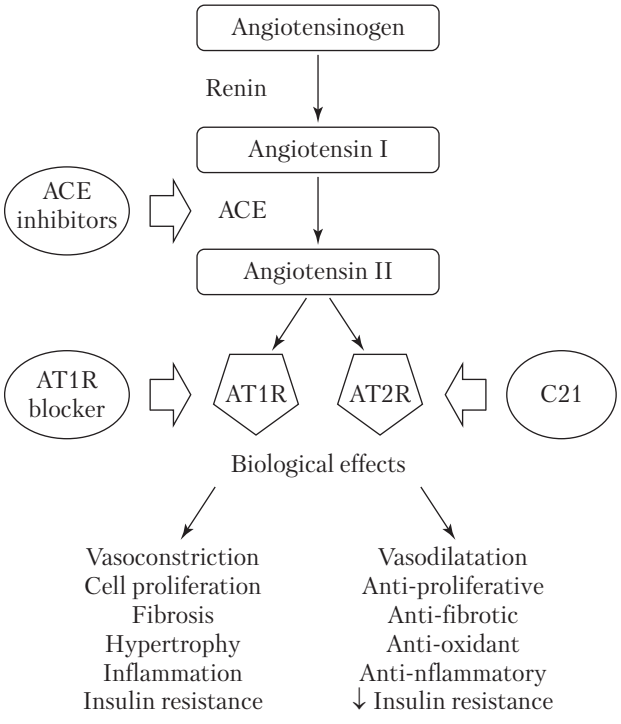
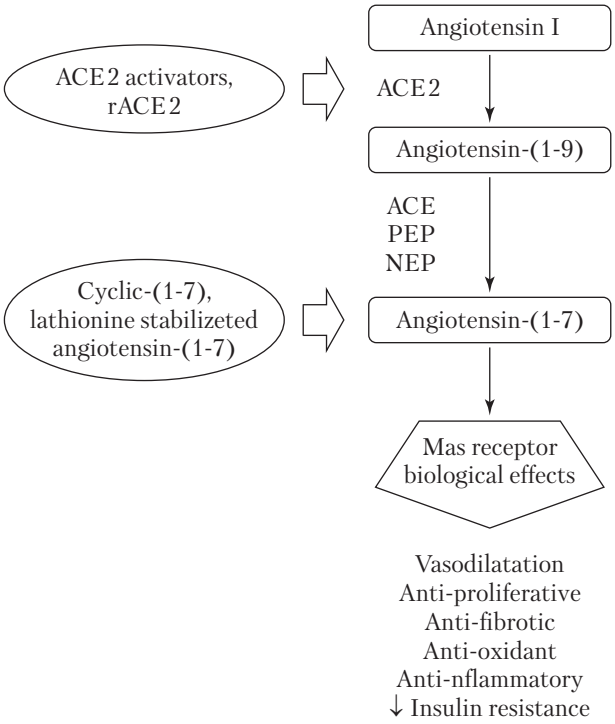


Figure 1. Antagonists and agonist of the classical renin-angiotensin system

a mechanism that involves NO production [7]. The antagonists of the classical RAS are widely recognized and understood. Currently, ACE inhibitors and AT1R blockers are the cornerstone of cardiovascular therapy, while drugs that activate AT2R are less well known. However, C21 could potentially serve as a therapeutic choice for diabetes prevention and may be a promising option for the treatment of hypertension in humans.

Therapeutic perspectives of the renin-angiotensin alternative axis

The results of experimental and clinical observations related to the RAS have formed a convincing basis for the implementation of theoretical knowledge into a practical approach. The strategy of forming a balance between two branches of RAS appeared, which was based on the verification of the specified effects in animals with simulated pathological conditions. For example, it was established that AT1R blockage restores angiotensin-(1—7)-induced dilation of coronary vessels in rats with hypertrophied heart [36]. The results of experimental studies showed that non-classical components of the RAS can lower blood pressure in animals with simulated arterial hypertension. Based on these findings, the group of authors made an assumption regarding the structure-based identification of small-molecule ACE 2 activators as a potential antihypertensive agent (Fig. 2).



