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Is There a Place for Bradykinin Agonists in Therapy of Cardioscaular Disorders?*

Jagdish N. Sharma

Department of Applied Therapeutics, Faculty of Pharmacy,
Center of Health Sciences, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

Abstract: Kinin is a vasoactive polypeptide known to be involved in many physiological and pathological states. An abnormality in the kinin-forming system in cardiovascular disorders has been widely suggested. It is possible that the these abnormalities can be corrected with the administration of the Bradykinin (BK) agonists and tissue kallikrein. Previous investigations have demonstrated that BK components might have cardioprotective effects in various cardiovascular related pathologies. This review briefly may provide evidence in this regard.

Key words: Congestive heart failure, bradykinin agonists, kallikrein, hypertension, cardiac hypertrophy, diabetes

Introduction

Several BK researchers have directed their investigations on the potential role of BK as endogenous paracrine (local) hormone in the treatment of cardiovascular diseases. This is mainly because of the facts all the BK-forming pathways are found to be located in the heart and vascular smooth muscle, which may improve the local blood and nutrients supply to the heart. In addition, the cardioprotective properties of the ACEIs treatment is mediated and modulated by BK release. In recent years, numerous BK agonists are being synthesized with the attempt for observe their potential therapeutic status in the treatment of cardiac diseases. However, BK is a powerful inflammatory mediator, therefore, the BK agonists therapy may have narrow window of safety. This may require extensive experimental and clinical evaluations. The present reseacher was intended to summarize in brief the role of BK in cardiovascular abnormalities and possible application of BK agonists and related compounds in the therapy of cardiac dysfunctions.

The Kallikrein-kinin System

The BK is pharmacologically active polypeptide, which is released in the tissues and body fluids as a result of the enzymatic action of kallikreins on kininogens. The kinins include 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. Kinins are rapidly (<15 sec) inactivated by circulating kininases (Sharma, 1992; Sharma and Buchanan, 1994). 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).

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These kininogens vary from each other in molecular weight, susceptibility to plasma and tissue kallikreins and in their physiological properties (Muller-Esterl *et al.*, 1986). They are synthesized in the liver and circulate in the plasma and other body fluids. Tissue kallikrein is found in various organs such as the kidney, heart and synovial tissue (Sharma, 1993). These kallikreins differ from one another in molecular weight, biological function, physicochemical and immunological properties. The tissue kallikrein is synthesized in the cells as a precursor and converted into active form by the cleavage of an amino terminal peptide (Takada *et al.*, 1985). Active tissue kallikrein acts on LMWK to release kallidin. The plasma kallikrein is found 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. 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 XIa for the participation in the intrinsic coagulation cascade. In immunological reactions, the tissue proteoglycone and mast cell heparin might act as an initiating surface for initial activation of the Hageman factor. 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 a 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.

Several Restriction Fragment Length Polymorphisms (RFLP) have been mapped in tissue kallikrein gene and their regulatory regions in Spontaneously Hypertensive Rats (SHR) (Woolly-Miller *et al.*, 1989). 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 cosegregate with high blood pressure (BP) in the F2 offspring of SHR and normotensive Brown Norway rats crosses (Pravenc *et al.*, 1991). This finding strongly suggests a possibility 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 enkephalinase. In plasma, kininase I cleaves the C-terminal arginine of BK to form des-Arg⁹-BK. Kininase II causes inactivation of BK by releasing pentapeptide (Arg-Pro-Pro-Gly-Phe⁰ and tripeptide (Ser-Pro-Phe) fragments. Figure 1 shows the BK-forming pathways.

The Mechanism of Bradykinin Action

Interaction between the kinins and their specific receptors can lead to activation of several second-messenger systems. The BK receptor stimulation in the intact cells or in tissues appears to initiate the second-messenger pathways, such as arachidonic acid products and the activation of calcium-sensitive systems (Farmer and Burch, 1992). 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 (Burch, 1990). It is of interest that indomethacin, a cyclooxygenase inhibitor, was able to cause potentiation of BK-induced contractions guinea-pig tracheal smooth muscle preparations Akbar *et al.*, 1998). 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.* (1990) demonstrated that the B₂ receptor stimulation causes production of cyclic guanosine monophosphate (cyclic GMP) in

