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Review Article

Renal Bradykinin (BK) System as Potential Drug Target for Salt-Sensitive Hypertension

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Abstract

The kallikrein-kinin system (KKS) has been known as a paracrine and/or autocrine hormonal system that is responsible for regulating arterial blood pressure (BP), kidney function, and electrolyte excretion. This system plays a vital role in cardiovascular and renal hemodynamics. Bioactive peptide kinins are generated from kininogens after cleavage by kallikrein and bind to two types of receptors, B1 and B2. Kinins are able to cause various biological functions such as vasodilatation, smooth muscle contraction, and regulation of blood pressure. There are varieties of antihypertensive drugs that offer a good control of hypertension. All people are believed to be salt sensitive, so it is recommended to restrict salt intake. There is a significant relation between dietary sodium and level of BP. Renal KKS plays an important role in excreting excess sodium. Thus, the dysfunction of this system leads to the development of hypertension as a result of sodium accumulation. The action of renal KKS could be beneficial for treating hypertension, so the development of a compound that has renal kallikrein-like activity may help in excreting excessive sodium from the body. Moreover, ebelactone B and poststatin can lead to excessive natriuresis and diuresis effects through prolonging the life of kinins in collecting ducts (CD) after high salt intake. Low renal synthesis and urinary excretion of tissue kallikrein have been associated with hypertension in animals and humans. However, potassium ions and ATP-sensitive potassium channel blocker accelerate the release of renal kallikrein. In summary, selective renal kininase inhibitors and renal kallikrein release accelerators are both novel types of antihypertensive agents that could treat salt-sensitive hypertension. Lately, the tissue kallikrein gene delivery may indicate as a future therapy for hypertension, as well as cardiovascular and renal abnormalities.

Keywords: *Bradykinin; Salt-Sensitive Hypertension; Kallikrein-Kinin System*

The discovery of kallikrein-kinin system

In Germany, 1926, Frey and his colleagues discovered a substance, which was a pancreatic extract that caused a fall in BP in anesthetized normotensive dogs [1]. They called it kallikrein, which is a Greek word for the pancreas. In 1948, Werle and Berek concluded that the pharmacologically active substance kallidin (KD) was produced from inactive precursor protein present in plasma by kallikrein, which is a proteolytic action of the enzyme [2]. In 1949, Rocha E Silva and his colleagues, in Brazil, found that incubating dog plasma with snake venoms or the enzyme trypsin, produces a new substance that causes slow contraction of the guinea pig ileum. They named this substance bradykinin (BK), which means slow movement in Greek [3].

Introduction

Hypertension is a condition in which there is persistently raised BP. It is known as the silent killer. Approximately, 50 million people have hypertension in the United States and one billion people worldwide [4]. Hypertension is a common risk factor for the development of cardiovascular and renal diseases. Complications of hypertension account for 9.4 million deaths worldwide every year. According to World Health Organization (WHO), the prevalence of raised blood pressure in the Americas in 2014 was 18% [5], whereas in the Kuwaiti population, the prevalence of hypertension and diabetes is around 15%, which leads to a high rate of mortality and morbidity related

to cardiac diseases [6]. BK is a pharmacologically active polypeptide that may enhance cardiovascular and renal functions. It is a potent vasodilator, which causes hypotension, natriuresis, diuresis, reduction in total peripheral resistance, an increase in renal blood flow as well as a release of nitric oxide (NO) and prostaglandin (PG) [7,8]. BK is considered to be a pro-inflammatory and/or cardioprotective. BK is also an inflammatory mediator because it can cause pain, cell proliferation, tissue edema, as well as the contraction of various smooth muscles. The effects of kinins are mediated by the activation of two G-protein-coupled receptors (GPCRs): B1 and B2 receptors, which are mainly expressed in tissue injury and inflammation. B2 is also present in various cell types and involved in physiological actions. B1 receptor displays high affinity and selectively sensitivity to des-Arg9-BK and des-Arg9-KD. B2 receptor, however, is activated by BK and Lys-BK. The activation of the B1 receptor may stimulate smooth muscle, elevated collagen synthesis, and cell proliferation. On the other hand, B2 receptor induces the release of NO and PG, increases vascular permeability, induces the release of pro-inflammatory and hyperalgesic mediators, as well as anti- hypertrophic and anti- ischemic properties [8,9].

The major components of this system are kininogen, kallikreins, kininases, and BK. The KKS is an endogenous cascade that has an important role in inflammation, pain, and coagulation. This system has unique activities in controlling BP, in addition to its cardioprotective effect. The deficiency of this system may lead to cardiac dysfunction because all the components of the KKS are present in cardiac muscle [10]. Furthermore, the dysfunction of KKS could result in sodium retention, arterial vasoconstriction, raised peripheral resistance and vascular or plasma volume, as well as, increased BP [7]. The decrease in production of BK in the blood stream can cause hypertension. It has been observed that the urinary kallikrein excretion is reduced in clinical and experimental hypertension [11]. Moreover, kallikrein excretion in the urine is an indicator of the activity of KKS in the renal system [17].

It has been found that higher levels of prekallikrein are considered a risk factor for hypertension and nephropathy in patients with clinical type 1 diabetes [12]. Furthermore, left ventricular hypertrophy (LVH) is an independent risk factor for hypertension. The clinical evidence has demonstrated that BK could counter the development of LVH in spontaneously hypertensive rats (SHR). The treatment with B2 receptor antagonist and NO synthetase inhibitor can abolish the antihypertrophic effect of BK. Hence, the BK has an important role in preventing the development of LVH by the release of NO. The deficiency in the cardiac KKS may account for the induction of LVH in SHR and SHR with diabetes [13]. The clinical studies have demonstrated the importance of tissue kallikrein system in providing the protection against hypertension, vascular remodeling, and renal fibrosis. Development of novel therapeutic approaches in order to support the kinin activity in the vascular wall and in the kidney, could be an effective strategy for the treatment of hypertension and its complications, for example, cardiac hypertrophy and renal failure [14].