PEP — prolyl endopeptidase;
NEP — neutral endopeptidase neprilysin

Figure 2. The activators of the renin-angiotensin alternative axis

The researchers, H. J. A. Prada et al., determined the study's goals were to identify substances that increase the activity of ACE 2 and analyze whether these compounds would affect the pathophysiological mechanism underlying hypertension [29]. The authors performed *in vitro* assays of two chemicals, xanthenone and resorcinolnaphthalein, which, in a dose-dependent manner, improved the activity of ACE 2. Xanthenon was administered *in vivo* to Wistar-Kyoto rats and spontaneously hypertensive rats. After acute administration of xanthenone, a robust decrease in blood pressure was observed in both studied groups, while chronic infusion resulted in a mild hypotensive effect only in spontaneously hypertensive rats. At the same time, recovery of heart function and reversal of myocardial, perivascular and renal fibrosis were observed in spontaneously hypertensive rats. The authors concluded that structure-based screening may help identify compounds that activate ACE 2, lower blood pressure, and reverse tissue remodeling. The use of ACE 2 activators represents a valid strategy for antihypertensive therapy. A similar study was later conducted involving two components, XNT (1- [(2-dimethylamino) ethylamino]-4-(hydroxymethyl)-7- [(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one) and diminazene (DIZE), in order to determine their mechanisms of action as possible activators of ACE 2 [14]. Ex vivo and *in vitro* animal studies have shown that the mechanisms of action of XNT and DIZE are ACE-independent and these substances are not ACE 2 activators. Despite the significance of ACE 2 activators as a therapeutic target, the scientists came to the opinion that direct administration of ACE 2 might be more successful.

Some studies have been devoted to the formation of a new class of drugs that specifically target the alternate axis of the RAS. The first publications on this topic were related to the experimental studies that highlighted the use of recombinant ACE 2 (rACE 2) in animal models of acute and long-term cardiometabolic diseases. J. Wysocki et al. (2010) conducted an acute experiment on mice to investigate the effects of angiotensin II administration followed by rACE 2 solution infusion [43]. They found that the subsequent infusion of rACE 2 solution led to a dose-dependent increase in serum ACE 2 activity and a decrease in systolic blood pressure and angiotensin II level. These findings suggest that rACE 2 has the ability to degrade angiotensin II and prevent hypertension. Similar results were presented in a study by J. Zhong et al. (2011), who presented the ability of rACE 2 to reverse angiotensin II-induced hypertension as well as reduce oxidative stress and tubulointerstitial fibrosis in mice with an ACE 2 knockout [43]. The

use of rACE 2 soluble infusion was shown to have a positive cardioprotective effect with suppression of myocardial hypertrophy, fibrosis and heart dysfunction according to other researchers [1, 20]. In a mouse model exhibiting systolic dysfunction, the administration of an angiotensin-(1—7) antagonist, called A779, has been demonstrated to hinder the favorable therapeutic impact of rACE 2 [28].

