

Chapter 2

The Kallikrein–Kinin Pathways in Hypertension and Diabetes

Jagdish N. Sharma and Parvathy Narayanan

Abstract Cardiovascular diseases are the most common causes of mortality worldwide. Hypertension and diabetes are the two major risk factors in the development of cardiac hypertrophy, ischemic heart disease, and cardiac failure. In Kuwait, high rate of prevalence of hypertension and diabetes has been documented. Previous studies have indicated altered activities of the BK-generating components in hypertension and diabetes. Bradykinin is pharmacologically active polypeptide that can promote both cardiovascular and renal function, for example, vasodilation, natriuresis, diuresis, and release of nitric oxide (NO). In addition, B₂ kinin receptors are present in the cardiac endothelial cells which may enhance the biosynthesis and release of NO. It has been demonstrated that reduced urinary (renal) kallikrein levels may be associated with the development of high blood pressure in humans and spontaneously hypertensive and diabetic rats. The BK may produce its pharmacological effects via NO and cyclic GMP release. Furthermore, it is established that the BK has cardioprotective actions in myocardial ischemia and can prevent left ventricular hypertrophy. Also, transgenic mice carrying tissue kallikrein gene and overexpressing tissue kallikrein had reduced blood pressure. NO synthase and renal tissue kallikrein are both involved in blood pressure regulation. The ability of kallikrein gene delivery and the use of kinin B₂ receptor agonists to produce a wide spectrum of beneficial effects make it a powerful candidate in treating hypertension, cardiovascular, and renal diseases. Strategies that activate kinin receptors might be applicable to the treatment of cardiovascular disease. Increased plasma prekallikrein levels in diabetic patients may serve as an indicator of developing hypertension and renal damage. Also high plasma and urine concentrations of tissue kallikrein may cause higher glucose levels in the blood.

J. N. Sharma (✉) · P. Narayanan
Faculty of Pharmacy, Department of Pharmacology and Therapeutics,
Health Sciences Centre, Kuwait University, Kuwait City, Kuwait
e-mail: j.n.sharma@hsc.edu.kw

Abbreviations

ACE	Angiotensin-converting enzyme
Ag II	Angiotensin II
AVP	Arginine vasopressin
BK	Bradykinin
BP	Blood pressure
DSR	Dahl salt resistance
DSS	Dahl salt sensitivity
GFR	Glomerular filtration rate
GMP	Guanosine monophosphate
HF	Hageman factor
HMW	High molecular weight
KKS	Kallikrein–kinin system
LMW	Low molecular weight
LVH	Left ventricular hypertrophy
NO	Nitric oxide
PGE	Prostaglandin E
PGF	Prostaglandin F
PGI	Prostacyclin
PGs	Prostaglandins
RAS	Renin–angiotensin system
RPF	Renal plasma flow
SHR	Spontaneously hypertensive rats
VP	Vasopressin

2.1 Introduction

The blood pressure (BP)-lowering effect of the kallikrein–kinin system (KKS) has been described for more than six decades (Frey 1926). It is now widely believed that the KKS is involved in controlling BP. Exogenously administered kinins cause hypotension, natriuresis, arterial vasodilatation, increased renal blood flow, and fall in peripheral resistance (de Freitas et al. 1964; Willis et al. 1969; Adetuyibi and Mills 1972; Nasjletti et al. 1978; Mills 1982). Thus, it is conceivable that reduced activity of the KKS could result in sodium retention, arterial vasoconstriction, raised peripheral resistance, increased vascular or plasma volume, and production of high BP (hypertension). Hence, reduced kinin generation in the blood stream is thought to play an important role in the development of hypertension. In this regard, it has been demonstrated that the urinary kallikrein excretion is diminished in clinical and experimental hypertension (Margolius et al. 1971; Adetuyibi and Mills 1972; Croxatto and Martin 1970; Lechi et al. 1978). Furthermore, kallikrein excretion in the urine is viewed as an index of the activity of KKS in the renal system. This review is intended to discuss the significant role of KKS in hypertension and diabetes.

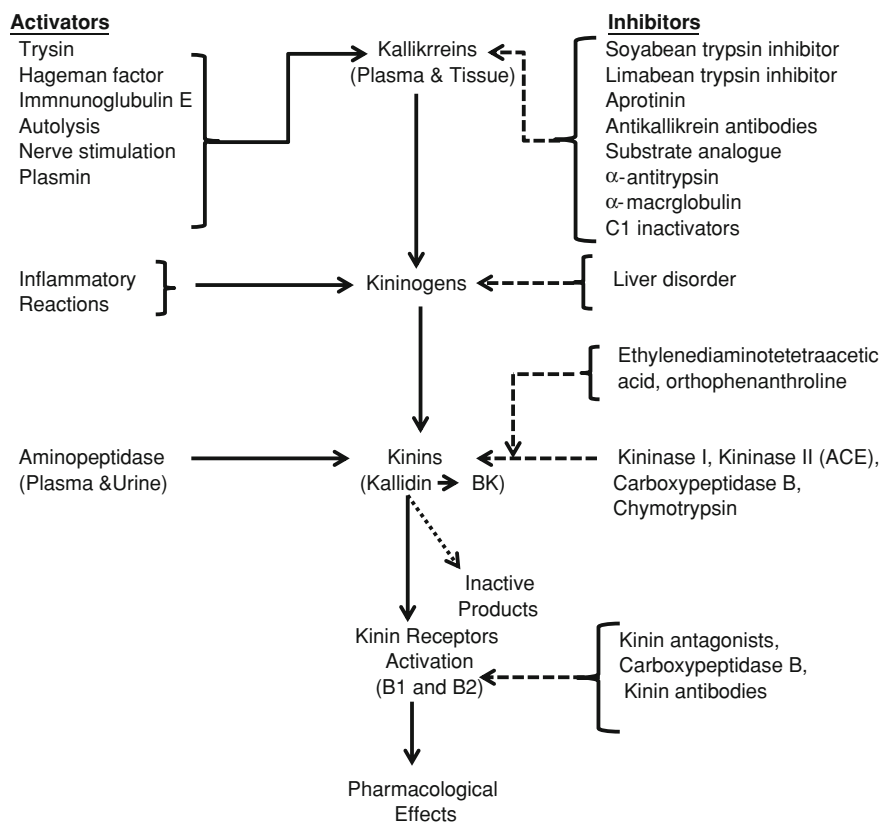


Fig. 2.1 Mode of bradykinin formation and inactivation

2.2 The Components of the Kallikrein–Kinin System

Vasoactive polypeptides, kinins, are released in the blood stream from precursors, kininogens, by the enzymatic actions of a group of serine proteases known as kallikreins (Fig. 2.1). Kinins are straight-chain peptides which resemble bradykinin (BK) ($\text{Arg}^1\text{-Pro}^2\text{-Pro}^3\text{)-Gly}^4\text{-Phe}^5\text{-Ser}^6\text{-Pro}^7\text{-Phe}^8\text{-Arg}^9$) in structure and in pharmacological actions (Sharma and Buchanan 1979; Schachter 1980).

2.2.1 Kininogens

Two kallikrein substrates, low molecular weight (LMW) and high molecular weight (HMW) kininogens, have been isolated from bovine plasma (Komiya et al. 1974). They differ in molecular weights (HMW-76,000; LMW-48,000) and in their susceptibility to plasma and tissue kallikreins. The HMW kininogen is the main

substrate for plasma kallikrein, and LMW kininogen is the most suitable substrate for tissue kallikrein. Two kininogens with different molecular weights (HMW-120000; LMW-78000) have also been isolated from human plasma (Jacobsen 1966; Nagasawa and Nakayasu 1975). The presence of a third form of human kininogen of about 200,000 daltons has been demonstrated (Pierce and Guimaraes 1975).

The deficiency of HMW kininogen appears to be the source of the multiple defects such as repaired clotting, kinin release, and surface-activated fibrinolysis in plasma. The HMW kininogen is also known as a “Fitzgerald factor,” because its absence was found first in the Fitzgerald family (Saito et al. 1974; Colman et al. 1975; Wuepper et al. 1975; Lacombe et al. 1975). Saito et al. (1975) have reported that purified preparations of “Fitzgerald factor” isolated from normal plasma contain HMW kininogen, however, the plasma from Mr. Fitzgerald contained about 50 % of the amount of kininogen found in normal plasma which is of the LMW form. It seems, therefore, HMW is essential not only in the kinin formation, but also in the regulation of blood coagulation pathway. This defect has been reversed by the treatment with purified HMW kininogen (Wuepper et al. 1975; Lacombe et al. 1975; Colman et al. 1975). Further, Hageman factor (HF) activates prekallikrein (inactive) to kallikrein (active), which is dependent on HMW kininogen. Thus, HMW could serve as a cofactor in the initiation of blood coagulation and the inactivation of kinin generation (Kaplan et al. 1981; Lynch and Shariat-Madar (2012).

2.2.2 Kallikreins

Kinin-forming enzymes, kallikreins, have been divided into two groups; plasma and tissue or glandular. They differ mainly in molecular weight, biological functions, physiochemical and immunological properties, and on the basis of their distribution in the body.