The beneficial effects of tissue kallikrein gene delivery make it an excellent candidate for treating hypertension, cardiovascular and renal abnormalities. Tissue kallikrein gene delivery plays an important role in improving cardiac reserve and attenuating remodeling after myocardial infarction [15]. Tissue kallikrein can induce a cardioprotective effect by directly acting on B2 receptor without kinin formation [16]. This project is intended to review the renal BK system as a potential drug target for salt-sensitive hypertension.

Bradykinin forming components

The kinin family includes BK, KD, and methionyl lysyl-BK, which are biologically active peptides. These peptides are derived from kininogens by the action of serine proteases called kallikreins. Kinin has a short half-life, which is less than 15 seconds. It is rapidly inactivated by kininases. The effects of kinins are mediated by the activation of two GPCRs: B1 and B2 receptors. The stimulation of these receptors will lead to the activation of second messenger systems, such as arachidonic acid (AA) products, cyclic GMP, calcium, and cyclic AMP [9].

Kininogens

Kininogens are multifunctional proteins that are synthesized in the liver and circulate in the plasma and other body fluids. Kininogen is the precursor of the BK that plays a role in releasing kinin. The two forms of kininogens are high molecular weight kininogen (HMWK) and low molecular weight kininogen (LMWK). These two forms differ in molecular size, physiological functions, and sensitivity to tissue. The

main substrate for plasma kallikrein is HMWK; however, the suitable substrate for tissue kallikrein is LMWK. The HMWK is also named as a "Fitzgerald factor" [17].

Kallikreins

Kallikreins are serine proteases that are responsible for cleaving kininogen to form BK. There are two major types of kallikreins: plasma kallikrein and tissue kallikrein. The plasma and tissue (renal) kallikrein work independently in the human body. They are found in the glandular cell, neutrophils, and biological fluids. Tissue kallikreins differ from plasma kallikreins in the physicochemical, functional, and immunological properties [8,10]. Plasma kallikrein-forming system involves HMWK, Hageman factor or factor XII, factor XI, and plasma prekallikrein. The prekallikrein, which is also called Fletcher factor, is a single chain glycoprotein that is synthesized in the liver and circulated in an inactive state. The activation of Hageman factor to factor XIIa occurs by plasma kallikrein through a positive feedback reaction. The inactive prekallikrein is converted into active kallikrein by activated Hageman factor and HMWK. Active plasma kallikrein acts on HMWK to release active BK, as illustrated in figure 1 [8].

Tissue kallikrein is widely distributed in many organs, such as the kidneys, pancreas, salivary glands, prostate glands, synovial tissue, and intestine. Inactive tissue kallikreins are detected in the kidneys and pancreas, however, active tissue kallikreins are present in submandibular tissue [18].

Bradykinin

Bradykinin is a nonapeptide, which consists of nine amino acids: Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg [17]. It is found in all body secretions, for example in urine, saliva, and sweat. Additionally, it is present in several tissues, such as the heart, vasculature, blood, kidney, colon, and liver. It is a vasoactive peptide produced by plasma kallikrein and can also be produced from kallidin by several aminopeptidases through cleavage of the amino terminal lysine [8]. BK is formed during an inflammatory response from HMWK or LMWK, via serine proteases called kallikrein. The Hageman factor, prekallikrein, and HMWK are involved in BK formation. Plasma prekallikrein forms a complex with HMWK and Hageman factor; these complex binds to negatively charged surfaces. When they are exposed to tissue damage, prolylcarboxypeptidase (PRCP) rapidly converts prekallikrein to plasma kallikrein. Plasma kallikrein converts HMWK to BK. On the other hand, tissue kallikrein converts LMWK to lysyl-BK (kallidin), which is a decapeptide found in the heart, urine, and circulation that is rapidly converted to BK by aminopeptidase N [8], as illustrated in figure 1 [8].

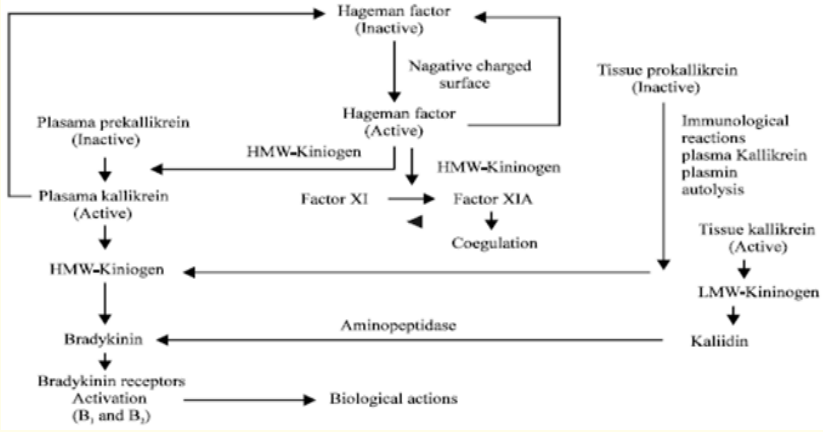

Figure 1: *The mechanism of bradykinin formation. Taken from (Sharma JN and Al-Sherif GJ, 2006).*

Bradykinin metabolizing enzymes

Kininases are enzymes responsible for inactivation of kinins, which are rapidly cleaved to inactive peptides. They are found in the plasma, urine, tissues, endothelial cells and the body fluids [3,8]. These enzymes cleave BK at either their amino- or carboxyterminal end.