The prolonged activation of angiotensin II leads to oxidative stress, inflammation, and fibrosis, which are significant factors in the development of complications of diabetes, namely, the formation of diabetic nephropathy. The ability of ACE 2 to simultaneously destroy angiotensin II and produce angiotensin-(1—7), leading to a shift in the balance of RAS from angiotensin II to angiotensin-(1—7), as confirmed in animal experiments, suggests that modulating the activity and/or expression of components of the alternative pathway of the RAS is a promising therapeutic strategy for managing diabetic nephropathy. A study conducted in 2006 involved the administration of a specific ACE 2 inhibitor (MLN-4760) either alone or in combination with the AT1R blocker telmisartan to mice of the db/db line for a duration of 16 weeks [46]. Upon concluding the experiment, it was determined that pharmacological inhibition of ACE 2 with MLN-4760 in diabetic mice resulted in an increased deposition of fibronectin and collagen in the glomeruli and tubulointerstitial zone, as well as the expansion of the mesangial matrix. The addition of telmisartan to treatment prevented the increase in renal albumin excretion brought on by the pharmacological inhibition of ACE 2. The study's authors concluded that ACE 2 can regulate the amount of glomerular angiotensin II by breaking it down. This finding suggests that targeting ACE 2 could be a potential therapeutic approach to reduce albuminuria and glomerular damage [46]. In an experiment on a diabetes model, rACE 2 was administered to Akita mice for 4 weeks [19]. The results showed a notable decrease in renal fibrosis, glomerular hypertrophy, and a reduction in the thickness of the glomerular basement membrane. Adeno*virus*-mediated overexpression of ACE-2 in streptozotocin-induced diabetic rats was found to significantly decrease transforming growth factor (TGF-β_1) and collagen IV levels, along with robust reductions in albuminuria, oxidative stress, and glomerular damage [19]. These renoprotective effects of ACE 2 overexpression were similar to those observed during treatment with ACE inhibitor benazepril. During the experiment, mice of the db/db line received daily injections of either 0.5 mg/kg of angiotensin-(1—7) or saline for 28 days. It was determined that the long-term administration of angiotensin-(1—7) inhibited the production of reactive oxygen species, suppressed inflammation in prerenal adipose tissue, renal fibrosis, and lipotoxicity, which are the markers of diabetic nephropathy [22]. P. Cassis et al. investigated the effectiveness of angiotensin-(1—7) in db/db mouse models with diabetic nephropathy [4]. The study was planned in a comparative format. Animals in the first group received cyclic angiotensin-(1—7), whereas those in the second group received an ACE inhibitor, lisinopril. Treatment was started in the 10th week of the animals' lives and was completed in the 19th or 20th week. Cyclic angiotensin-(1—7) therapy was found to reduce albuminuria and podocyte dysfunction, similar to the effects of lisinopril, which also reduced glomerular fibrosis and inflammation. Moreover, it was established that the addition of cyclic angiotensin-(1—7) to ACE inhibitor therapy had a positive add-on effect in experimental diabetic nephropathy. Lanthionine-stabilized angiotensin-(1—7), which is resistant to ACE and other peptidases, was employed in an experimental investigation on mice with type I diabetes (streptozotocin-induced model) or type II diabetes (db/db model) [17]. It has been proven that lanthionine-stabilized angiotensin-(1—7) consistently raises insulin levels while lowering glucose and glycated hemoglobin levels in the blood of test animals. Thus, the medications that enhance the catalytic activity of ACE 2 and specifically target the tubular and glomerular structures of the kidneys provide new possibilities for treating diabetic nephropathy. Hence, it is imperative to develop pharmaceuticals that possess stimulatory properties on ACE 2 for practical application in clinical settings [24].

Encouraging findings regarding the effects of rACE 2 in animal models justified the transfer of these studies to humans. Since the components of non-classical branch of the RAS are aimed at correcting the pathogenetic mechanisms of arterial hypertension and heart failure, the protective properties of angiotensin-(1—7) and ACE 2 create a perspective for the development of a new therapeutic approach for the treatment of cardiovascular pathology. Recombinant human ACE 2 (rACE 2) was proposed as a new RAS peptidase for treating heart failure [25]. 2013 publication reports the findings of a randomized, double-blind, placebo-controlled study on the pharmacokinetics, pharmacodynamics, and tolerability of rACE 2 in healthy individuals [15].

The drug was administered intravenously in a single dose (100—1,200 mcg/kg). ACE 2 activity was assessed by measuring the enzyme levels in plasma by the ELISA method, while concentrations of angiotensin II, angiotensin-(1—5) and angiotensin-(1—7) were analyzed in serum using liquid chromatography-mass spectrometry. 30 minutes after the administration of a single dose of rACE 2,

the level of angiotensin II decreased, the level of angiotensin-(1—7) increased, decreased, or remained unchanged, and the level of angiotensin-(1—5) increased. The authors conclude that rACE 2, with a half-life of 10 hours, is well tolerated in healthy individuals, leading to a reduction in angiotensin II levels within 24 hours after intravenous injection [15].

Arterial hypertension is an actual problem in cardiology that results in structural remodeling of the heart, ultimately leading to a decline in myocardial function and heart failure. One of the additional methods of correction of arterial hypertension and heart failure is a non-pharmacological strategy with the use of physical exercises. This can lower blood pressure, slow down clinical manifestations of myocardial dysfunction, and even improve cognitive function. At the same time, it is important to note that physical activity enhances the vasoprotective and cardioprotective effects of the components of the alternative RAS, specifically ACE 2/angiotensin-(1—7) pathway [42].

Investigations demonstrated that physical exercises alter the level of the RAS compounds in experimental animals with hypertension and heart failure. U. Tyrankiewicz et al. studied the impact of physical activity and pharmacological ACE inhibition on the ACE/ACE 2 balance in transgenic, homozygous female Tgαq*44 mice with induced heart failure [40]. The experimental animals were randomly assigned to two groups: an exercise training group and a group with a sedentary lifestyle. Each group was further divided into a control group and a group that received the ACE inhibitor perindopril at a dose of 10 mg/kg daily in their drinking water. After two months of follow-up, the results showed a beneficial effect of the combination of physical activity with pharmacological inhibition of ACE on the ACE/ACE 2 balance. Additionally, there was a significant increase in the angiotensin-(1—7)/angiotensin II ratio, a crucial indicator for evaluating therapeutic outcomes in heart failure.