2.2.2.1 Plasma Kallikrein

The plasma kallikrein is present in the circulation in an inactive form known as prekallikrein or Fletcher factor. It has been described that a plasma designated Fletcher trait deficiency possessed a reduced rate of surface-mediated coagulation (prolonged partial thromboplastin time) which approached normal when the incubation time with kaolin is increased. (Hathaway and Alsever 1970). Prekallikrein is activated by HF (Kaplan and Austen 1971). Plasma kallikrein has also been shown to activate inactivated HF to active HF in the fluid phase (Cochrane et al. 1973). Kaplan et al. (1977) suggested the conversion of a small amount of prekallikrein to kallikrein by activated HF is necessary prior to feedback activation of HF. This finding has further demonstrated that plasma kallikrein does not only liberate kinins, but it is also required for the regulation of normal circulatory homeostasis. A genetic defect resulting in prolonged blood clotting time (Fletcher disease) has been corrected successfully with plasma prekallikrein (Wuepper 1973).

2.2.2.2 Tissue Kallikrein

Tissue kallikreins are present in the kidney, pancreas, intestine, salivary gland, bronchoalveolar lavage fluid of asthmatic patients, and synovial tissue (Nustad et al. 1975; Fiedler et al. 1970; Zeitlin 1972; Bhoola et al. 1965; Christiansen et al. 1987; Sharma et al. 1983a). However, the presence of tissue kallikreins in the plasma has also been reported (Nustad et al. 1979; Rabito et al. 1979; Lawton et al. 1981; Rabito et al. 1982). The value of these observations remains unclear. Although, the release of submandibular gland kallikrein into the circulation has been indicated after sympathetic nervous system stimulation, which may cause reactive vasodilation in the rat submandibular gland (Rabito et al. 1983). Tissue kallikreins have similar physiochemical properties, and these enzymes are immunologically identical within the same species (Fiedler 1979); though, the factors which determine tissue kallikrein secretion are not well defined and could exhibit tissue as well as species differences. It has been reported that the salivary secretion of kallikrein in the rat is regulated by the sympathetic and parasympathetic nervous systems, although the stimulation of sympathetic produces an increased secretion of kallikrein than the stimulation of parasympathetic system (Beilenson et al. 1968; Orstavik and Gautvik 1977; Rabito et al. 1983). On the other hand, α -adrenergic stimulation appeared to inhibit urinary kallikrein excretion from the kidney of the dog and the rat (Olsen 1980, 1982). In the kidney, tissue kallikrein is synthesized in the distal tubular cells (Orstavik et al. 1976). It has been suggested that part of the kallikrein excreted in the urine could be of plasma origin (Fink et al. 1980), although the urinary kallikrein appears to be secreted in the distal segments of the nephron (Scicli et al. 1976). The urinary excretion of kallikrein reflects the activity of the enzyme in the rat kidney (Marin-Grez et al. 1982). The renal kallikrein has been suggested to regulate BP and its possible involvement in the physiopathology of hypertension (Carretero and Scicli 1981; Orstavik 1981; Sharma 2013; Sharma and Fernandez 1982). Furthermore, tissue kallikreins are implicated in a variety of physiological actions, including salt and water excretion, and activation of both striopeptigen and prorenin, as well as release of lysyl-bradykinin (kallidin) from kininogens. Several agents that non-specifically block serine proteases, including kallikreins, have been reviewed by Vogel (1979). A recent study has provided new data on the specificity of tissue kallikreins and its involvement in enkephalin biosynthesis (Prado et al. 1983).

2.2.3 Kininases

When a kinin is incubated with blood or with a tissue homogenate, it is rapidly cleaved to inactive peptides. Therefore, kinin-inactivating enzymes are collectively known as kininases. Kininase I (carboxypeptidase N) is present in the plasma of man and animals that cleaves basic C-terminal amino acids, including Arg9 of BK (Erdos and Sloane 1962). This enzyme has been purified from human

plasma (Erdos et al. 1967; Oshima et al. 1974). Whereas Erdos and Yang (1966, 1967) first detected an enzyme in the kidney cortex and subsequently in the plasma (Yang and Erdos 1967) which inactivates BK by cleaving the C-terminal of the nonapeptide. This kinase was named as kininase II (peptidyl dipeptide hydrolase) or angiotensin I-converting enzyme (ACE). At present, kininase II (ACE) inhibitors are clinically more important in the treatment of hypertension.

2.3 Interactions with Other Endogenous Agents

2.3.1 Renin–Angiotensin System

It has been suggested that the rennin–angiotensin system (RAS) and KKS act as opposing forces in the regulation of BP. Under certain situations, the inhibition of a vasodilator system (KKS) occurring during the activation of a vasoconstrictor system (RAS) might function together in control or increase of BP. The inactive renin is activated in vitro by plasma and tissue kallikreins (Sealey et al. 1978; Derkx et al. 1979). Although it has been reported that the inactive renin separated from active renin could not be activated by tissue kallikrein, however, after acid treatment, the inactive renin was activated in the presence of tissue kallikrein (Yokosawa et al. 1979). This finding was confirmed when Hiwada et al. (1983) reported that tissue kallikrein does not directly activate inactive renin but participates in the activation process of inactive renin. An increased urinary kallikrein excretion has been observed in dogs after intra-arterial infusions of angiotensin II (MacFarlane et al. 1974). Mills et al. (1976) suggested that under situations of raised renin–angiotensin production, the renal KKS might also be activated to antagonize raised vasoconstriction of renal vasculatures. Indeed, kinase II (ACE) is known for the conversion of angiotensin I into the potent vasoconstrictor angiotensin II, as well as responsible for the biodegradation of BK, a potent vasodilator agent (Erdos and Skidgel 1985). The multihormonal regulation of renal kallikrein and its possible interactions with the renin–angiotensin–aldosterone system, the corticotropin–glucocorticoid system, antidiuretic hormone, catecholamine, and prostaglandins (PGs) have been discussed in an excellent review by Marin-Grez (1982). However, there was no correlation between renal tissue kallikrein and plasma renin activity in either two-kidney or one-kidney renal hypertension (Carretero et al. 1974).

2.3.2 Prostaglandins

PGE possesses a wide range of pharmacological actions. It is synthesized by vascular tissue, and participates in regulation of vascular tone, and also acts as a local vasoactive agent in the kidney through influencing local blood flow, salt and

water excretion (Bunting et al. 1976; Gryglewski et al. 1976; Vane and McGriff 1975). Nonetheless, there is considerable evidence to suggest the pharmacological interactions between BK and PGs. BK-mediated production of PGs has been observed in a variety of tissue such as the kidney (McGiff et al. 1972), spleen (Ferreira et al. 1971), and the lung (Palmer et al. 1973). Furthermore, intrarenal arterial infusions of BK into the canine kidney caused release of PGE-like agents. In the rat, it has been reported that administration of tissue kallikrein inhibitor Trasylol, produced reduction in PGE, and kallikrein concentration in the urine (Nasjletti et al. 1978). In this way, alterations in KKS might have profound effects on PGs concentrations in the renal circulation (Colina-Chourio et al. 1976), therefore, PGs could contribute to the actions of BK on salt and water excretion (McGiff et al. 1975). Intraperitoneal administration of PGE₂ can produce reduction in plasma kininogen levels in the rat (Sharma and Zeitlin 1982). It is suggested that PGE₂, but not PGF₂, might produce kinins by activating plasma prekallikrein to kallikrein (Sharma and Zeitlin 1982). Also, the duration of hypotensive action of BK in Dahl rats is inhibited by PGs synthetase inhibitor such as indomethacin (Sharma et al. 1984a). This reduction in the duration of the hypotensive effect of BK is the result from an inhibition of the cyclo-oxygenase system in the Dahl rats. It has also been reported that BK activates a phospholipase (Hong and Levine 1976) which releases arachidonic acid and lead to increased synthesis of PGs (Damas and Bourdon 1974).

In patients with Bartter's Syndrome, there is high plasma renin, hyperaldosteronism, hypokalemic alkalosis, and juxtaglomerular hyperplasia, however, in spite of the raised plasma renin, the BP remains normal (Bartter et al. 1962). Enhanced renal kallikrein and PG have been implicated in the etiology of this syndrome. These suggestions are supported by the findings of raised PGE₂ and kallikrein concentrations in the urine (Gill et al. 1976; Vinci et al. 1976; Lechi et al. 1976). In patients with Bartter's syndrome, indomethacin and other cyclo-oxygenase inhibitors therapy caused a remarkable reduction in the plasma renin concentrations and aldosterone, PGE₂ and kallikreins levels in the urine and also corrected the hypokalemic alkalosis without altering the BP (Gill et al. 1976; Halushka et al. 1977). These observations strongly suggest that PGE is involved in the renal regulation of renin and kallikrein systems. Thus, reduction in angiotensin II might cause fall in the aldosterone levels to normal so that hypokalemia could be corrected (Mills 1979). However, Strand and Gilmore reported that PGs do not mediate the renal effects of BK in the dog.

