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Renin-angiotensin and kallikrein-kinin systems in diabetic renal damage

Renin-angiotenzin sistem i kalikrein-kinin sistem u dijabetesnom bubrežnom oštećenju

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Introduction

Erdös [1] recognized that biologically active peptides generated by the renin-angiotensin and kallikrein-kinin systems, e.g., angiotensin II, bradykinin, and kallidin (Lys-bradykinin), are so rapidly metabolized and inactivated that their transient effects would never be useful medications, but the role of these peptides in certain physiological or pathological conditions could be determined by agents that directly block their effects or inhibit either their enzymatic degradation or production. This concept enabled investigators to discover captopril and later other angiotensin I converting enzyme (ACE) inhibitors and turn them into clinically useful drugs for treatment of hypertension and related cardiovascular diseases. The aim of this presentation is to assess a role of the renin angiotensin system (RAS) and the kallikrein kinin system (KKS) in a diabetic renal damage.

Renin-angiotensin and kallikrein-kinin systems

With the finding that ACE is identical to kininase II, an enzyme that inactivates bradykinin by removing the C-terminal Phe_8–Arg_9 dipeptide, it has become clear that ACE is involved both in the RAS and KKS [2–4]. The dual action of ACE converts both the inactive decapeptide Ang I to the hypertensive octapeptide Ang II, and inactivates potent hypotensive kinins, bradykinin and kallidin, into inactive metabolites (Figure 1).

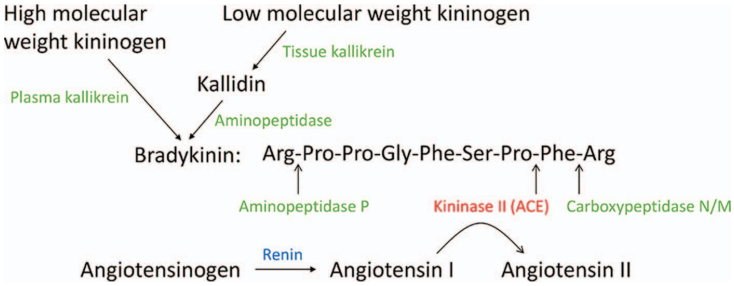

Fig. 1 – Peptides and peptidases of the kallikrein kinin system (KKS) and a portion of the renin angiotensin system (RAS). The enzymes in the KKS are shown in green, while renin is shown in blue; angiotensin converting enzyme (ACE), which acts in both systems, is shown in red.
Credit *Journal of Biological Chemistry* [4].

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The RAS is a complex system, including about twenty peptides and peptidases, and six receptors [5, 6]. This system operates at systemic and cellular levels, and it is an important volume regulator in vertebrates. Ang II is a potent vasoconstrictor that contributes to regulation of blood pressure, fluid volume, electrolytic balance, and inflammation. Its bioavailability depends on activity of two enzymes: renin, which is produced by the renal juxtaglomerular cells and acts on angiotensinogen to form Ang I and the ACE. Once formed, the inactive Ang I is converted to the active Ang II by ACE. The released Ang II then activates two types of Ang II receptors, AT1 and AT2. The AT1 receptors induce vasoconstriction, including the renal arteries, while AT2 receptors may oppose this effect. In addition to the beneficial effects of decreased blood pressure, the AT2 receptors are involved in nitric oxide and cyclic guanosine monophosphate (cGMP) production, inhibition of apoptosis, and anti-proliferative action which is beneficial in reducing tissue damage.

ACE is unevenly distributed in the vascular tissue [7]. The lungs have the highest and the kidneys have the lowest amount compared to other organs, including the heart. Individuals with genetically high ACE levels have the higher risk for renal and cardiac damage; this is especially true for diabetic subjects, due to a greater inactivation of bradykinin than Ang II production by this enzyme [8].

All components of the KKS exist only in mammals; thus the system evolved quite late during evolution [9]. Humans have more tissue kallikrein, which mostly originates from the kidney, than the circulatory enzyme; in rodents, kallikrein originates primarily from the salivary glands.