Enzymes that cleave at the amino terminal are aminopeptidase M (APM), which is responsible for degrading KD into BK, and aminopeptidase P (APP), which cleaves the first amino acid of BK to give BK-(2-9). On the other hand, angiotensin-converting enzyme (ACE), carboxypeptidase N and M (CPN, CPM), and neutral endopeptidase (NEP) are the four main enzymes responsible for carboxyterminal degradation of BK. There are two main groups of kininases, which are kininase I and kininase II. The kininase I include CPN and CPM, which cleave the carboxyterminal arginine from either BK or KD to give des-Arg9-BK or des-Arg10-KD. The kininase II includes ACE and NEP, which cleave the dipeptide Phe8-Arg9 from both BK and KD to give BK-(1-7) and KD-(1-8), and ACE further cleaves these to give BK-(1-5) and KD-(1-6) [8]. The function of these enzymes is to monitor the needed BK in the body [3].

Mechanism of Bradykinin Action

Bradykinin may lead to activation of several second-messenger systems through interaction with its specific receptors. The stimulation of BK receptor initiates the second-messenger pathway, like the activation of calcium-sensitive systems and AA products. BK receptors are GPCRs that are coupled to phospholipase C (PLC) through Gαq. PLC accumulates inositol 1,4,5-triphosphate (IP3), which regulates cellular Ca^{2+} flux and induces the release of Ca^{2+} [19]. Moreover, these receptors mediate AA release via cytosolic phospholipase A2 (PLA2) in Madin-Darby canine kidney (MDCK-D1 cells) [20].

These receptors stimulate the PLC pathway followed by phosphoinositide hydrolysis and elevation of cytosolic calcium ion levels to induce contractile responses. Additionally, the stimulation of B2 receptor causes the production of cGMP in endothelial cells, which stimulates the release of NO [21].

Bradykinin system and hypertension

The relationship between KKS and hypertension was observed in 1934 by Elliott and Nuzum [22]. The antihypertension mechanism of kallikrein is unclear. It has been suggested that kallikrein could induce the changes in local blood flow due to the release of BK and PG. They found that there is less kallikrein excreted in the urine in patients with essential hypertension compared with normotensive people. The factors that result in a defect in the kinin-generation are reduced activity of renal kallikrein, increased levels of kallikrein inhibitor, decreased production of HMWK and/or LMWK, and high concentrations of kininases [17]. The deficiency of KKS may contribute to the genesis of hypertension [23]. The tissue kallikrein excretion is influenced by the sodium intake [23]. In 1962, DahI and his colleagues administered L-3, 5, 3' -triiodothyronine along with 7.3 % NaCl resulted in developed two strains from Sprague-Dawley (SD) rats, which are known as DahI salt-sensitive (DSS) hypertensive and DahI salt-resistant (DSR) normotensive rats. It has been observed that urinary kallikrein activity is reduced in DSS hypertensive rats compared with the DSR normotensive rats due to alteration in KKS [24].

Mechanism of salt-induced hypertension

The lack of universal consensus on the definition of salt sensitivity makes it difficult to assess the salt sensitivity of blood pressure. Change in BP by at least 5-10% in response to a change in intake of NaCl has been defined as salt sensitivity [25]. Excessive salt intake may reduce the production of NO [26]. In addition, high salt intake activates angiotensin II signaling in blood vessels, kidney, and brain [27] and contributes to resistance to antihypertensive therapy [28].

The reduced activity of tissue kallikrein in hypertensive patients could be due to decreased synthesis or/and increased levels of kallikrein inhibitor [17]. In 1971, Margolius measured urinary kallikrein in controls and people with essential hypertension using an esterolytic assay. It was observed that urinary kallikrein was lower in the essential hypertension group compared with the control population, which suggests an essential role for the KKS in developing hypertension [30]. Some studies indicate that reduced circulating kinin could activate the vasoconstrictor action of angiotension II, as well as potentiate the development of hypertension [31]. Alteration in the KKS has provided further evidence regarding the mechanism of various hypertensive conditions. Kininogen levels and a kinin-potentiating factor are reduced in essential and malignant hypertension [29]. It has been concluded that not only tissue kallikrein is reduced in essential hypertension, but also plasma kininogen [32].

The role of KKS in the regulation of renal physiology and the pathogenesis of hypertension remain unclear. There are studies that evaluate urinary kallikrein levels in large populations of patients with hypertension and their families. It has been shown that whites excrete more kallikrein than blacks. Also, the white patients with hypertension excrete less kallikrein than white normotensive people. When all groups were kept on a low sodium intake, they had higher kallikrein excretion [33]. In 1985, Arbeit and Serra [35] observed reduced urinary kallikrein excretion in DSS rats fed on 0.0064% and 0.4% sodium chloride. It has been shown that elevation in the sodium concentrations in the cerebrospinal fluid (CSF) may lead to sodium retention, which can activate sympathetic nerve cells and increase vasoconstriction and cardiac output or heart rate. In fact, sodium accumulation and water retention are two factors that are mostly associated with the development of hypertension [36]. The effects of chronic excess salt ingestion in both man and animals have been identified. Evidence showed that dietary salt plays an etiologic role in developing essential hypertension in human. However, some individuals remained normotensive despite the fact that they were chronically consuming excess salt. It has been reported that Kininogen-deficient Brown Norway Katholiek (deficient BN-Ka) rats excreted less amount of kinin in their urine compared with normal Brown Norway Kitasato (normal BN-Ki) rats. Intra-arterial infusion of 0.15 M or 0.3 M NaCl for 4 days into normal BN-Ki rats did not increased mean arterial blood pressure (MBP) or accumulated sodium in the serum, erythrocytes, or CSF. However, 0.3 M NaCl infusion into Kininogen-deficient BN-Ka rats significantly elevated MBP with increased sodium levels in these locations. These results indicate that a deficiency in kinin generation leads to sodium accumulation [38]. It has been found that the administration of supplementation of LMWK to deficient BN-Ka rats led to a decrease in the systemic BP with elevated urinary kinin excretion, urinary sodium, and urine volume, while bradykinin B2 receptor antagonist infusion elevated the BP with reduced urinary sodium and urine volume. These results indicate the relationship between the release of kinin, elevated in blood pressure, and sodium excretion [38].