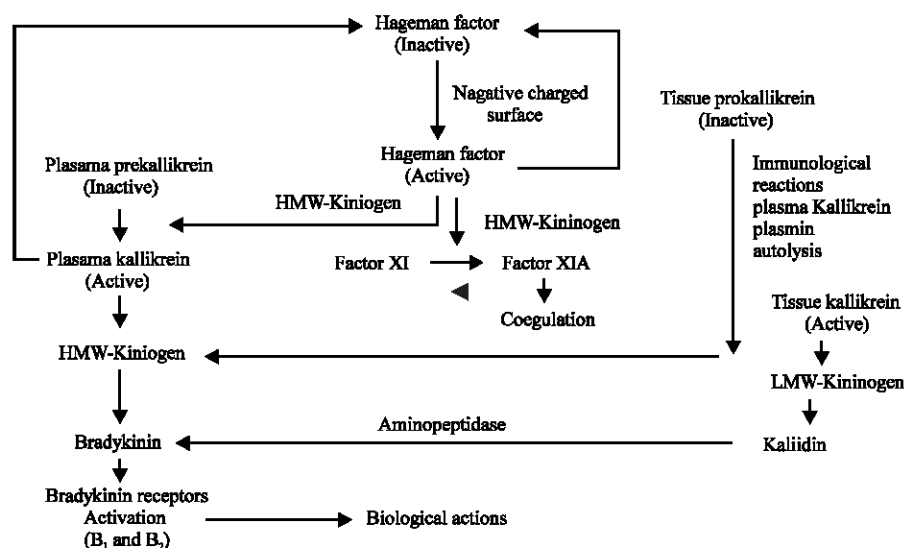


Fig. 1: The mode of bradykinin formation and its inactivations

cultured porcine aortic endothelial cells. The formation of cyclic GMP may be an important step for the biological actions as well as release of nitric oxide evoked by BK in the endothelial cells and in the vascular smooth muscle.

The Bradykinin System in Cardioprotection

The components of the BK system are localized in the vascular smooth muscle, heart and kidney to regulate the cardiovascular physiological homeostasis. BK exerts its pharmacological effects by activating G protein-coupled BK-1 and BK-2 receptors.

Interaction between the kinins and their specific receptors can lead to activation of several second-messenger systems. The BK receptors stimulation in the intact cells or in tissues appear to initiate the second-messenger pathways, such as arachidonic acid products and the activation of calcium-sensitive systems. 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. It is of interest that indomethacin, a cyclooxygenase inhibitor, was able to cause potentiation of BK-induced contractions of both isolated oestrous rat uterus and guinea pig tracheal smooth muscle preparations. These findings may suggest that there could be non-eicosanoid pathways for the cellular and molecular actions of BK (Sharma *et al.*, 2000). 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. It has been demonstrated that the B2 receptor stimulation causes production of cyclic guanosine monophosphate (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 Nitric Oxide (NO) evoked by BK in the endothelial cells and in the vascular smooth muscles (Sharma and Sharma, 2002; Sharma, 2003). The kinin system is known to have a prime role in the regulation of systemic blood pressure. BK is able to produce vasodilatation, diuresis, natriuresis and reduction in the total vascular peripheral resistance. There is ample evidence documenting the reduced activities of kinin system in the genesis of hypertension. Hypertension is a