2.3.3 Vasopressin

There are several reports to suggest a complex interaction between vasopressin (VP) and KKS. Kinins are powerful antagonists of the hydro-osmotic effect of VP in the toad urinary bladder (Furtado 1981; Carvounis et al. 1981) and water permeability

in the renal medulla. These investigators also observed that this action of kinin was antagonized by antidiuretic hormone. Kinins are known as potent activators of PG synthesis in the kidney (McGiff et al. 1972). Further, it has been reported that PGs interfere with the hydroosmotic actions of VP (Fejes-Toth et al. 1977). VP administration can cause PGE release in the rabbit kidney (Miller et al. 1986a), which might reduce the response of the collecting duct to VP (Zusman and Keiser 1977). Fejes-Toth and Fejes-Totah (1986) provided indirect evidence to support the notion that arginine-vasopressin might activate renal KKS, but the mechanism of action and its implication in hypertension remains to be determined. Hence, it is possible to suggest that interactions between the renal KKS and renal PGs might contribute to the control of renal blood flow, and salt and water homeostasis. Recently, it has been shown that arachidonic acid-stimulating PG release takes place in pre-glomerular blood vessels and hence 6-keto-PGE 1α , whereas arginine-vasopressin (AVP) activates PGE 2 release from post-glomerular sites, an action shared with angiotensin II (Miller et al. 1986a, b). It indicates that arachidonic acid and AVP differ in profile of PG release in the renal vascular compartments. Interactions between the KKS, PGs, and VP might have greater physiological importance in the control and counter balance of antidiuretic hormone, however, such evidence needs to be established. In this regard, Fejes-Toth et al. (1982) and Fejes-Toth and Fejes-Totah (1986) reported that VP is a potent activator of kallikrein when given during water diuresis and the kinin released may antagonize the effect of VP thus, completing a full negative feedback system.

2.4 Pathophysiological Roles of Bradykinin System in Hypertension and Diabetes

2.4.1 Clinical Hypertension

Hypertension is a major risk factor in the development of cardiovascular diseases, such as coronary heart disease, congestive heart failure, and peripheral vascular and renal diseases. There is ample evidence documenting the role of BK in the pathogenesis of hypertension (Sharma 2009a; Katori and Majima 2006). The pharmacological actions of BK in regulation of systemic BP are vasodilation in most areas of circulation, reduction in total peripheral vascular resistance, and regulation of sodium excretion from the kidney (de Freitas et al. 1964). When BK is injected into the renal artery, it causes diuresis and natriuresis by increasing renal blood flow (Webster and Gilmore 1964). These actions of BK have been attributed to PGs release in the renal circulation (McGiff et al. 1975). In 1934, Elliot and Nuzum had already noticed that hypertensive patients without clinically apparent renal disease have significantly low levels of urinary kallikrein than normotensive subjects (Elliot and Nuzum 1934). This abnormality in human hypertension was not confirmed until 1971.

The role of KKS in hypertension was established by Margolius and co-investigators (Margolius et al. 1971, 1972, 1974) with the observations that urinary kallikrein excretion is significantly reduced in hypertensive patients and hypertensive rats. This led to the suggestion that reduced urinary kallikrein excretion might result from a reduction in kinin generation in hypertensive situations. Kallikrein excretion in white hypertensive men was lower than that in white normotensives during normal sodium intake, but was not different from that in black hypertensives and black control subjects under the same conditions. The kallikrein levels in the urine of normotensive black subjects are significantly lower than those in normal white subjects. All groups have greater urinary kallikrein activity on a low-sodium diet versus an unrestricted sodium intake, but the increase in black hypertensives is small. Plasma renin activity shows similar increments after sodium restriction in all groups. Similar results on reduced excretion of urinary kallikrein in black subjects were obtained (Carretero et al. 1978). Plasma kinins in clinical hypertension is known to be modulated by loss of sodium. These findings strongly support the view that sodium intake can modulate the kinin system.

Furthermore, patients with malignant essential hypertension excrete less urinary kallikrein than those with non-malignant essential hypertension and normotensive control subjects (Hilme et al. 1992). Some studies have reported that white patients with uncomplicated essential hypertension show normal kallikrein excretion rates with normal plasma renin activity and aldosterone. Only hypertensives over 40 years old excrete a significantly lower excretion of urinary kallikrein (Koolen et al. 1984). Moreover, recently in Brazilian study showed lower urinary kallikrein activity in hypertensive patients than control subjects (Belo et al. 2009). On the other hand, it is noted that hormone replacement therapy caused a significant rise in urinary kallikrein levels that might have cardioprotective effect (Farag et al. 2003).

It has been suggested that the race and sodium intake in hypertension have greater influence upon kallikrein excretion (Zinner et al. 1976; Levy et al. 1977; Azizi et al. 2008). These investigators evaluated urinary kallikrein levels in large populations of hypertensive cases and their families. The result showed that whites excrete more kallikrein than blacks and white hypertensives excrete less kallikrein than white normotensive individuals. All test groups had higher kallikrein excretion when kept on low-sodium intake. Black hypertensives excreted less kallikrein than black normotensives during sodium reduction. Furthermore, families with reduced kallikrein excretion had higher BP than those with increased urinary kallikrein excretion. This could suggest a genetic defect in the renal kallikrein and/or the presence of higher amounts of tissue kallikrein inhibitor in certain races. An altered frequency of a promoter polymorphism of kinin B2 receptor (B2R) gene in hypertensive African-Americans has been documented well (Gainer et al. 2000). Also, pregnancy-induced hypertension has been suggested to be due to decreased kidney kallikrein excretion, which could be lacking of BP-lowering factors in pregnancy to cause rise in BP (Karlberg and Wichman 1984). The identification of a subset of subjects with genetically reduced kallikrein activity as a result of an

amino acid mutation could facilitate analysis of the role of the KKS in renal and vascular diseases (Slim et al. 2002).

Kallikrein excretion was decreased in hypertensive patients with mild renal insufficiency (Holland et al. 1980). Although no significant difference in the urinary kallikrein excretion of patients with low-renin essential hypertension was found, hypertensive patients with mild renal insufficiency showed reduced urinary kallikrein excretion (Holland et al. 1980). Patients with reduced glomerular filtration rates showed markedly decreased urinary kallikrein excretion, like those with hypertension (Mitas et al. 1978). Renal parenchymal diseases with hypertension, such as chronic glomerulonephritis, are associated with diminished kallikrein activity (Holland et al. 1980).

However, recent studies suggest a strong influence of urinary kallikrein excretion on the salt sensitivity of BP in normotensive patients. In a randomized crossover double-blind study, the urinary excretion of active kallikrein was significantly lower in salt-sensitive hypertensives than in salt-resistant hypertensive patients and it showed an inverse correlation with plasma atrial natriuretic peptide levels. Thus, at least some of the hypertensive patients excrete lower levels of kallikrein without reduced renal function.

Research on the systemic changes in the kallikrein has provided further insight regarding the mechanisms of various hypertensive conditions. In this connection, it is known that kininogen levels and kinin-forming factors are reduced in essential and malignant hypertension (Almeida et al. 1981; Sharma and Zeitlin 1981). It may be that a deficiency of plasma HMWK due to a decrease in liver synthesis (which decreases kinin production) occurs in an individual who develops hypertension after mild exercise (James and Donaldson 1981). It is proposed that a deficiency in BK might be a significant factor in the pathophysiology of hypertension. In this regard, it is suggested that the role of renal BK is to excrete the excess of sodium. Therefore, a reduction in the generation of renal BK may be the cause in the development of hypertension as a result of the accumulation of sodium in the body (Katori and Majima 2006). Thus, the development of a compound having renal kallikrein-like activity may serve the purpose of excreting excessive sodium from the kidney in the treatment of hypertension.

2.4.2 Experimental Hypertension

Rats with renovascular hypertension have decreased kallikrein levels both in renal tissue and urine. In two kidney-one clip Goldblatt hypertensive rats, the urinary kallikrein level was low in the urine from stenotic kidney, whereas that of the contra lateral kidney was normal. In Dahl salt-sensitive rats fed a normal sodium diet (0.45 % NaCl), the urinary kallikrein level determined by the kinin-generating activity is lower than the level determined by direct radioimmunoassay for the enzymic protein. The level of urinary protein is higher in these rats. The lower level of kallikrein may be due to inhibitors leaking from the plasma. The reduced

levels of kallikrein in hypertension should be distinguished from those due to impaired renal function.

It has been demonstrated that transgenic mice overexpressing renal tissue kallikrein were hypotensive and that administration of aprotinin, a tissue kallikrein inhibitor, restored the BP of the transgenic mice. We have shown the suppression of hypotensive responses of ACEIs by aprotinin in spontaneously hypertensive rats (SHR). These findings highlight a role of tissue kallikrein in the regulation of BP. Recently, it has been proposed that tissue kallikrein gene delivery into various hypertensive models exhibits protection, such as reduction in high BP, attenuation of cardiac hypertrophy, inhibition of renal damage, and stenosis (Chao and Chao 2005; Chao et al. 1998, 2006). This may indicate the future therapeutics aspect of kallikrein gene therapy for cardiovascular and renal pathology. Tissue kallikrein can have antihypertensive function in physiological states where sodium retention can trigger high BP (Potier et al. 2013).