Role of renal Bradykinin in salt induced hypertension

Recently, it has been shown that the renal KKS plays an important role in the kidney because the components of tissue KKS are localized along the distal nephron [39], as illustrated in figure 2 [39].

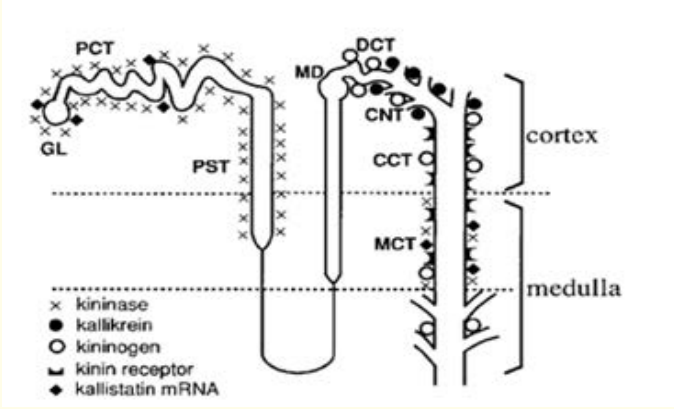

Figure 2: *Localization of the components of renal kallikrein-kinin system along the nephron. GL: glomerulus; PCT: proximal convoluted tubule; PST: proximal straight tubule; MD: macula densa; DCT: distal convoluted tubule; CNT: connecting tubule; CCT: cortical collecting tubules (duct); MCT: medullary collecting tubules (duct).*

When on a normal sodium diet, more than 95% of sodium is reabsorbed in the proximal tubules of the kidney, and the reabsorption from the CD is minimal, which is around 2 - 3% [40]. However, excess sodium can cause reabsorption of sodium along the CD especially in the patients with reduced renal kallikrein secretion. The renal kallikrein is secreted from the distal connecting tubule cells (CNT). The location of the CNT cells that secret renal kallikrein is essential because this location allows the secretion of renal kallikrein to take place in the kidney after the major tubular reabsorption process and before the additional reabsorption of NaCl occurs in the CD [41]. However,

the principal cells of the CD are responsible for secreting LMWK [41,42]. In addition, BK-B2 receptors, tubular-specific kinin-degradation enzymes, and kallistatin, which is a specific inhibitor of tissue kallikrein, are found in the cortical and medullary collecting ducts [46]. Kallikrein-binding protein (KBP) mRNA, which is an analog of human kallistatin, is mainly present in the inner medullary CD with small amounts in the outer medullary CD, the proximal convoluted tubules, and glomeruli. However, the mRNA of KBP is not expressed in the CNT or the cortical CD [43].

The renal KKS plays important role in the development of hypertension in animal models. Renal kallikrein defects may be associated with the development of hypertension, whereas high urinary kallikrein may provide a protective effect against high BP [44]. Clinical studies have an inverse relationship between renal kallikrein levels and elevated BP in essential hypertension [34]. The decreased in urinary kallikrein levels indicate impaired renal function because urinary kallikrein originates in the kidney. Thus, renal KKS dysfunction can cause salt-sensitivity in rats [37].

Renal kallikrein is involved in the homeostasis of sodium and water balance in the kidney because it is synthesized in the connecting tubule cells in the distal nephron. Its reduction is considered as a potential etiological factor in salt-sensitive hypertension [46,47]. Renal kallikrein is considered to be a type of tissue kallikrein that acts on LMWK to release kallidin. Renal kininases immediately hydrolyze renal BK and kallidin into an inactive peptide, as illustrated in figure 3 [45]. Renal kininases rapidly destroy BK generation. They are distributed in the proximal tubules and medullary collecting duct. Almost 81% of the injected kinin is inactivated into the proximal tubules by renal kininases [48]. It has been suggested that plasma kininase II is concentrated in the proximal tubules along the brush border membrane of the cells [49]. This finding indicates that kinins are generated in the plasma and filtered through the glomeruli are destroyed in the proximal tubules before reaching the distal tubules. Thus, renal KKS is completely independent from the plasma KKS.

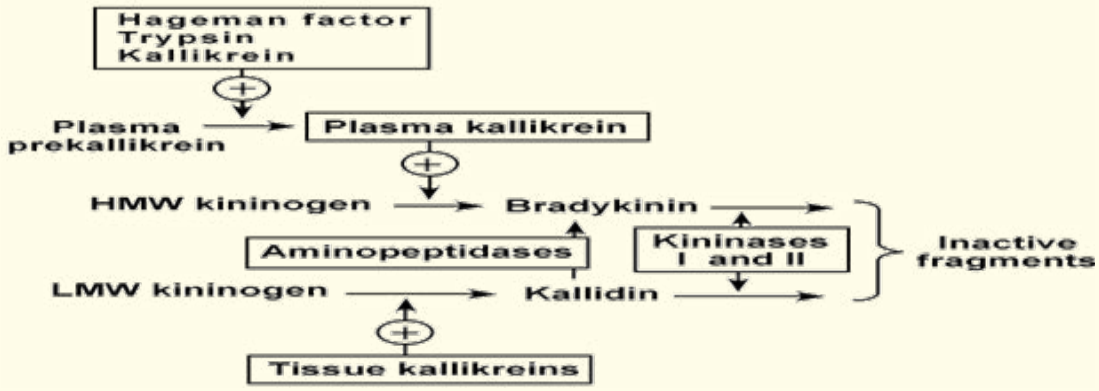

Figure 3: *The Kallikrein-kinn system. Taken from (Sharma JN and Al-Banoon A., 2012).*

The degradation pathways of the BK in the rat urine differs from the renal degradation pathways in rat plasma. It has been found that kininases in the urine are different from those in the plasma because they are not inhibited by angiotensin-converting enzyme inhibitor (ACEI). Carboxypeptidase Y-like exopeptidase (CPY) and NEP are the major kininases in rat urine [50]. However, in rat plasma, the main kininases are kininase I and kininases II, as illustrated in figure 4 [39].