major risk factor for 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 kinins in pathogenesis of hypertension. The pharmacological action of BK in the regulation of systemic BP was vasodilatation in most areas of the circulation, a reduction of total peripheral vascular resistance and a regulation of sodium excretion from the kidney. When BK is injected into the renal artery, it causes diuresis and natriuresis by increasing renal blood flow. These actions of BK have been attributed to prostaglandin release in the renal circulation. The role kinin system in hypertension was established by Morgolius *et al.* (1972). These investigators 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 defect in kinin generation in hypertensive situations. Research on the systemic changes in the kinins has provided further insight regarding the mechanisms of various hypertensive conditions. In this connection, it is known that kininogen levels and a kinin-potentiating factor are reduced in essential and malignant hypertension. It may be possible that the deficiency in plasma high molecular weight kininogen is due to decrease in liver synthesis in individuals who develop hypertension after mild exercise. It can be proposed that a deficient kinin system might be a significant factor in the pathophysiology of hypertension. In this connection, it is suggested that the role of renal kinin system is to excrete excess of sodium. Therefore, a reduction in the generation of renal kinin system may be the cause of the development of hypertension as a result of sodium accumulation 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. This action may be useful for the treatment of hypertension. Also, it has been demonstrated that transgenic mice over-expressing renal tissue kallikrein were hypotensive and that the administration of aprotinin, a tissue kallikrein inhibitor, restored the BP in the transgenic mice. It is known that the hypertension may lead to coronary heart disease, congestive heart failure, left ventricular hypertrophy and renal diseases. The suppression of the hypotensive responses of ACE inhibitors by a tissue kallikrein inhibitor (aprotinin) in hypertensive rats supports the view that tissue kallikrein may have a role in the regulation of BP (Sharma *et al.*, 1995). In this regard, it has been proposed that tissue kallikrein gene delivery into various hypertensive models exhibits protection against high BP, cardiac hypertrophy and renal damage (Chao and Chao, 1998). Furthermore, coronary artery ligation is known to result in cardiac ischaemia-induced arrhythmia in experimental animals. We have demonstrated that BK and tissue kallikrein administration can significantly increase the survival time of hypertensive rats and this effect was abolished in presence of their respective antagonists (Sharma *et al.*, 2003; 2004). Cardiac failure and ischaemia are the leading cause of death in the developed and many developing countries. These conditions are considered as the new emerging epidemic of the third millennium. The role of kinins in the heart did not receive much attention, despite the fact that it was shown earlier (Lochner and Parratt, 1966) that local and systemic administration of BK could increase coronary blood flow and improve myocardial metabolism. It is well known that ACE inhibitors limit ventricular dilatation, delays the progression of clinical symptom and improve mortality rate. This beneficial action appears to be related to the reduced formation of Ang II, which results in a decreased growth response and attenuated pressure load. In addition, the ability of ACEIs to prevent kinins from enzymatic breakdown represents a relevant mechanism contributing to cardioprotection. This concept fueled a series of studies demonstrating the presence of a local kinin system in the heart. The bindings of kinin to endothelial B2 receptors leads to the release of NO and PGI₂, exerting vasodilatation, anti-ischaemic, anti-proliferative effects and preserving myocardial stores of energy-rich phosphates and glycogen (Zhu *et al.*, 1995). Kinins contribute to the maintenance of

cardiovascular homeostasis by opposing the vasoconstrictor activity of Ang II. Circumstantial evidence also suggests that a dysfunctional kinin system may contribute to the pathogenesis of heart failure. In fact, reduced local BK generation and blunted NO formation have been reported in micro vessels of failing human hearts (Kichuck *et al.*, 1996). Furthermore, in dogs with pacing-induced congestive heart failure, selective blockade of B2 receptors by Hoe 140 reduces coronary blood flow and contractility and increases left ventricular end diastolic pressure. Thus, the reduced activity of the cardiac kinins may facilitate the development of cardiac failure. On the other hand, kinins are continuously released during cardiac hypoxia and ischaemia. They act as cardioprotective agents in perfusion and participate in the process of ischaemic preconditioning. There is evidence to suggest that BK infusion into coronary artery reduces significantly the severity of ischaemia-induced arrhythmia in anaesthetized dogs (Koide *et al.*, 1993). Studies undertaken in rats, dogs and humans revealed that kinins are released under the conditions of ischaemia and myocardial infarction. This process may be indicator of the role of kinin in protecting the heart at the time of myocardial infarction. This raised local kinin release might be able to exert a protective effect on the heart by activating signal transduction pathways generating NO and PGI₂. Coronary artery ligation for shorter and longer duration in hypertensive and normotensive rats showed that administration of BK could increase the survival time of these rats. This effect of BK was reverted by pretreatment with a specific B2 receptor antagonist. These results support the hypothesis that BK might be regarded as prime mediator in protecting the heart in ischaemic conditions. However, extensive investigations on the molecular biology and gene mapping of kinin in the heart during health and cardiovascular diseases can provide many questions be answered regarding the significance of kinins in cardiovascular pathophysiology. This may allow us to develop kinins based therapeutics for the cardiovascular diseases. BK is able to prevent the development of Left Ventricular Hypertrophy (LVH) in hypertensive rats, which can be abolished with the treatment of B2 receptor antagonist (HOE 140) (Linz *et al.*, 1993). The cardiac tissue kallikrein and kininogen levels have been found to be reduced highly in diabetic normotensive and hypertensive rats associated with the LVH (Sharma *et al.*, 1998). This may suggest that the lack cardiac BK releasing components may induce the development of LVH. The kallikrein-kinin based gene therapy may have future prospects in treating hypertension and cardiovascular diseases. The discovery of the first non-peptide full agonist for the human BK-2 receptor is currently being investigated by Sawada *et al.* (2004). Most recently, we have provided evidence on the role of BK in the treatment of cardiovascular diseases (Sharma and Abbas, 2005; Sharma, 2004; Sharma and Thani, 2004). In summary, it is possible to suggest that the BK agonists and tissue kallikrein may be proven as therapeutics agents in the management of cardiovascular abnormalities.

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