Two kallikrein enzymes differ in the molecular weight, amino acid sequence and immunogenicity [4]. Plasma kallikrein, also known as Fletcher factor, releases the nonapeptide bradykinin (Arg1-Pro2-Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9), while tissue kallikrein (K1) releases Lys-bradykinin (kallidin). Kallidin can be converted to bradykinin by aminopeptidase (Figure 1). Kallikrein produces kinins by cleaving a high molecular weight (110 kDa) kininogen substrate (HMWK, also known as Fitzgerald factor or factor XII) as well as the low molecular weight (LMWK, 50–68 kDa) kininogen substrate. Both types of kininogen substrates (high and low molecular weight) are synthesized in the liver and are present in high concentrations in plasma.

Kinins act through two types of receptors, B1 and B2. The activation of B2 receptors increase vasodilation, vascular permeability and sweating. The B2 receptors also increase intracellular calcium in the smooth muscle and endothelial cells and activate signaling cascades (e.g., the phospholipase A2). The B1 receptors are normally expressed only at low levels, but the tissue injury, inflammation, ischemia, chronic hyperglycemia, or endotoxin can induce their synthesis. They are also stimulated by ACE inhibitor therapy [10]. Kinins release nitric oxide, prostacyclin and tissue plasmin activator (t-PA) from the endothelial cells. These peptides are protectors against oxidative stress and organ damage in the heart and kidney. Their increase by the ACE inhibitors and vasopeptidase inhibitors is beneficial both in cardiovascular diseases and nephropathy. Icatibant is a specific antagonist of B2 receptors that is used to treat acute attacks of hereditary angioedema. The half-life of kinins in the circulation is short, less than 15 seconds [11]. However, because of their potent effects on various systems, they may be important for end-organ protection, particularly in the kidney. Locally generated kinins could thus help to prevent diabetic renal damage, known as diabetic nephropathy (DN).

Diabetic nephropathy

DN is a major cause of the end-stage renal disease. It affects approximately one-third of individuals with diabetes mellitus and is associated with the great morbidity and mortality [12]. Chronic hyperglycemia causes hypertrophy of glomeruli, thickening of renal basement membranes, microalbuminuria, glomerulosclerosis, tubular and interstitial fibrosis and the reduction in glomerular filtration [13]. It takes about ten years of this diabetic condition for development of albuminuria. Hyperglycemia and hypertension accelerate the progression to end-stage renal disease. DN may cause nephrotic syndrome, especially in the elderly patients. As of now, there is no cure for DN available, but it is possible to slow its progress. The established DN treatment includes strict glycemic control, blood pressure control and RAS blockade.

In diabetes, endothelial ACE increases and local generation of Ang II rises, but at the same time, the kinin levels decreases more rapidly. The diabetic patients with the genetically increased ACE levels have a higher risk for nephropathy and cardiovascular damage, including neuropathy and retinopathy. The initial observations suggested that the genetically higher ACE levels slightly increase the risk for development of myocardial infarction, but in the diabetic patients the risk is much greater [14]. Many studies [15–20] indicate that the genetically increased ACE production in diabetes, of both type 1 and type 2, poses a risk for nephropathy.

ACE inhibitors and AT1 receptor blockers (ARBs) are used therapeutically to block the RAS to decrease morbidity and mortality in the patients with chronic heart failure. The use of these drugs delays progression of vascular lesions, controls hypertension, diabetic nephropathy, and nondiabetic chronic renal disease [21]. Correcting the imbalance between the RAS and the KKS with ACE inhibitors restores cardiovascular homeostasis and helps to reduce the damage by various cardiovascular diseases [22]. Many clinical studies using ACE inhibitors and ARBs separately, or in the combination, explored the role of the RAS in diabetic nephropathy. The RAS is thought to promote nephropathy mainly by releasing Ang II to act systemically and at the cellular level. The effects include: constriction of arteriolar smooth muscle, increased vascular pressure, inflammation, enhanced cell growth, migration and apoptosis.