ACEIs are currently used in the treatment of both clinical and experimental hypertension (Antonaccio 1982; Silberbauer et al. 1982; Sharma et al. 1983a, b, 1984a, b, c). Kininase II inhibitors could lower BP by inhibiting the biodegradation of kinin as well as blocking the formation of angiotensin II (AngII). A calcium-channel blocker, nifedipine, used in the treatment of patients with essential hypertension can normalize the reduced urinary kallikrein excretion (Edery et al. 1981). Smith et al. have suggested that women with reduced activity of the renal BK may be at increased risk of developing pregnancy-induced hypertension. A previous study has demonstrated that urinary kallikrein excretion was found to be diminished in family members at risk of hereditary hypertension and that urinary kallikrein may be one of the major genetic markers associated with family history of hypertension (Kailasam et al. 1998).

The earlier studies have clearly indicated that there is influence of race, diet, sodium, and potassium intake on the BK-producing components. However, there has been no such study on the BK system and its related mediator (NO) in the Arab population with special interest to Kuwaiti population. Hence, such an investigation will highlight the significance of the role of BK system and its interacting mediator (NO) in the pathophysiology of hypertension and diabetes in Kuwaiti patients with and without treatment. Also, the beneficial effects of the treatment could be mediated by alterations in the BK system and NO.

Left ventricular hypertrophy (LVH) is regarded as an independent risk factor in hypertensive patients in inducing cardiac abnormalities. BK can counter the development of LVH in rats with hypertension produced by aortic banding (Linz et al. 1993; Madeddu et al. 2007). This antihypertrophic effect of BK was abolished by the B2R antagonist treatment as well as by NO synthetase inhibitor. Thus, the BK has a role in protecting the heart against developing LVH by releasing NO in this model of hypertension induced by aortic banding. In this regard, we have for the first time demonstrated that the lack of the cardiac KKS could be responsible for the induction of LVH in SHR and SHR with diabetes (Sharma et al. 1998, 1999). It is suggested that the reduced cardiac tissue kallikrein and cardiac kininogen may be responsible for reduced BK generation in the heart. Therefore, deficient components

of the BK in the heart may be responsible for inducing excessive hypertrophy and myocardial dysfunction in cases of hypertension. It is highly desirable to develop stable compounds of BK to evaluate their efficacy and potency in cases of cardiac failure, cardiac ischemia, and hypertension (Sharma et al. 1999).

It is the generally accepted view that the BK-induced BP-lowering effect is mediated by the B2R, but B₁ might also be involved under special situations (Regoli 1984). It has been demonstrated that a B2R antagonist (B5630) can generally abolish the hypotensive effects of BK as well as captopril, an ACEI (Sharma 2009b). This led to the proposal that the hypotensive action of ACE inhibitors might be due to the activation of B2R (Sharma 2009b). The accumulation of BK after treatment with ACEIs with subsequent release of NO, PGs, and prostaglandin I₂ (PGI₂) could account for additional mediators released in the process of antihypertensive action of these drugs in hypertensive patients.

2.4.3 Diabetes

Diabetes is a major risk factor in the development of cardiovascular and renal complications. Previous studies have indicated conflicting results of the BK-forming components (Leeb-Lundberg et al. 2005) in diabetic patients and experimental animals. High prevalence rates (20–25 %) of type 2 diabetes have been documented in Kuwaiti population (Abdella et al. 1998; Al-Shoumer et al. 2008). Type 2 diabetes can lead to hypertension, renal, and cardiac complications, resulting in high rates of mortality worldwide and in Kuwait as well. BK, a pharmacologically active polypeptide, is one of the kinins which is released in the tissues and body fluids as a result of enzymatic action of kallikreins on kininogens. The two types of kallikrein are tissue kallikrein and plasma kallikrein. Plasma kallikrein is also present in inactive form known as prekallikrein, which can be activated into kallikrein. Tissue kallikrein is mainly expressed in the kidney (urine), glandular tissue, vasculature (Sharma and Narayanan 2011) heart, and brain. It preferentially acts on LMW kininogen substrate to release lysyl-BK. Tissue kallikrein has also been reported to be present in plasma (Rabito et al. 1982; Yayami et al. 2003). Plasma kallikrein preferentially acts on HMW kininogen substrate to release BK. BK promotes both cardiovascular and renal functions, for example, vasodilation, natriuresis and diuresis (Katori and Majima 2006; Sharma et al. 1998); BK is rapidly (<15 s) inactivated by circulating kinases (Sharma et al. 1996); BK acts on B1 receptor (B1R) and B2R (Jaffa et al. 2003) to elicit physiological and pharmacological actions. It has been shown previously that type 1 diabetic patients are at a risk of developing nephropathy with increased renal tissue kallikrein and BK levels (Harvey et al. 1990). In addition, raised plasma prekallikrein levels in type 1 diabetes has been considered as a risk marker for hypertension and nephropathy (Jaffa et al. 1995). This has not yet been reported in type 2 diabetic patients. However, in diabetic rats, it has been shown that moderate hyperglycemia, in association with increased urinary kallikrein excretion, can result in reduced

renal vascular resistance (RVR) and increased both renal plasma flow (RPF) and glomerular filtration rate (GFR) (Harvey et al. 1990; Jaffa et al. 1995). The treatment with aprotinin, a kallikrein inhibitor, to these rats increased the RVR and reduced the GFR and RPF (Harvey et al. 1990; Jaffa et al. 1995). In diabetic patients, urinary and plasma tissue kallikrein concentrations were significantly increased. In addition, plasma prekallikrein levels were also reduced in diabetic patients when compared with healthy subjects. This is the first investigation among Kuwaiti Arab patients with type 2 diabetes, showing abnormal activities in the BK-forming system. High levels of plasma prekallikrein may be a risk factor for developing high BP as well as nephropathy. The urinary and plasma tissue kallikrein concentrations were higher in diabetic patients that could indicate the hyperactivities of these components, which may result in increased level of plasma glucose to induce diabetes. Furthermore, the urinary kininogen levels were reduced in diabetic patients. These alterations might reflect the utilization of urinary kininogen to form BK, a potent inflammatory agent. However, this hypothesis needs further investigation.

Several investigators (Jaffa et al. 1995; Harvey et al. 1990) have reported alterations in the renal KKS in the diabetic state. Insulin-treated moderately hyperglycemic diabetic rats and patients with diabetes mellitus have been reported to show increased urinary kallikrein and BK excretion (Jaffa et al. 1995). These findings suggest that alterations in the kinin-forming components may be the indicator of vascular disease in type 1 diabetics. The renal hyperfiltration in diabetic rats was reduced after pretreatment with aprotinin, a tissue kallikrein inhibitor, suggesting a role of KKS in diabetic state of increased glomerular hemodynamics. In addition, Vieira et al. (1994) demonstrated the renal conversion of T-kinin (present in the rats) to BK. The conversion of T-kinin, which is the main kinin in inflammation in rats, could be an important alternative pathway for the generation of renal BK in diabetic rats. On the other hand, the metabolism of BK might be impaired and it has to be shown whether changes in the activity of kininases could lead to an increased urinary BK excretion under diabetic conditions. In previous studies, it has been observed the reduction in cardiac and plasma kallikrein and kininogen concentrations in hypertensive and diabetic rats (Sharma et al. 1998). These studies suggested that the development of LVH and high BP in these diabetic rats could be the reflection of hypo-activity of the KKS. These research findings were indeed supported by the fact that the reduced synthesis of the myocardial tissue kallikrein implies a reduced capacity to generate BK in diabetic rats (Jaffa et al. 2003). It can be postulated therefore that alterations in the KKS may contribute to the cardiac dysfunction in diabetes mellitus in human patients. Furthermore, it is suggested that the treatment with the KKS components in diabetic conditions may reverse the myocardial abnormalities observed in diabetic patients. Recently, it has been reported that high plasma prekallikrein activity may serve as a marker for the diabetic hypertensive nephropathy (Jaffa et al. 2003), which may be the marker of vascular disease in diabetic patients. It has been recently pointed out that cardioprotective effects on the KKS in the

diabetic heart suggest that the stimulation of the KKS might open new avenues for the treatment of diabetic cardiopathy due to down regulation of kinins-inactivating enzymes (Spillmann et al. 2006; Koch et al. 2003). Also, BK₂ receptor activation may contribute to the development of diabetic nephropathy (Tan et al. 2005). On the other hand, kallikrein gene delivery improves serum glucose, lipid profile, and cardiac function in experimental diabetic rats (Montanari et al. 2005). Recently, it has been suggested that BK system may be a therapeutic target in preventing and treating diabetic nephropathy (Riad et al. 2007). Also, the suppressed KKS within podocytes under diabetic condition is associated with podocyte apoptosis, suggesting that BK may be beneficial in preventing podocyte loss in diabetic nephropathy (Kwak et al. 2011). Recently, it has been documented that urinary and plasma tissue kallikrein levels were higher in type 2 diabetic patients than in healthy controls (Campbell et al. 2010; Sharma et al. 2013). This has been suggested to cause increased level of glucose in the circulation by blocking the glucose utilization. In addition, Liu and Feener (2013) has proposed that plasma KKS are potential therapeutic targets for diabetic retinopathy (macular edema) and nephropathy (Tomita et al. 2012; Liu and Feener 2013).