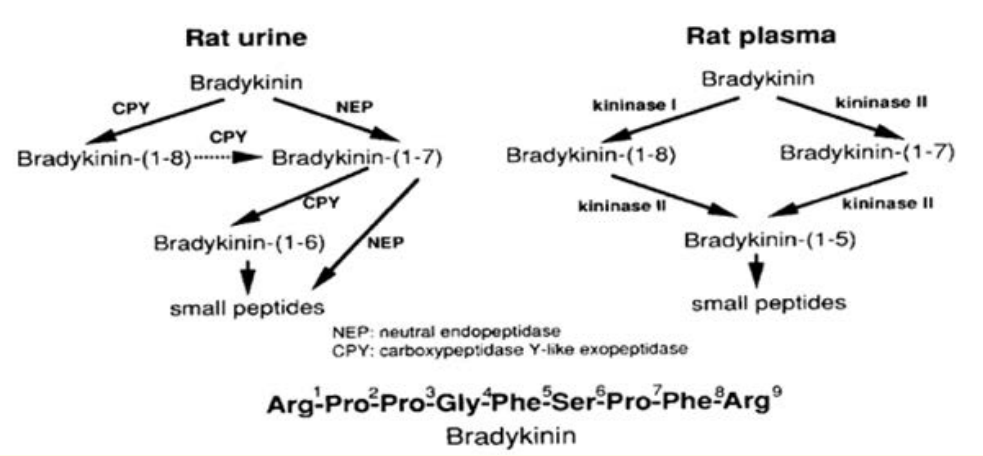

Figure 4: *Pathways of bradykinin degradation by rat urine and rat plasma. Bradykinin-(1-n) indicates bradykinin degradation products with n amino acids from the N terminal.*

The role of exogenous Bradykinin in the kidney

The renal KKS can regulate BP and is possibly involved in hypertension This system has an important role in excreting excess sodium when sodium accumulates in the body [47] and can inhibit the reabsorption of NaCl through the activation of BK-B2 receptors. CPY and NEP are two kidney-specific kinin-inactivating enzymes (kininases) that immediately inactivate the kinins generated in the CD. When the ACEIs are administered, plasma kinin levels are increased from 16.1 ± 1.9 pmol/l to 22.4 ± 2.8 or 29.1- ± 4.7 pmol/l in healthy subjects [51]. In the arterial blood of anesthetized rats, captopril slightly increases the BK level (from 10 ± 3 to 29 ± 7 pg/ml). However, this elevation in BK is not enough to decrease the systemic BP, so an intravenous infusion of 1000 ng/min of BK is required in order to decrease the systemic BP [52]. It has been observed that there is an increase in glomerular filtration rate (GFR) and kallikrein excretion with kallikrein treatment [53]. The administration of exogenous kallikrein results in increased NO/cGMP and cAMP levels and decreased NAD(P)H oxidase activities, superoxide formation, and pro-inflammatory cytokine levels that indicate a novel role of kallikrein-kinin via the kinin B2 receptor in protection against cardiovascular and renal abnormalities as an antioxidant and anti-inflammatory agent [54].

Many clinical studies and reviews have been published on the role of the renal KKS and the effects of the exogenous BK in the kidney. These reviews focused mainly on vasodilatation and the natriuretic and diuretic action of BK in the kidney.

Vasodilatation

The administration of BK or kallidin through intravenous or intra-arterial route caused renal arteriolar dilatation in the normal individuals [56] and in anesthetized dogs [57]. The infusion of BK into the renal medullary interstitium significantly increased renal papillary blood flow without changing cortical blood flow or the BP in anesthetized Munich-Wistar rats. In addition, interstitial infusion of captopril increased renal papillary blood flow without altering cortical blood flow or the BP. These actions of BK and captopril infusion were eliminated by pretreatment with the nitric oxide inhibitor, NG-nitro-L-arginine-methyl ester. It has been concluded that renal medullary interstitial infusion of BK increase sodium and water excretion, which is correlated with the increase in papillary blood flow by a nitric oxide-dependent mechanism [58].

Renal kallikrein is distributed not only in the luminal membranes, but also in the basolateral in foldings in the granular cells of the CNTs of the kidney. Thus, the kinins produced in the inner medullary CD can diffuse into the interstitial space to prompt vasodilation [59].

Natriuresis and Diuresis

Intravenous injection of kinins or into the renal artery can induce diuresis and natriuresis [56]. The natriuretic effect of kinin can be induced by inhibiting the sodium reabsorption in the distal part of nephron or altering absorption in the deep nephron due to change in the blood flow. Whereas, the intra-renal infusion of kinin increased sodium excretion in rats fed a normal-diet through medullary BK-B2 receptors, which is independent to their capacity to change the inner medullary blood flow [39].

The BK inhibits the net absorption of sodium and chloride in the isolated perfused rat cortical CD, without affecting net potassium transport, bicarbonate flux, or the transmembrane potential difference [60].

The mechanisms of renal kallikrein release

Potassium

The potassium and ATP-sensitive potassium channel blockers have a capacity to accelerate the release of renal kallikrein from the CNT cells of the kidney. Therefore, the potassium and ATP-sensitive potassium channel blockers can be considered as reliable agents to control hypertension.

