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An Overview on Relation between the Bradykinin System and Hypertension and Diabetes

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Summary

It is proposed here that a deficiency of BK might be a significant factor in the pathophysiology of hypertension and diabetes. In this regard, it is suggested that the role of renal BK is to excrete the excess sodium. Therefore, a reduction in the generation of renal BK may be the cause for the development of hypertension as a result of the 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 that administration of aprotinin, a tissue kallikrein inhibitor, restored the BP of the transgenic mice. Recently, it has been proposed that tissue kallikrein gene delivery into various hypertensive models exhibits protection, such as reduction in high blood pressure, attenuation of cardiac hypertrophy, inhibition of renal damage and stenosis. This may indicate the future therapeutic aspect of kallikrein gene therapy for hypertension, cardiovascular and renal pathology.

Keywords: bradykinin system; diabetes; hypertension; overview.

Introduction

Cardiovascular diseases are the most common cause of mortality worldwide. Hypertension and diabetes are the two major risk factors in the development of cardiac hypertrophy, ischemic heart disease and cardiac failure. Previous studies have indicated altered activities of the bradykinin (BK)-generating components in hypertension and diabetes [1]. Bradykinin is a pharmacologically active polypeptide that can promote both cardiovascular and renal function, for example,

vasodilation, natriuresis, diuresis and release of nitric oxide (NO) [2, 3]. In addition, B2 kinin receptors are present in the cardiac endothelial cells which may enhance the biosynthesis and release of NO. Sharma and Uma [4] demonstrated that reduced tissue kallikrein levels may be associated with the development of high blood pressure in spontaneously hypertensive and diabetic rats (SHR). The BK may produce their pharmacological effects via NO and cyclic GMP release [5].

Furthermore, it has been established that the kinin has cardioprotective action in myocardial ischemia and can prevent left ventricular hypertrophy [3]. Also, transgenic mice carrying tissue kallikrein gene and over expressing tissue kallikrein had reduced blood pressure [6]. NO synthase and renal tissue kallikrein are both involved in blood pressure regulation [7,8]

The bradykinin system

Bradykinin (BK) is one of kinins, a pharmacologically active polypeptide, which is released in the tissues and body fluids as a result of enzymatic action of kallikreins on kininogens. The kinins are the BK (Arg-Pro-Pro-gly-Phe-Ser-Pro-Phe-Arg), Kallidin (Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and methionyl-lysyl-BK (Met-Lys-Arg-Pro-Pro-Gly-Phe-Arg). Kallidin and methionyl-lysyl-BK are converted into BK by aminopeptidases present in plasma and urine. BK is rapidly (< 15 sec) inactivated by circulating kinases (Sharma 2006). Once BK is released in the blood and body fluids, it may act on two BK receptors known as B1 and B2.

Kininogens are multifunctional proteins derived mainly from alpha- 2 globulin. In humans the two forms of kininogens are high molecular weight kininogen (HMWK) and low molecular weight kininogen (LMWK). These kininogens vary from each other in molecular weight, susceptibility to plasma and tissue kallikreins and in their physiological properties [1]. They are synthesized in the liver and circulate in the plasma and other body fluids.

There are two forms of kallikreins known as tissue kallikrein and plasma kallikrein. Tissue kallikrein is found in various organs such as the kidney, heart and synovial tissue. The tissue kallikrein is synthesized in the cell as a precursor and converted into the active form by the cleavage of an amino terminal peptide [9]. Active tissue kallikrein acts on LMWK to release kallidin. Tissue and plasma kallikreins differ from one another in molecular weight, biological functions, physicochemical and immunological properties. The plasma kallikrein is present in circulation in an inactive form, which is known as prekallikrein or Fletcher factor. This inactive prekallikrein is converted to active kallikrein by activated Hageman factor (XIIa). In addition, plasma kallikrein is able to convert inactive factor XII to XIIa by positive feedback reaction [9]. The plasma prekallikrein and HMWK are present together in a complex form. Factor XIIa and factor XI circulate with HMWK in bound form. In this way, factor XI can be converted into XIIa for the participation in the intrinsic coagulation cascade. In immunological reactions, the tissue proteoglycan and mast cell heparin might act as an initiating surface for initial activation of the Hageman factor [10]. It seems that the kinins may be generated in parallel with the formation of thrombin at inflammatory sites, since inactive plasma kallikrein can be activated by coagulant Hageman factor. The tissue kallikrein multigene family comprises closely related cluster of genes that vary in number between the different mammalian species: 24 genes have been identified in the mouse, 20 in the rat, 3 in humans and 3 in the hamster [11,1].