2.5 Tissue Kallikrein and Kininase II Inhibitors as Antihypertensive Agents

The kallikrein might have a prime action in the regulation of systemic BP, because administration of tissue kallikrein to hypertensive patients can bring the BP to the normal levels. It has been shown that the pig pancreatic kallikrein therapy lowered the BP significantly and normalized their reduced urinary kallikrein excretion in patients with essential hypertension (Overlack et al. 1980, 1981). These data provide favorable evidence that the presence of subnormal activity of kinin-generating system might be a prominent predisposing cause in the genesis of hypertension. Since the antihypertensive mechanism(s) of pancreatic kallikrein treatment remains unknown, the possibility exists that tissue kallikrein may have independent actions in regulating arterial BP. There is, however, no direct evidence in support of this hypothesis.

Kininase II (ACE) inhibitors such as captopril, enalapril, and teprotide are currently used in the treatment of both clinical and experimental hypertension (Silberbauer et al. 1982; Antonaccio 1982; Sharma et al. 1983b, 1984b; Fernandez et al. 1983a, b; Edery et al. 1981). Kininase II inhibitors might possibly lower BP by inhibiting the biodegradation of kinin as well as inhibiting angiotensin II formation at the renin site. Katz et al. (1980) determine the inter-relationship between the changes in plasma kinin levels and BP reduction during i.v. infusions of BK and reported that increased plasma kinin levels of 1–2 ng/ml caused a significant reduction in BP (nearly 30 mm Hg). The magnitude of the increment in plasma kinin levels was similar to that observed during the administration of kininase II inhibitor (Swartz et al. 1979). Although there are methodological difficulties on the

estimation of plasma kinin concentrations, these findings do suggest that circulating kinin contributes to the antihypertensive effects of kininase II inhibition. Plasma kininogen decrease has been reported in clinical condition after administration of nonsteroidal anti-inflammatory agents (Sharma et al. 1976, 1980; Zeitlin et al. 1976, 1977). It is important to emphasize that inhibition of kininase leading to kinin accumulation may play a major contributing role in the mechanism of hypotensive action of teprotide, kininase II inhibitor, in humans (Edery et al. 1981). Abnormality in the urinary kallikrein excretion has also been corrected after nifedipine, a calcium-channel blocker treatment in patients with essential hypertension (Tsunoda et al. 1986). Whereas Sharma et al. (1984c) demonstrated differential sensitivity of Dhal salt-sensitive (DSS) hypertensive and Dhal salt-resistance (DSR) normotensive rats to the hypotensive action of nifedipine. This might reflect a significantly more important role of diminished renal kallikrein–kinin activity in DSS hypertensive than DSR normotensive rats. Tissue kallikrein is documented to be involved in the cardioprotective effect of AT1-receptor blockade in acute myocardial ischemia in mice (Messadi-Laribi et al. 2007).

2.6 Conclusion

Reduced kinin-forming components might be responsible for the pathophysiology of hypertension. In this regard, it is suggested that the role of renal BK is to excrete the excess sodium. Reduction in the generation of renal BK may be the cause in the development of hypertension as a result of accumulation of sodium in the body. Thus, the development of a compound having renal kallikrein-like activity may serve the purpose of excreting excessive sodium from the kidney in the treatment of hypertension. Transgenic mice over expressing renal tissue kallikrein were hypotensive, and administration of aprotinin, a tissue kallikrein inhibitor, restored the BP of transgenic mice. Recently, it has been proposed that tissue kallikrein gene delivered into various hypertensive models exhibits protection, such as reduction in high BP, attenuation of cardiac hypertrophy, inhibition of renal damage, and stenosis.

Also, abnormalities in the BK system have been documented in diabetes mellitus. It has been suggested that high levels of renal tissue kallikrein and BK may mediate renal hyper-filtration in diabetes. In addition, higher concentration of prekallikrein in plasma may serve as indicator for the development of hypertension and kidney damage.

References

- Abdella N, Arouj M, Al Nakhi A et al (1998) Non-insulin- dependent diabetes in Kuwait: prevalence rates and associated risk factors. *Diabetes Res Clin Pract* 42:187–196
- Adetuyibi A, Mills IH (1972) Relationship between urinary kallikrein and renal function, hypertension, and excretion of sodium and water in man. *Lancet* 2:203–207

- Al-Shoumer KA, Al-Asoosi S et al (2008) Serum leptin and metabolic variables in Arabs with type 2 diabetes. *Ann Saudi Med* 28:367–370
- Almeida FA, Stella RCR, Voos A et al (1981) Malignant hypertension: a syndrome associated with low plasma kininogen and kinin potentiating factor. *Hypertension* 3:II46–II50
- Antonaccio MJ (1982) Angiotensin converting enzyme (ACE) inhibitors. *A Rev Pharmac Tox* 22:57–87
- Azizi M, Emanuelli C, Peyrard S et al (2008) Genetic and dietary control of plasma tissue kallikrein secretion and urinary kinins excretion in man. *J Hypertens* 26(4):714–720
- Bartter FC, Pronove P, Gill JR et al (1962) Hyperplasia of the juxtaglomerular cortex with hyperaldo-steronism and hypokalemic alkalosis. *Am J Med* 33:811–828
- Beilenson S, Schachter M, Smaje LH (1968) Secretion of kallikrein and its role in vasodilation in the submaxillary gland. *J Physiol Lond.* 199:303–317
- Belo AA, Sousa Mde O, Machado EL et al (2009) On human tissue kallikrein activity in urine of Brazilian white and black primary hypertensive patients. *Ethn Dis* 19(3):265–270
- Bhoola KD, Mordy J, Schachter M et al (1965) Vasodilatation in the submaxillary gland of the cat. *J Physiol Lond* 179:172–184
- Bunting S, Gryglewski R, Moncada S et al (1976) Arterial walls generation from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strip of mesenteric and coeliac artery and inhibits plate aggregation. *Prostaglandins* 12:897–913
- Campbell DJ, Kladis A, Zhang Y (2010) Increase tissue kallikrein levels in type 2 diabetes. *Diabetologia* 53:779–785
- Carretero OA, Amin VM, Ocholik T et al (1978) Urinary kallikrein in rats bred for their susceptibility and resistance to the hypertensive effect of salt. A new radio-immunoassay for its direct determination. *Circ Res* 42:727–731
- Carretero OA, Scicli AG (1981) Possible role of kinins in circulatory homeostasis: state of the art review. *Hypertension* 3:366–369
- Carretero OA, Oza NB, Schork A (1974) Renal tissue kallikrein, plasma renin, and plasma aldosterone in renal hypertension. *Acta physiol Lat Am* 24:448–452
- Carvounis CP, Carvounis G, Arbveit LA (1981) Role of the endogenous kallikrein-kinin system modulating vassopressin-stimulated water flow and urea permeability in the toad urinary bladder. *J Clin Invest* 67:1792–1796
- Chao J, Chao L (2005) Kallikrein-kinin in stroke, cardiovascular and renal disease. *Exp Physiol* 90(3):291–298
- Chao J, Bledsoe G, Yin H et al (2006) The tissue kallikrein-kinin system protects against cardiovascular and renal diseases and ischemic stroke independently of blood pressure reduction. *Biol Chem* 387(6):665–675
- Chao J, Zhang JJ, Lin KF et al (1998) Human kallikrein gene delivery attenuates hypertension, cardiac hypertrophy, and renal injury in Dahl salt-sensitive rats. *Hum Gene Ther* 9(1):21–31
- Christiansen SC, Proud D, Cochrane CG (1987) Detection of tissue kallikrein in the bronchoalveolar lavage fluid of asthmatic subjects. *J Clin Invest* 79:188–197
- Cochrane CG, Revak SD, Wuepper KD (1973) Activation of Hageman factor in solid liquid phases. A critical role of kallikrein. *J Exp Med* 138:1564–1583
- Colina-Chourio J, McGiff JC, Miller MP et al (1976) Possible influence of intrarenal generation of kinins on prostaglandin release from the rabbit perfused kidney. *Br J Pharmac* 58:165–172
- Colman RW, Bagdasarian A, Talamo RC et al (1975) Williams trait: human kininogen deficiency with diminished levels of plasminogen pro activator and pre-kallikrein associated with abnormalities of the Hageman factor-dependent pathways. *J Clin Invest* 56:1650–1662
- Croxatto HR, Martin M (1970) Kallikrein-like activity in the urine of renal hypertensive rats. *Experientia* 26:1261–1271
- Damas J, Bourdon V (1974) Liberation d'acide arachidonique par la bradykinine. *C R Seances Soc Biol Fil* 168:1445–1448
- De Freitas FM, Farraco EZ, De Azevedo DF (1964) General circulatory alterations induced by intravenous infusion of synthetic bradykinin in man. *Circulation* 29:66–70