Clinical studies propose that there is an inverse relationship between potassium intake and systolic and diastolic BP. It has been demonstrated that a mean baseline diastolic BP was higher by 13 mm Hg in salt-sensitive individuals compared to salt-insensitive subjects. The diastolic BP was reduced by at least 5 mm Hg when a high potassium intake was ingested in 10 out of 20 subjects because potassium intake can result in increased renal kallikrein secretion. The findings suggest that moderate salt restriction together with a high potassium intake can help in preventing hypertension [61]. Furthermore, intravenous infusion of potassium gluconate solution into anesthetized SD rats immediately accelerated the urinary kallikrein secretion and reduction of BP [62].

The increase of potassium intake can decrease the high prevalence and incidence of hypertension especially, in black individuals [63]. However, if the potassium diet increased within its normal range, it can attenuate salt sensitivity in blacks [64] and it can accelerate the release of renal kallikrein.

ATP-sensitive Potassium Channel Blockers

Kidney specific ATP-sensitive potassium channel blockers are considered as the most reliable agents for controlling salt-sensitive hypertension. ATP-sensitive potassium channel blockers accelerate the release of renal kallikrein and can suppress sodium-induced hypertension. It has been reported that hypertension induced by excess sodium-ingestion in SD rats is suppressed by an ATP-sensitive potassium channel blocker through increased secretion of urinary kallikrein. For example, glibenclamide is a nonspecific ATP-sensitive potassium channel blocker and has been found to reduce systolic BP and increased urinary kallikrein and sodium excretion. It has been shown that glibenclamide accelerated dose-dependent secretion of renal kallikrein in sliced kidney cortex and in vivo in rats [65]. U-18177 is a kidney-selective ATP-sensitive potassium blocker that significantly increased urinary kallikrein and sodium excretion, as well as reduced the SBP, as illustrated in figure 5 [65].

Moreover, BK-B2 receptor antagonist, FR173657, together with glibenclamide, can abolish the hypotensive and natriuretic effects of glibenclamide in sodium-induced hypertension; however, urinary kallikrein secretion was unchanged [65]. These findings indicate that the hypotensive and natriuretic effects of ATP-sensitive potassium channel blockers are related to the activity of renal KKS, as illustrated in figure 6 [65].

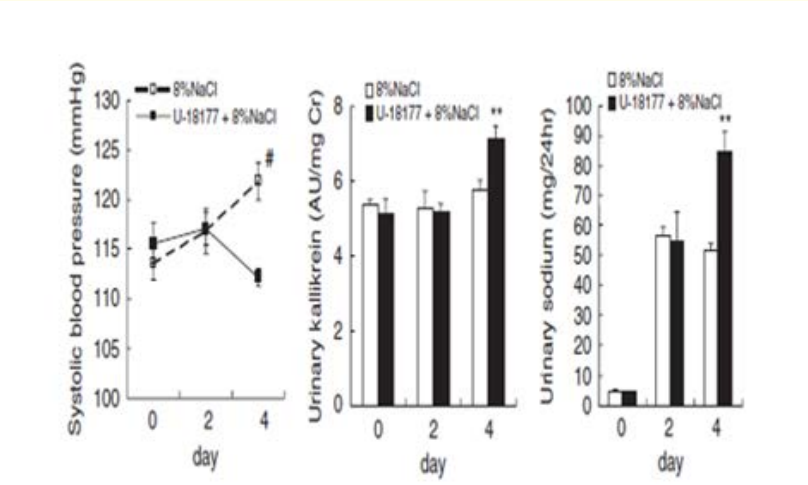

Figure 5: *Systolic blood pressure (SBP), urinary kallikrein and urinary sodium in Sprague–Dawley strain (SD) rats fed an 8% NaCl diet. A kidney-selective ATP-sensitive potassium blocker (U-18177) was given to rats (60 mg kg^{-1}). Blood pressure, urinary kallikrein and urinary sodium were measured on days 0, 2 and 4.*

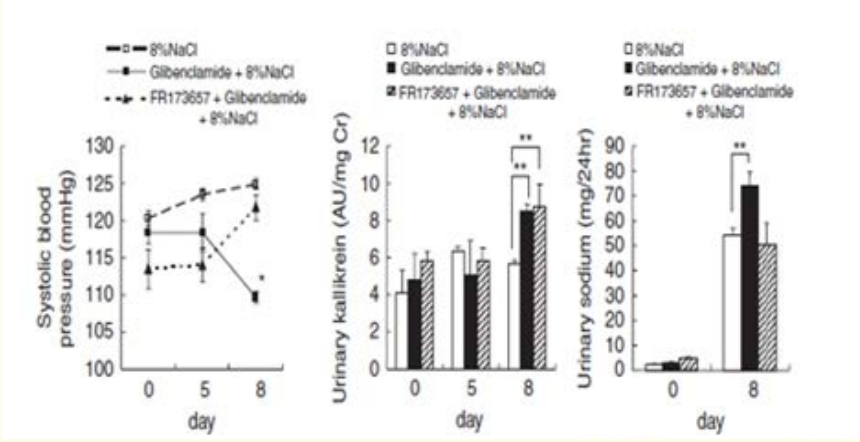

Figure 6: *Systolic blood pressure (SBP), urinary kallikrein and urinary sodium in Sprague–Dawley strain (SD) rats fed an 8% NaCl diet. A bradykinin B 2 receptor antagonist (FR173657) was given to rats at a doze of 100 mg/kg. Blood pressure, urinary kallikrein and urinary sodium were measured on days 0, 5 and 8.*

Inhibitors of Renal Kininases (Kinin-Inactivating Enzymes)

Renal kininases inhibitors are considered as potential antihypertensive drugs that prolong the life of kinins in the tubular lumen of the CD by inhibiting renal kininases. Renal kininases inhibitors, such as ebelactone B and poststatin, are the main agents for controlling salt-sensitive hypertension. Moreover, BP102 is another kininase inhibitor that is an oral prodrug of the NEP inhibitor thiorphan [78].