Several restriction fragment length polymorphisms (RFLP) have been mapped in tissue kallikrein gene and their regulatory regions in SHR[12]. These findings may reflect a possible difference in the tissue kallikrein gene locus between SHR and normotensive Wistar-Kyoto rats (WKYR). A tissue kallikrein RFLP has been indicated to co segregate with high blood pressure (BP) in the F2 offspring of SHR and normotensive Brown Norway rat crosses [11]. This finding strongly suggests a possibility of a close linkage between the kallikrein gene locus and the hypertensive phenotype of SHR.

The kininases, kinin inactivating enzymes, are present in the plasma, endothelial cells and in the tissues to regulate the physiological functions

of the kinins in the body. These are known as kininase I, kininase II or angiotensin converting enzyme (ACE) and encephalinase. In plasma, kininase I cleaves the C-terminal argentine of BK to form des-Arg9-BK. Kininase II causes inactivation of BK by releasing pentapeptide (Arg-Pro-Pro-gly-Pheo and tripeptide (Ser-Pro-Phe) fragments. Figure 1 shows the formation of BK.

Interaction between the kinins and their specific receptors can lead to activation of several second messenger systems. The BK receptor stimulation of the intact cells or in tissues appears to initiate the second messenger pathways, such as the arachidonic acid products and the activation of calcium sensitive systems [13]. The elevation of cellular inositol phosphates by BK involves G-protein coupled activation of phospholipase A2 and C that are used in the synthesis of eicosanoids [14]. It is of interest that indomethacin, a cyclooxygenase inhibitor, was able to cause potentiation of BK-induced contractions in guinea pig tracheal smooth muscle preparations [15]. These findings may suggest that there could be non-eicosanoid pathways for the cellular and molecular actions of BK. Furthermore, it is known that BK significantly stimulates phosphoinositide hydrolysis in guinea pig ileum longitudinal muscle that may result in elevation of cytosolic calcium ion levels to induce contractile responses. Schini et al. [16] demonstrated that the B2 receptor stimulation causes production of cyclic GMP in cultured porcine aortic endothelial cells. The formation of cyclic GMP may be an important step for the biological actions as well as release of NO evoked by BK in the endothelial cells and in the vascular smooth muscles.