- Derkx FHM, Tan-Tjong HL, Manint Veld AJ et al (1979) Activation of inactive plasma reinin by tissue kallikreins. *J Clin Endocrinol Metab* 49:765–769
- Ederly H, Rosenthal T, Amitzur G et al (1981) The influence of SQ 20881 on the blood kinin system of renal hypertensive patients. *Drugs Exptl Clin Res* VII:749–756
- Elliot AH, Nuzum FR (1934) Urinary excretion of a depressor substance (kallikrein of Frey and Kraut) in arterial hypertension. *Endocrinology* 18:462–474
- Erdos EG, Sloane EM (1962) An enzyme in human plasma that inactivated bradykinin and kallidin. *Biochem Pharmacol* 11:585–592
- Erdos EG, Skidgel RA (1985) Structure and functions of human angiotensin I converting enzyme (kininase II). *Biochem Soc Trans* 13:42–44
- Erdos EG, Yang HYT (1966) Inactivation and potentiation of the effects of bradykinin. In: Erdos EG, Back N, Sicuteri F (eds) *Hypotensive peptides*. Springer, Berlin, pp 235–250
- Erdos EG, Yang HYT (1967) An enzyme in microsomal fraction of kidney that inactivates bradykinin. *Life Sci* 6:569–574
- Erdos EG, Yang HYT, Tague LL et al (1967) Carboxypeptidase in blood and other fluids III. The esterase activity of the enzyme. *Biochem Pharmacol* 16:1287–1297
- Farag NH, Mahata M, Ziegler MG et al (2003) Hormone replacement therapy increases renal kallikrein excretion in healthy postmenopausal women. *Life Sci* 72(11):1279–1288
- Fejes-Toth AN, Fejes-Toth G (1986) Urinary kinin excretion following alterations of vasopressin levels in man and rat. *Renal Physiol* 9:302–307
- Fejes-Toth G, Magyar A, Walter J (1977) Renal response to vasopressin after inhibition of prostaglandin synthesis. *Am J Physiol* 232:F416–F423
- Fejes-Toth G, Zahajszky T, Filep J (1982) Effect of vasopressin on the renal kallikrein-kinin system. *Agents Actions (Suppl)* 9:491–495
- Fernandez PG, Sharma JN, Kim BK et al (1983a) Left ventricular regression and blood pressure control of Dahl (D) rat with MK-42 1 (an angiotensin I converting enzyme inhibitor, CEI) and hydrochlorothiazide (HTZ). *Clin Res* 31:332A (Abst)
- Fernandez PG, Kim BK, Sharma JN et al (1983b) Left ventricular regression (LVR) in association with blood pressure control in the Dahl model of hypertensive that (DS and DR) treated with enalapril maleate (MK-42 1, an angiotensin converting enzyme inhibitor) or hydrochlorothiazide (HTZ). *Clin Invest Med* 6(Suppl 2):55 (Abst.)
- Ferreira SH, Moncada S, Vane JR (1971) Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nature* 231:237–239
- Fiedler F (1979) Enzymology of glandular kallikreins. In: Erdos EG (ed) *Handbook of experimental pharmacology*. Springer, Berlin, pp 103–161
- Fiedler F, Muller C, Warle E (1970) Purification of prekallikrein B from pig pancreas with p-nitrophenyl-pguanidinobenzoate. *FEBS Lett* 24:41–44
- Fink E, Geiger R, Witte J et al (1980) Biochemical, pharmacological, and functional aspects of glandular kallikreins. In: Gross F, Vogel G (eds) *Enzyme release of vasoactive peptides*. Raven Press, New York, pp 101–115
- Frey EK (1926) Zusammenhänge zwischen Herzarbeit und Nierentätigkeit. *Langenbecks Arch klin Chir.* 142:663–669
- Furtado MRF (1981) Inhibition of the permeability response to vasopressin and oxytocin in the toad bladder effects of bradykinin, kallidin, eleodoisin and physalaemin. *J Membr Biol* 4:165–168
- Gainer JV, Brown NJ, Bachvarova M et al (2000) Altered frequency of a promoter polymorphism of the kinin B₂ receptor gene in hypertensive African-Americans. *Am J Hypertens* 13:1268–1273
- Gill JR, Frolich JC, Bowden RE et al (1976) Bartter's Syndrome: a disorder characterized by high urinary prostaglandins and a dependence of hyperreninemia on prostaglandin synthesis. *Am J Med* 61:43–51
- Gryglewski RJ, Bunting S, Moncada S (1976) Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins* 12:685–714

- Halushka PV, Wohltman H, Privitero PJ et al (1977) Bartter's syndrome: urinary prostaglandin E-like material and kallikrein; indomethacin effects. *Ann Intern Med* 87:281–286
- Harvey JN, Jaffa AA, Margolius HS et al (1990) Renal kallikrein and the hemodynamic abnormalities of the diabetic kidney. *Diabetes* 39:299–304
- Hathaway WE, Alsever J (1970) The relation of "Fletcher factor" to factors XI and XII. *Br J Haemat* 18:161–169
- Hilme E, Herlitz H, Gyzander E, Hansson L (1992) Urinary kallikrein excretion is low in malignant essential hypertension. *J Hypertens* 10(8):869–874
- Hiwada K, Matsumoto C, Kokubu T (1983) Role of glandular kallikrein in the activation process of human plasma inactive renin. *Hypertension* 5:191–197
- Holland B, Chud JM, Braunstein H (1980) Urinary kallikrein excretion in essential and mineralocorticoid hypertension. *J Clin Invest* 65:347–356
- Hong SL, Levine L (1976) Stimulation of prostaglandin synthesis by bradykinin and thrombin and their mechanisms of action on MC5-5 fibroblasts. *J Biol Chem* 251:5814–5816
- Jacobsen S (1966) Substrate for plasma kinin-forming enzymes in human, dog and rabbit plasma. *Br J Pharmacol* 26:403–411
- Jaffa AA, Durazo-Arvizu R, Zheng D et al (2003) Plasma prekallikrein: a risk marker for hypertension and nephropathy in type 1 diabetes. *Diabetes* 52:1215–1221
- Jaffa AA, Rust PF, Mayfield RK (1995) Kinin, a mediator of diabetes induced glomerular hyperfiltration. *Diabetes* 44:156–160
- James FW, Donaldson VH (1981) Decreased exercise tolerance and hypertension in severe hereditary deficiency of plasma kininogens. *Lancet* 1:889
- Kailasam MT, Martinez JA, Cervenka JH et al (1998) Racial differences in renal kallikrein excretion: Effect of the ovulatory cycle. *Kidney Int* 54:1652–1658
- Kaplan AP, Austen KF (1971) A prealbumin activator of prekallikrein II. Derivation of activators of prekallikrein from active Hageman factor by digestion with plasmin. *J Exp Med* 133:696–712
- Kaplan AP, Silverberg M, Dunn JT et al (1981) Mechanisms for Hageman factor activation and role of HMW kininogen as a coagulation cofactor. *Ann NY Acad Sci* 370:253–260
- Kaplan AP, Meiler HL, Yecies D et al (1977) Hageman factor and its substrates: the role of factor XI, prekallikrein, and plasminogen proactivator in coagulation, fibrinolysis and kinin generation. In: Pisano JJ, Austen KF (eds) *Chemistry and biology of the kallikrein-kinin system in health and disease*. US Government Printing Office, Washington, pp 237–254
- Karlberg BE, Wichman K (1984) Hypertension in pregnancy. Prostaglandins, kinins and kallikrein. *Scand J Clin Lab Invest Suppl* 169:39–47
- Katori M, Majima M (2006) A missing link between a high salt intake and blood pressure increase. *J Pharmacol Sci* 100:370–390
- Katz J, Williams GH, Hollenberg NK (1980) Plasma concentration and the depressor response to bradykinin infusion. *Life Sci* 27:573–576
- Koch M, Wendorf M, Dendorfer A et al (2003) Cardiac kinin level in experimental diabetes mellitus: role of kinases. *Am J Physiol Heart Circ Physiol* 285(1):H418–H423
- Koolen ML, Daha MR, Frolich M et al (1984) Direct and indirect measurement of urinary kallikrein excretion in patients with essential hypertension and normotensives: relation to age and plasma renin and aldosterone levels. *Eur J Clin Invest* 14:171–174
- Komiya M, Kato H, Suzuki T (1974) Structural comparison of high molecular weight and low molecular weight kininogen. *J Biochem Tokyo* 76:833–845
- Kwak S-J, Paeng J, Kim DH et al (2011) Local kallikrein-kinin system is involved in podocyte apoptosis under diabetic condition. *Apoptosis* 16:478–490
- Lacombe MJ, Varet B, Levy JP (1975) A hitherto undescribed plasma factor acting at the contact phase of blood coagulation (Flaujeac factor) case report and coagulation studies. *Blood* 46:761–768
- Lawton WJ, Proud D, French ME et al (1981) Characterization and origin of immunoreactive glandular kallikrein in rat plasma. *Biochem Pharmacol* 30:1731–1737