The potential of Bradykinin system to treat salt sensitive hypertensive

Drugs that enhance KKS activity in the kidney may be considered as novel agents for the treatment of salt-sensitive hypertension. Drugs that accelerate renal kallikrein release and drugs that inhibit renal kininases are two candidates for novel antihypertensive drugs for the treatment of patients with salt-sensitive hypertension.

Anti-hypertensive drugs

The cardioprotective effects of the antihypertensive drugs, such as ACEIs are currently used to treat both clinical and experimental hypertension. It has been found that kininase II inhibitors can reduce BP by blocking angiotensin II production and/or inhibiting the biodegradation of kinin at the renal site [10]. Clinical evidence showed that the MBP was significantly elevated in diabetic SHR compared with nondiabetic SHR. Captopril may cause a reduction in BP and regression of LVH in both diabetic and non-diabetic SHR due to improved renal tissue kallikrein activity [13]. In addition, aprotinin can abolish the hypotensive responses of ACEIs in SHR [69] and in transgenic mice [70]. These findings indicate an important role of tissue kallikrein in controlling the BP.

The administration of purified tissue kallikrein or kinin into experimental animals caused a transient reduction in BP. Tissue kallikrein inhibitors are present in the circulation that rapidly cleave the kinin peptides by degrading enzymes in the vasculature [71]. Clinical studies have demonstrated that oral administration of porcine pancreatic kallikrein can reduce the BP temporarily in hypertensive patients, but repeated administration of purified tissue kallikrein is needed to achieve the hypotensive effect because the effect reduces as soon as the treatment is finished [53]. Tissue kallikrein treatment decreases BP significantly in patients with essential hypertension compared with placebo, as illustrated in figure 7 [53].

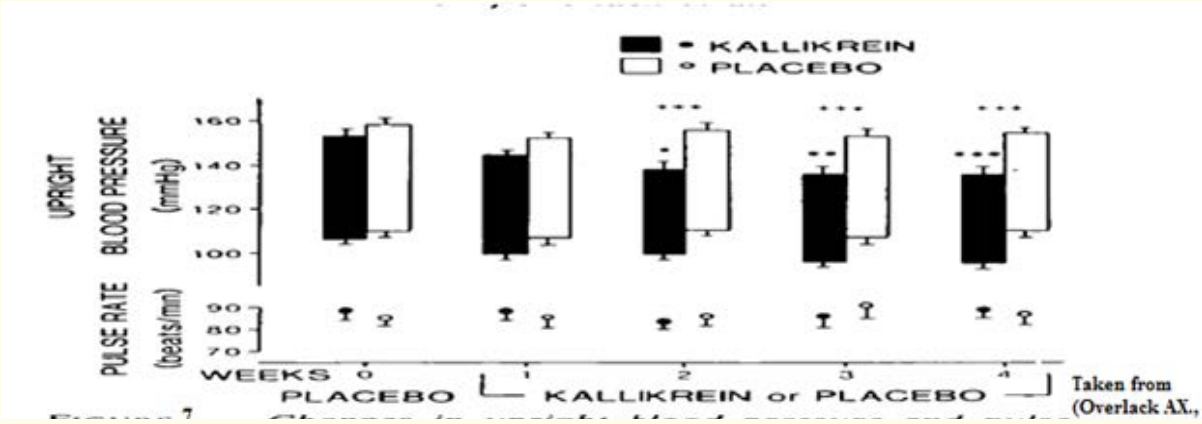

Figure 7: *Changes in upright blood pressure and pulse rate in the kallikrein and placebo treated patients.*

Gene therapy with tissue kallikrein

Gene therapy is considered an effective treatment in controlling BP via long-term expression of target genes in hypertensive patients [72]. Gene therapy with human tissue kallikrein may have beneficial effects as the treatment for hypertension. Kallikrein gene delivery can reduce BP and cardiac hypertrophy and can increase renal function in Goldblatt hypertensive rats [44]. Clinical studies have demonstrated that the transfer of tissue kallikrein gene leads to normalization of both BP and blood in rats with fructose-induced hypertension and type 2 diabetes, as illustrated in the figure 8 [73].

It has been shown that a dominant allele expressed as high urinary kallikrein excretion may be correlated with a reduced risk of essential hypertension in a large family pedigree study [72]. The studies showed that human tissue kallikrein gene delivery has beneficial effects in protecting against renovascular hypertension, cardiovascular and renal abnormalities. This therapy provides a significant reduction in the left ventricular mass and cardiomyocyte size and increased renal blood flow, glomerular filtration rates, urine flow, and electrolyte output and urine excretion. It has been demonstrated that enhanced renal responses were associated with a significant increase in urinary kinin, nitrite/nitrate, and cyclic GMP levels [44]. There is an association between alteration of tissue kallikrein gene expression and regulation of blood pressure. Transgenic mice overexpressing human tissue kallikrein are hypotensive throughout their life span under the control of the metallothionein metal response element or albumin gene enhancer/promoter. In order to restore BP of

these transgenic mice, aprotinin, a tissue kallikrein inhibitor, or Hoe 140, a bradykinin B2 receptor antagonist is administered. It has been found that transgenic mice overexpressing human bradykinin B2 receptor are hypotensive, which indicate that hypotension in kallikrein transgenic mice is mediated by binding of kinin to B2 receptors [73].