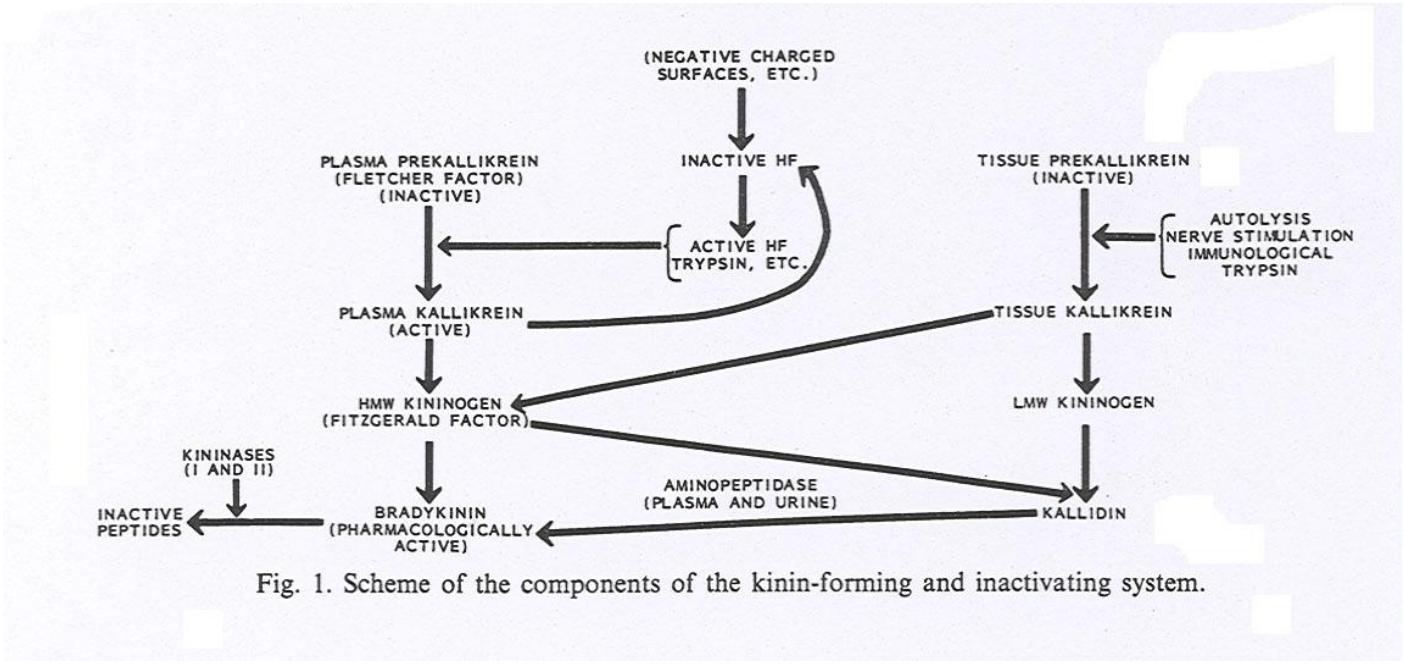

Fig. 1. Scheme of the components of the kinin-forming and inactivating system.

Hypertension and the kinin system

Hypertension is a major risk factor in the development of cardiovascular diseases, such as coronary heart disease, congestive heart failure and peripheral vascular & renal diseases. There is ample evidence documenting the role of BK in the pathogenesis of hypertension [17, 2]. 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 [18]. The role of KKS in hypertension was established by Margolius and co-investigators [19-21] 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. 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 [22, 23]. 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 [24]. It is proposed here 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 sodium. Therefore, a reduction in the generation of renal BK may be the cause of the development of hypertension as a result of the accumulation of sodium in the body [2]. 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. Also it has been demonstrated that transgenic mice over-expressing renal tissue kallikrein were hypotensive and that administration of aprotinin, a tissue kallikrein inhibitor, restored the BP of the transgenic mice [6]. We have shown the suppression of hypotensive responses of ACEIs by aprotinin in SHR [25]. 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 [26-29]. This may indicate the future therapeutics aspect of kallikrein gene therapy for cardiovascular and renal pathology.

ACEIs are currently used in the treatment of both clinical and experimental hypertension [30,31]. Kininase II inhibitors could lower BP by inhibiting the biodegradation of kinin as well as blocking the formation of angiotensin II (AgII). A calcium-channel blocker, nifedipine, used in treatment of patients with essential hypertension can normalize the reduced urinary kallikrein excretion [32]. Smith et al. [33] have suggested that women with reduced activity of the renal BK may be at increased risk of developing pregnancy-induced hypertension. Previous study has demonstrated that urinary kallikrein excretion was found to be diminished in family members at risk for hereditary hypertension and that urinary kallikrein may be one of the major genetic markers associated with family history of hypertension [34].

Left ventricular hypertrophy 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 [35, 36]. This anti-hypertrophic effect of BK was abolished by the B_2 receptor antagonist treatment as well as by NO 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 [37, 38]. 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 system 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.

It is the generally accepted view that the BK-induced BP lowering effect is mediated by the B_2 receptor, but B_1 might also be involved under special situations [39]. It has been demonstrated that a B_2 receptor antagonist (B5630) can generally abolish the hypotensive effects of BK as well as captopril, an ACEI [40]. This led to the proposal that the hypotensive action of ACE inhibitors might be due to the activation of B_2 receptor The accumulation of BK after treatment with ACEIs with subsequent release of NO, PGs and PGI_2 could account for additional mediators released in the process of anti-hypertensive action of these drugs in hypertensive patients.

Diabetes and the kinin system

Several investigators [41-45] have reported alterations of 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 [42]. These findings suggest that alterations in the kinin-forming components may be the indicator of vascular disease in type 1 diabetics. The renal hyper filtration 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 [46]. In addition, Vieira et al. [47] 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 our earlier studies, we observed the reduction in cardiac and plasma kallikrein and kininogen concentrations in hypertensive and diabetic rats [37]. These studies suggested that the development of left ventricular hypertrophy (LVH) and high blood pressure 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 [48,43,49]. It can be postulated therefore that alterations of 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 [43], which may be the marker of vascular disease in diabetic patients. It has been recently pointed out that cardioprotective effects of 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 [50,10,51]. Also, BK 2 receptor activation may contribute to the development of diabetic nephropathy [52]. On the other hand, kallikrein gene delivery improves serum glucose and lipid profile and cardiac function in experimental diabetics [53]. Recently, it has been suggested that BK system may be a therapeutic target for preventing and treating diabetic nephropathy [54].

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