- Leeb-Lundberg LMF, Marceau F, Muller-Esterl W et al (2005) Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences. *International union of pharmacology. XLV. Pharmacol Rev* 57:27–77
- Lechi A, Covi G, Lechi C et al (1978) Urinary kallikrein excretion and plasma renin activity in patients with essential hypertension and primary aldosteronism. *Clin Sci Molec Med* 55:51–55
- Lechi A, Covi G, Lechi C et al (1976) Urinary kallikrein excretion in Bartter's syndrome. *J Clin Endocr Metab* 43:1175–1178
- Levy SB, Lilley JJ, Frigon RP (1977) Urinary kallikrein and plasma renin activity as determinants of renal blood flow; the influence of race and dietary sodium intake. *J Clin Invest* 60:129–138
- Linz W, Wiemer G, Schölkens BA (1993) Contribution of bradykinin to the cardiovascular effects of ramipril. *J Cardiovasc Pharmacol* 22(Suppl 9):S1–S8
- Liu J, Feener EP (2013) Plasma kallikrein-kinin system and diabetic retinopathy. *Biological Chem* 394:319–328
- Lynch J, Shariat-Madar Z (2012) Physiological effects of plasma kallikrein-kinin system: role of the blood coagulation Factor XII (Hageman Factor). *Clin Toxicol* 2:100–105
- MacFarlane NAA, Mills IH, Wraight EP (1974) Changes in kallikrein excretion during arterial infusion of angiotensin. *J Endocr* 61:72P
- Madeddu P, Emanuele C, El-Dahr S (2007) Mechanisms of disease; tissue kallikrein-kinin system in hypertension and vascular remodeling. *Nat Clin Pract Nephrol* 3:208–221
- Margolius HS, Geller R, deJong W et al (1972) Altered urinary kallikrein excretion in rat with hypertension. *Circ Res* 30:358–362
- Margolius HS, Geller R, Pisano JJ et al (1971) Altered urinary kallikrein excretion in human hypertension. *Lancet* 2:1063–1065
- Margolius HS, Horwitz D, Pisano JJ et al (1974) Urinary kallikrein excretion in hypertensive man: relationships to sodium intake and sodium retaining steroids. *Circ Res* 35:820–825
- Marin-Grez M (1982) Multihormone regulation of renal kallikrein. *Biochem Pharmacol* 31:3941–3947
- Marin-Grez M, Schaechtelin G, Bonner G (1982) Relationship between the renal kallikrein activity and the urinary excretion of kallikrein in rats. *Experientia* 38:941–943
- Messadi-Laribi E, Griol-Chrbili V, Pizard A et al (2007) Tissue kallikrein is involved in the cardioprotective effect of AT1-receptor blockade in acute myocardial ischemia. *J Pharmacol Exp Ther* 323:210–216
- Montanari D, Yin H, Dobrzynski E et al (2005) Kallikrein gene delivery improves serum glucose and lipid profiles and cardiac function in streptozotocin-induced diabetic rats. *Diabetes* 54:1573–1580
- McGiff JC, Terragno NA, Malik KU et al (1972) Release of a prostaglandin E-like substance from canine kidney by bradykinin: comparison with edoisin. *Circ Res* 31:36–43
- McGiff JC, Itskovitz HD, Terragno NA (1975) The action of bradykinin and edoisin in the canine isolated kidney; relationship to prostaglandins. *Clin Sci Molec Med* 49:125–131
- Miller MJS, Westlin WF, McNeill H et al (1986a) Renal prostaglandin efflux induced by vasopressin, dDA VP and arachidonic acid: contrasting profile and sites of release. *Clin Exp Pharmacol Physiol* 13:577–584
- Miller MJS, Carrara MC, Westlin WF et al (1986b) Compartmental prostaglandin release by angiotensin II and arginine-vasopressin in rabbit isolated perfused kidneys. *Eur J Pharmacol* 120:43–50
- Mills IH (1982) The renal kallikrein-kinin system and sodium excretion. *Q J expo Physiol* 67:393–399
- Mills IH (1979) Kallikrein, kininogen and kinin in control of blood pressure. *Nephron* 23:61–71
- Mills IH, MacFarlane NAA, Adetuyibi A (1976) On the role of kallikrein in the renal adaptation to intra-arterial infusion of angiotensin II. *Excerpta Med Int Congr Ser No* 256:586 (Abst.)
- Mitas JA, Levy SB, Holle R et al (1978) Urinary kallikrein activity in the hypertension of renal parenchymal disease. *New Engl J Med*. 299:162–165

- Nagasawa S, Nakayasu T (1975) Enzymatic and chemical cleavages of human kininogens. *Life Sci* 16:791–792
- Nasjletti A, McGiff JC, Colina-Chourio J (1978) Interrelationships of the renal kallikrein-kinin system and renal prostaglandins in the conscious rat. *Circ Res* 43:799–807
- Nustad K, Gautvik K, Orstavik T (1979) Radioimmunoassay of rat submandibular gland kallikrein and the detection of immuno-reactive antigen in blood. In: Fujii S, Moriya H, Suzuki T (eds) *The kinins II, biochemistry, pathophysiology and clinical aspects*. Plenum Press, New York, pp 225–234
- Nustad K, Vaaje K, Pierce JV (1975) Synthesis of kallikrein by rat kidney slices. *Br J Pharmac* 53:229–234
- Olsen UB (1982) Clonidine decreases rat urine kallikrein excretion by α -adrenergic receptor stimulation. *Eur J Pharmac* 79:311–314
- Olsen UB (1980) Changes of urinary kallikrein and kinin excretions induced by adrenalin infusion in conscious dogs. *Scand J Clin Lab Invest* 40:173–178
- Oshima G, Kato J, Erdos EG (1974) Subunits of human plasma carboxypeptidase N (kininase I; anaphylatoxin inactivator). *Biochim Biophys Acta* 365:344–348
- Ostravik TB (1981) The kallikrein-kinin system in exocrine organs. *J Histochem Cytochem* 28:881–889
- Orstavik TB, Gautvik KM (1977) Regulation of salivary kallikrein secretion in the submandibular gland. *Acta Physiol Scand* 100:33–44
- Orstavik TB, Nustad K, Brandtzaeg P et al (1976) Cellular arginine of urinary kallikreins. *J Histochem Cytochem* 24:1037–1039
- Overlack A, Stumpe KO, Ressel C et al (1980) Decreased urinary kallikrein activity and elevated blood pressure normalized by orally applied kallikrein in essential hypertension. *Klin Wsch* 58:37–40
- Overlack A, Stumpe KO, Kollock R et al (1981) Antihypertensive effect of orally administered glandular kallikrein in essential hypertension. *Hypertension* 3:118–121
- Palmer MA, Piper PJ, Vane JR (1973) Release of rabbit aorta contracting substances (RCS) and prostaglandins induced by chemical or mechanical stimulation of guinea pig lungs. *Br J Pharmac* 49:226–242
- Pierce JV, Guimaraes JA (1975) Further characterization of highly purified human plasma kininogen. *Life Sci* 16:790–795
- Potier L, Waecker L, Richer C et al (2013) Tissue kallikrein, blood pressure regulation, and hypertension: insight from genetic kallikrein deficiency. *Biol Chem* 394:329–333
- Prado ES, Carvalho LPD, Araujo-Viel MS et al (1983) A met-enkephalin-containing peptide, BAM 22P, as a novel substrate for glandular kallikreins. *Biochem Biophys Res Commun* 112:366–371
- Rabito SF, Orstavik TB, Scicli AG et al (1983) Role of the autonomic nervous system in the release of rat submandibular gland kallikrein into the circulation. *Circ Res* 52:635–641
- Rabito SF, Scicli AG, Kher V, et al (1979) Glandular kallikrein in plasma and urine: evaluation of a direct RIA for its determination. In: Fujii S, Moriya H, Suzuki T (eds) *The kinins II, biochemistry, pathophysiology and clinical aspects*. Plenum Press, New York, pp 127–142
- Rabito SF, Scicli AG, Kher V et al (1982) Immunoreactive glandular kallikrein in rat plasma: a radioimmunoassay for its determination. *Am J Physiol* 242:H602–H610
- Regoli D (1984) Neurohumoral regulation of precapillary vessels: the kallikrein-kinin system. *J Cardiovasc Pharmacol* 6(suppl. 3):S401–S412
- Riad A, Zhuo JL, Schultheiss HP et al (2007) The role of the renal kallikrein-kinin system in diabetic nephropathy. *Curr Opin Nephrol Hypertens* 16:22–26
- Saito H, Ratnoff OD, Donaldson VH (1974) Defective activation of clotting, fibrinolytic, and permeability enhancing system in human Fletcher trait plasma. *Circ Res* 34:641–651
- Saito H, Ratnoff OD, Waldmann R et al (1975) Fitzgerald trait. Deficiency of a hitherto unrecognized agent, Fitzgerald factor, participating in surface mediated reactions of clotting, fibrinolysis, generation of kinins, and the property of diluted plasma enhancing vascular permeability (PF/dil). *J Clin Invest* 55:1082–1089