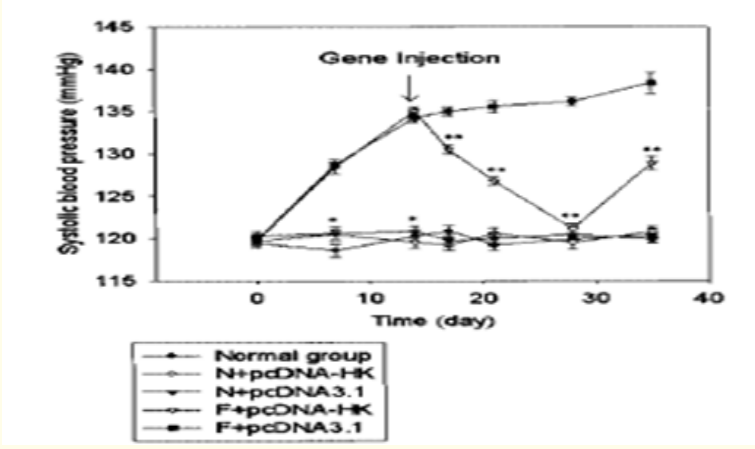

Figure 8: *Systolic blood pressure in fructose-induced hypertensive rats injected with pcDNA3.1-HK.*

Clinical studies showed that the recombinant adeno-associated viral-mediated human tissue kallikrein (rAAV-HK) gene delivery is considered a safe method for long treatment of hypertension that may be applied in the salt-sensitive population in order to prevent the incidence of hypertension. Recently, a single injection of the human tissue kallikrein gene in plasmid DNA or an adenoviral vector provides the reduction in BP, attenuation of cardiac hypertrophy, and inhibition of renal damage and renal stenosis [54]. It has been reported that in normal SD rats, a high-salt intake induces hypertension, while rAAV-HK delivery provides a protective effect against increased BP, as illustrated in the figure 9 [74]. Moreover, the rAAV-HK delivery was administered through intravenous route into SHR, which caused persistent expression of recombinant human kallikrein and a significant reduction in systemic blood pressure for several months [74]. These findings can indicate the prospect of using tissue kallikrein gene therapy for treating cardiovascular and renal abnormalities.

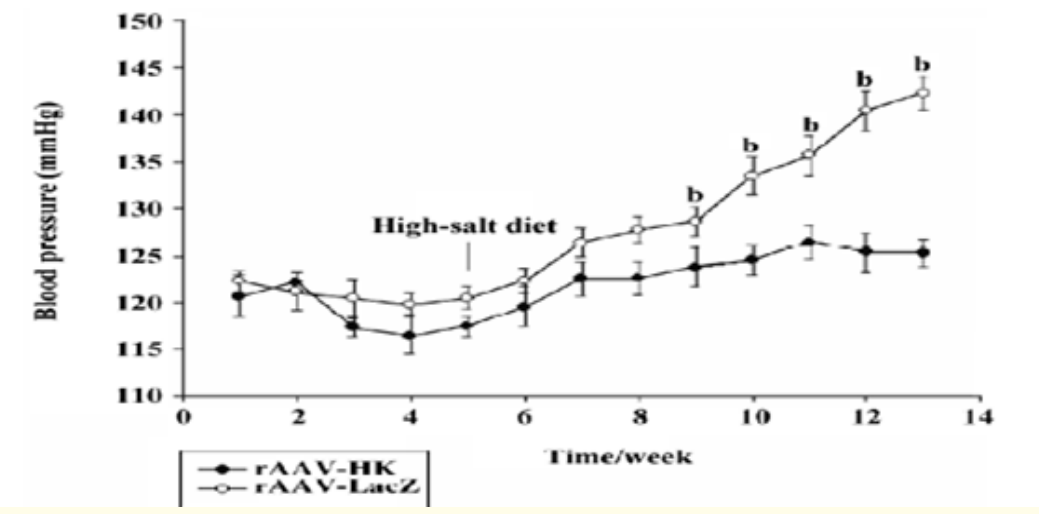

Figure 9: *Regulation of blood pressure in SD rats injected intravenously with rAAV–HK and rAAV–LacZ.*

Recently, human kallikrein gene delivery therapy and adenovirus-mediated human tissue kallikrein gene delivery were suggested as therapeutic tools for the regulation of hypertension. It has been demonstrated that in transgenic mice, sustenance of high levels of tissue kallikrein in the circulation may induce long-lasting hypotension. The kallikrein gene transfer can provide a wide spectrum of beneficial effects that makes it an excellent candidate for treating salt-related hypertension and cardiac and renal dysfunction [70,75].

The BK can stimulate the B2 receptor and cause the generation of cGMP that induces the release of NO from the endothelial cells. Also, the nitric oxide synthase (iNOS) can produce NO that contributes in preventing salt-sensitive hypertension in the DSR rats and reduced salt sensitivity in the DSS rats [76]. The administration of L-arginine, which is the substrate for NO synthesis, reduced the BP of salt-sensitive rats that fed on high dietary sodium chloride to normotensive levels [77]. Furthermore, Glu298Asp is a new coding variant of the endothelial NO synthase gene that showed an essential role in the development of hypertension [46].

Conclusion

The renal KKS system has an important role in the pathophysiological process of hypertension and more specifically salt-sensitive hypertension. The application of tissue kallikrein and BK B2 receptor agonist can reverse the pathologic consequences of salt induced hypertension. The reduced activity of this system may contribute to the development of hypertension and renal abnormalities. These pathologic consequences may be due to genetic dysfunction of BK or BK receptors downregulation. The cardioprotective effects of the antihypertensive drugs, such as ACEI, could be mediated through the BK activation pathways. The administration of potassium or ATP-sensitive potassium channel blockers can accelerate the release of renal kallikrein through stimulation of kinin production in the tubular lumen of the CD and inhibit sodium reabsorption through BK-B2 receptors. Furthermore, the tissue kallikrein gene delivery may provide a safe method to prevent and treat salt-sensitive hypertension.

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