Various ACE inhibitors and ARBs are used successfully in clinical practice. In some conditions ARBs are superior to ACE. For example, ARBs are more effective in diabetic proteinuria than ACE inhibitors, as it was shown in the Diabetes Exposed to Telmisartan and Enalapril (DETAIL) study. Combined blockade of the RAS by the ACE inhibitor

and ARBs is more beneficial in reducing proteinuria, blood pressure and vascular morbidity and mortality [22]. Many studies of the RAS blockade in diabetic nephropathy have shown a significant improvement, although none completely blocked the harmful peptides. From the available information provided by these clinical studies, it is clear that ACE inhibitors and/or ARBs remain the first line among pharmacological treatments in diabetic nephropathy.

Future therapeutic development

Due to their dual action, ACE inhibitors obstruct both Ang II release and bradykinin inactivation, producing a beneficial effect on diabetic nephropathy independent of their effects on the blood pressure and Ang II levels. The KKS is clearly involved in the pathophysiology of this disease. In fact, an increased ACE activity has a greater effect on the kinin levels than on the Ang II levels. Many studies were done to determine which kinin receptors are involved in the renal protection. The studies with the mice lacking either the B1 or B2 receptor, or both [23], coupled with the observations in the human patients revealed the important role of B1 receptors [14]. In addition, a selective blockade of the B2 receptors resulted in the increased B1 receptor activation by kinins. Thus, it would seem that the kinin B1 receptor agonists might provide an additional armament against diabetic nephropathy and end-organ damage in other tissues. By reducing the inactivation of kinins, ACE inhibitors could further enhance the therapeutic effects.

Peptide analogs of kinins resistant to the actions of peptidases already have been synthesized [14, 24, 25] but they are still used primarily in research and applied only intravenously, or through osmotic mini-pumps. Among the future difficult endeavors, there should be a goal to discover the convenient B1 receptor agonist that could be ideally given orally.

Another approach would be to induce kallikrein production by the genetic modification of stem cells, or progenitor cells with a kallikrein gene designed to enhance their viability and proliferative, migratory and functional properties. Thus, it could be a novel therapeutic target in the treatment of a wide range of cardiovascular, cerebrovascular and renal disorders [26]. If successful, gene editing would be an important treatment for the type 1 diabetes elimination.

Note

I devote this article to Ervin G. Erdös (96), my teacher and good friend. We have collaborated in research for several decades [4]. He visited the former Yugoslavia several times where he presented seminars (Sarajevo, Tuzla, Sombor, and Belgrade) and stimulated local scientists to study metabolism and activity of vasoactive peptides.