- Schachter M (1980) Kallikrein (kininogenases) a group of serine proteases with biological actions. *Pharmacol Rev* 31:1–17
- Scicli AG, Carretero OA, Hampton A et al (1976) Site of kininogenase secretion in the dog nephron. *Am J Physiol* 230:533–536
- Sealey JE, Atlas SA, Laragh JH et al (1978) Human urinary kallikrein converts inactive to active renin and is a possible physiological activator of renin. *Nature* 275:144–145
- Sharma JN (2009a) Hypertension and the bradykinin system. *Curr Hypertens Rep* 11:178–181
- Sharma JN (2009b) The kallikrein-kinin pathways in mediating the hypotensive action of angiotensin converting enzyme (ACE) inhibitors. In: DeBrue AN (ed) *Angiotensin converting enzyme inhibitors*. Nova Science Publishers, USA, pp 185–198
- Sharma JN (2013) The kinin system in hypertension pathophysiology. *Inflammopharmacol* 21:1–9
- Sharma JN, Al-Shoumer AKS, Matar KM et al (2013) Bradykinin-forming components in Kuwaiti patients with type 2 diabetes. *Int J Immunopathol Pharmacol*. 26:699–705
- Sharma JN, Buchanan WW (1979) Kinin system in clinical and experimental rheumatoid inflammation. *Curro Med Res Optimum* 6:314–321
- Sharma JN, Fernandez PG (1982) Pharmacological abnormality of kallikrein-kinin system in hypertension. *Med Hypoth* 9:379–384
- Sharma JN, Fernandez PG, Triggle CR (1984a) The effect of indomethacin on the duration of the hypotensive action of bradykinin in Dahl salt-resistant rats: role of cyclo-oxygenase inhibition. *Prost Leukotri Med* 14:131–135
- Sharma JN, Fernandez PG, Kim BK et al (1984b) Systolic blood pressure responses to enalapril maleate (MK 421, an angiotensin converting enzyme inhibitor) and hydrochlorothiazide in conscious Dahl salt-sensitive (S) and salt-resistant (R) rats. *Can J Physiol Pharmacol* 62:846–849
- Sharma JN, Fernandez PG, Laher I et al (1984c) Differential sensitivity of Dahl salt-sensitive and salt-resistant rats to the hypotensive action of acute nifedipine administration. *Can J Physiol Pharmacol* 62:241–243
- Sharma JN, Narayanan P (2011) Hypertension and diabetes: contribution of kallikrein-kinin system. *Diabetes Metabolism* S4:1–5
- Sharma JN, Uma K, Yusof APM (1998) Left ventricular hypertrophy and its relation to cardiac kinin-forming system in hypertensive and diabetic rats. *Int J Cardiol* 63:229–235
- Sharma JN, Uma K, Noor AR et al (1996) Blood pressure regulation by the kallikrein-kinin system. *Gen Pharmacol* 27:55–63
- Sharma JN, Zeitlin IJ, Brooks PM et al (1976) A novel relationship between plasma kininogen and rheumatoid disease. *Agents Actions* 6:148–153
- Sharma JN, Zeitlin IJ, Brooks PM et al (1980) The action of aspirin on plasma kininogen and other proteins in rheumatoid patients: relationship to disease activity. *Clin Expo Pharmacol Physiol* 7:347–354
- Sharma JN, Zeitlin IJ (1981) Altered plasma kininogen in clinical hypertension. *Lancet* 1:1259–1260
- Sharma JN, Zeitlin IJ (1982) Reduced plasma kininogen concentrated by prostaglandin E2 in rats. *Eur J Pharmacol* 83:119–121
- Sharma JN, Zeitlin IJ, Deodhar SD et al (1983a) Detection of kallikrein-like activity in inflamed synovial tissue. *Arch into Pharmacodyn Ther* 262:279–286
- Sharma JN, Fernandez PG, Kim BK et al (1983b) Cardiac regression and blood pressure control in the Dahl rat treated with enalapril maleate (MK 421, an angiotensin converting enzyme inhibitor) and hydrochlorothiazide. *J Hypertens* 1:251–256
- Silberbauer K, Stanek B, Temple H (1982) Acute hypotensive effect of captopril in man modified by prostaglandin synthesis inhibition. *Br J Clin Pharmacol* 14:87S–93S
- Slim R, Torremocha F, Moreau T et al (2002) Loss-of-function polymorphism of the human kallikrein gene with reduced urinary kallikrein activity. *J Am Soc Nephrol* 13:968–976
- Spillmann F, Van Linthout S, Schultheiss HP et al (2006) Cardioprotective mechanisms of the kallikrein-kinin system in diabetic cardiopathy. *Curr Opin Nephrol Hypertens* 15:22–29

- Swartz SL, Williams GH, Hollenberg NK et al (1979) Converting enzyme inhibition in essential hypertension: the hypotensive response does not reflect only reduced angiotensin II formation. *Hypertension* 1:106–111
- Tan Y, Wang B, Keum JS, Jaffa AA (2005) Mechanisms through which bradykinin promotes glomerular injury in diabetes. *Am J Physiol Renal Physiol*. 288: F483–F492
- Tomita H, Sanford RB, Smithies O et al (2012) The kallikrein-kinin system in diabetic nephropathy. *Kidney Int* 81:733–744
- Tsunoda K, Abe K, Ornata K et al (1986) Hypotensive and natriuretic effects of nifedipine in essential hypertension. Role of renal kallikrein-kinin-prostaglandin and renin-angiotensin aldosterone systems. *J Clin Hypertens* 2:263–270
- Vane JR, McGriff JC (1975) Possible contributions of endogenous prostaglandins to the control of blood pressure. *Circ Res* 36–37(Suppl 1):163–175
- Vieira MAR, Moreira FM, Maack T (1994) Conversion of T-kinin to bradykinin by the rat kidney. *Biochem Pharmacol* 47:1693–1699
- Vinci JM, Telles DA, Bowden RW et al (1976) The kallikrein-kinin system (KKS) in Bartter's syndrome (BS) and its response to prostaglandin synthesis inhibition (PGI). *Clin Res* 24:414A
- Vogel R (1979) Kallikrein inhibitors. In: Erdos G (ed) *Handbook of experimental pharmacology*. Springer, Berlin, Heidelberg, New York, pp 163–225
- Webster ME, Gilmore JP (1964) Influence of kallidin-10 on renal function. *Am J Physiol* 206:714–718
- Willis LR, Luden JH, Hook JB et al (1969) Mechanism of natriuretic action of bradykinin. *Am J Physiol* 217:1–5
- Wuepper KD, Miller KR, Lacombe MJ (1975) Flaujeac trait deficiency of human plasma kininogen. *J Clin Invest* 56:1663–1672
- Wuepper KD (1973) Prekallikrein deficiency in man. *J Exp Med* 138:1345–1355
- Yang HYT, Erdos EG (1967) Second kininase in human blood plasma. *Nature* 215:1402–1403
- Yayami M, Kunimatsu N, Teranishi Y et al (2003) Tissue kallikrein is synthesized and secreted by human vascular endothelial cells. *Biochim Biophys Acta* 1593:231–238
- Yokosawa N, Takahashi N, Inagami T et al (1979) Isolation of completely inactive plasma prorenin and its activation by kallikreins. *Biochim Biophys Acta* 569:211–215
- Zeitlin IJ (1972) Rat intestinal kallikrein. *Adv Exp Med Biol* 21:289–296
- Zeitlin IJ, Sharma JN, Brooks PM et al (1976) Raised plasma kininogen levels in rheumatoid arthritis-response to therapy with non-steroidal anti-inflammatory drugs. *Adv Exp Med Biol* 70:335–343
- Zeitlin IJ, Sharma JN, Brooks PM, et al (1977) An effect of indomethacin on raised plasma kininogen levels in rheumatoid patients. In: Pisano JJ, Austen KF (eds) *Chemistry and biology of the kallikrein-kinin system in health and disease*. US Government Printing Office, Washington, pp 483–486
- Zinner SH, Margolius HS, Rosner B et al (1976) Familial aggregation of urinary kallikrein concentration in childhood. *Am J Epidemiol* 104:124–132
- Zusman RM, Keiser HR (1977) Prostaglandin E2 biosynthesis by rabbit renomedullary interstitial cells in tissue culture. Mechanism of stimulation by angiotensin II, bradykinin, and arginine vasopressin. *J Clin Invest* 60:215–233

Recent Developments in the Regulation of Kinins

Sharma, J.N. (Ed.)

2014, IX, 198 p. 17 illus., 7 illus. in color., Hardcover

ISBN: 978-3-319-06682-0