A similar study was conducted on a rat model with diabetes in order to determine the effect of physical activity on the balance of the RAS and inflammation in the kidneys [34]. Wistar rats were randomly divided into 4 groups: non-trained, trained, non-trained with diabetes and trained with diabetes. Blood glucose, albuminuria and urinary volume were determined. Renal levels of angiotensin peptides (angiotensin-(1—7)), angiotensin I and II), inflammatory markers, as well as the activities of ACE and ACE 2 were assessed. In diabetic rats physical exercise reduced the levels of albuminuria, angiotensin I, and angiotensin II. Also, in this group of rats there was a shift in the balance of renal RAS towards ACE 2/angiotensin-(1—7) axis, along with a reduction in the elevated levels of pro-inflammatory cytokine (interleukin-1β) in the context of diabetes. Physical exercises enhance kidney function by altering intrarenal RAS towards non-classical components, decreasing pro-inflammatory cytokine levels, and can be considered a convincing strategy for the prevention of renal complications induced by diabetes.

Conclusions

Starting with the discovery of the first components of RAS, scientific achievements contribute to the identification of this system as one of the leading regulators of the functional state of organs and systems in the human body. Scientific studies demonstrate the beneficial effects of the components of alternative RAS, as they prevent the injuring effects of angiotensin II stimulating AT1R. Many experiments have shown that ACE 2 and angiotensin-(1—7) have organ-protective properties, exhibiting antifibrotic, anti-inflammatory, and antioxidant effects. This served as justification for the implementation of a new approach to the treatment of cardiovascular pathology and metabolic disorders. Evidence has shown the effectiveness of exogenous substances that boost the catalytic activity of ACE 2 in treating diabetic nephropathy. Therefore, we can assume that further in-depth research on the RAS multifunctional complex should be focused on the creation of pharmaceuticals with clinical translational potential.

Conflicts of interest: none.

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Органозахисна роль альтернативної ренін-ангіотензинової системи та перспективи терапевтичного лікування. Огляд

Наведено дані щодо ідентифікації біохімічних і функціональних особливостей компонентів ренін-ангіотензинової системи. Проведено бібліометричний аналіз бази наукових періодичних видань. Згідно із сучасною інтерпретацією в мультифункціональному комплексі виділено дві складові на підставі біологічних ефектів — класичну ренін-ангіотензинову систему й альтернативну ренін-ангіотензинову систему. Висвітлено ферментативний каскад, який бере участь у продукції та метаболізмі пептидів як у класичних, так і в некласичних шляхах ренін-ангіотензинової системи, згідно із сучасними уявленнями. Доведено тригерну роль компонентів класичної ренін-ангіотензинової системи в патофізіологічних процесах із трансформацією в серцево-судинні захворювання та метаболічну дисфункцію. Наведено історію створення фармакологічних препаратів для корекції класичної ренін-ангіотензинової системи. Завдяки відкриттю контррегуляторної дії ангіотензин-перетворювального ферменту-2, ангіотензину-(1—7), Mas-рецептора щодо корекції метаболічних процесів, регуляції артеріального тиску, наявності антифіброзних протизапальних і антиоксидантних властивостей виявлено альтернативну ренін-ангіотензинову систему. Позитивний вплив компонентів некласичної ренін-ангіотензинової системи на серцево-судинну систему, що полягає в її захисті, та нирок виявлено за результатами експериментальних досліджень на моделях з використанням тварин. Висвітлено фармакокінетичні та фармакодинамічні характеристики рекомбінатного ангіотензин-перетворювального ферменту-2, які визначено при дослідженнях на здорових добровольцях. Наведено потенційні протекторні ефекти ангіотензин-перетворювального ферменту-2 і ангіотензину-(1—7) щодо кардіометаболічного ризику. Наявні дані свідчать про необхідність проведення комплексних досліджень компонентів альтернативної ренін-ангіотензинової системи з метою створення нового класу фармакологічних засобів для впровадження їх в лікувальну практику.

Ключові слова: ренін-ангіотензинова система, ангіотензин-(1—7), ангіотензин-перетворювальний фермент 2, Mas-рецептор.

ДЛЯ ЦИТУВАННЯ

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