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R E F E R E N C E S

1. *Erdös EG.* Hypotensive peptides: bradykinin, kallidin, and eledoisin. In: *Garattini S, Shore PA,* editors. Advances in Pharmacology. New York: Academic Press; 1966; 4: 1–90.
2. *Yang HY, Erdös EG, Levin Y.* A dipeptidyl carboxypeptidase that converts angiotensin I and inactivates bradykinin. Biochim Biophys Acta 1970; 214(2): 374–6.
3. *Igić R, Sorrells K, Nakajima T, Erdös EG.* Identity of kininase II with an angiotensin I converting enzyme. In: *Back N,Sicuteri F,* editors. Vasopeptides. New York: Plenum Press; 1972. p. 149–53.
4. *Igić R.* An exploration of bioactive peptides: My collaboration with Ervin G. Erdös. J Biol Chem 2018; 293(21): 7907–15.
5. *Škrbić R, Igić R.* Seven decades of angiotensin (1939-2009). Peptides 2009; 30(10): 1945–50.
6. *Ferrão FM, Lara LS, Lowe J.* Renin-angiotensin system in the kidney: What is new? World J Nephrol 2014; 3(3): 64–76.
7. *Metzger R, Franke FE, Bohle RM, Alhenc-Gelas F, Danilov SM.* Heterogeneous distribution of angiotensin I-converting enzyme (CD143) in the human and rat vascular systems: vessel, organ and species specificity. Microvasc Res 2011; 81(2): 206–15.
8. *Alexiou T, Boon WM, Denton DA, Nicolantonio RD, Walker LL, McKinley MJ,* et al. Angiotensinogen and angiotensin-converting enzyme gene copy number and angiotensin and bradykinin peptide levels in mice. J Hypertens 2005; 23(5): 945–54.
9. *Seki T, Miwa I, Nakajima T, Erdös EG.* Plasma kallikrein-kinin system in nonmammalian blood: evolutionary aspects. Am J Physiol 1973; 224(6): 1425–30.
10. *Ignjatovic T, Tan F, Brovkovych V, Skidgel RA, Erdös EG.* Novel mode of action of angiotensin I converting enzyme inhibitors: direct activation of bradykinin B1 receptor. J Biol Chem 2002; 277(19): 16847–52.
11. *Igić R.* Four decades of ocular renin-angiotensin and kallikrein-kinin systems (1977-2017). Exp Eye Res 2018; 166: 74–83.
12. *Chan GC, Tang SC.* Diabetic nephropathy: landmark clinical trials and tribulations. Nephrol Dial Transplant 2016; 31(3): 359–68.
13. *Chawla T, Sharma D, Singh A.* Role of the renin angiotensin system in diabetic nephropathy. World J Diabetes 2010; 1(5): 141–5.
14. *Alhenc-Gelas F, Bouby N, Girolami JP.* Kallikrein/K1, Kinins, and ACE/Kininase II in Homeostasis and in Disease Insight From Human and Experimental Genetic Studies, Therapeutic Implication. Front Med (Lausanne) 2019; 6: 136.
15. *Sayed-Tabatabaei FA, Oostra BA, Isaacs A, van Duijn CM, Witteman JC.* ACE polymorphisms. Circ Res 2006; 98(9): 1123–33.
16. *Doria A, Warram JH, Krolewski AS.* Genetic predisposition to diabetic nephropathy. Evidence for a role of the angiotensin I--converting enzyme gene. Diabetes 1994; 43(5): 690–5.
17. *Marre M, Jeunemaitre X, Gallois Y, Rodier M, Chatellier G, Sert C,* et al. Contribution of genetic polymorphism in the renin-angiotensin system to the development of renal complications in insulin-dependent diabetes: Genetique de la Nephropathie Diabetique (GENEDIAB) study group. J Clin Invest 1997; 99(7): 1585–95.

18. *Parving HH, Jacobsen P, Tarnow L, Rossing P, Lecerf L, Poirier O,* et al. Effect of deletion polymorphism of angiotensin converting enzyme gene on progression of diabetic nephropathy during inhibition of angiotensin converting enzyme: observational follow up study. BMJ 1996; 313(7057): 591–4.
19. *Boright AP, Paterson AD, Mirea L, Bull SB, Monjoodi A, Scherer SW,* et al. Genetic variation at the ACE gene is associated with persistent microalbuminuria and severe nephropathy in type 1 diabetes: the DCCT/EDIC Genetics Study. Diabetes 2005; 54(4): 1238–44.
20. *Costacou T, Chang Y, Ferrell RE, Orchard TJ.* Identifying genetic susceptibilities to diabetes-related complications among individuals at low risk of complications: An application of tree-structured survival analysis. Am J Epidemiol 2006; 164(9): 862–72.
21. *Azizi M, Ménard J.* Combined blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists. Circulation 2004; 109(21): 2492–9.
22. *Regoli D, Gobeil F Jr.* Critical insights into the beneficial and protective actions of the kallikrein-kinin system. Vascul Pharmacol 2015; 64: 1–10.
23. *Tomita H, Sanford RB, Smithies O, Kakoki M.* The kallikrein-kinin system in diabetic nephropathy. Kidney Int 2012; 81(8): 733–44.
24. *Bélanger S, Bovenzi V, Côté J, Neugebauer W, Amblard M, Martinez J,* et al. Structure-activity relationships of novel peptide agonistsof the human bradykinin B2 receptor. Peptides 2009; 30(4): 777–87.
25. *Côté J, Savard M, Bovenzi V, Bélanger S, Morin J, Neugebauer W,* et al. Novel kinin B1 receptor agonists with improved pharmacological profiles. Peptides 2009; 30(4): 788–95.
26. *Devetzi M, Goulielmaki M, Khoury N, Spandidos DA, Sotiropoulou G, Christodoulou I,* et al. Genetically- modified stem cells in treatment of human diseases: Tissue kallikrein KLK1)- based targeted therapy (Review). Int J Mol Med 2018; 41(3): 1177–86.

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