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Bradykinin, an Important Mediator of the Cardiovascular Effects of Metallopeptidase Inhibitors: Experimental and Clinical Evidences

M. Perez, G. Molinaro, A. Adam

Bradykinin (BK), a nanopeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), is the prototype of a family of powerful vasodilatory peptides, the kinins. Although known for a long time only as a pro-inflammatory peptide, BK is now considered an important mediator of the benefits of angiotensin I-converting enzyme inhibitors (ACEi). In fact, over the years, numerous papers have been dedicated to BK, and a number of them dealt with its cardiovascular effects.

Different experimental and clinical arguments plead for a role of BK in the cardiovascular effects of ACEi. BK may also be an important mediator of a new class of drugs, vasopeptidase inhibitors. These single molecules simultaneously inhibit the activity of neutral endopeptidase 24.11 and angiotensin-converting enzyme, two kininases, with similar nanomolar inhibitory constants. The protective effect of omapatrilat, the first of this new class of drugs, on BK degradation at the cardiomyocyte and endothelial level, two target sites for metallopeptidase inhibitors, has also been documented and compared to that of ACEi.

The purpose of this paper is to review the different experimental and clinical arguments that support a cardioprotective role of this vasodilatory peptide, BK. J Clin Basic Cardiol 2001; 4: 39–46.

Key words: bradykinin, angiotensin I converting encyme inhibitors (ACEi), vasopeptidase inhibitors, cardioprotection

B radykinin (BK), a nanopeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), is the prototype of a family of powerful vasodilatory peptides, the kinins. It originates from kininogens when hydrolyzed by kininogenases. BK exerts its pharmacological activity by stimulating specific receptors before being metabolized by different peptidases. Although known for a long time only as a pro-inflammatory peptide, BK is now considered an important mediator of the benefits of angiotensin I-converting enzyme inhibitors (ACEi). Nearly one century after the first description by Abelous and Bardier [1] of the hypotensive action of a fraction of the human urine, later attributed to the kallikrein-kininogen-kinin system (KKKS), this cascade, and mostly BK still raises much scientific interest. In fact, in the past five years, numerous papers have been dedicated to BK, and a number of them dealt with its cardiovascular effects.

The purpose of this paper is to review the different experimental and clinical arguments that suggest a cardioprotective role of this class of vasodilatory peptides, the kinins.

Bradykinin: Definition and Origin

Like the renin-angiotensin system, the kallikrein-kininogenkinin system (KKKS) is a cascade system. Although present in plasma, local kallikrein-kininogen systems have been found to be present in different cells such as cardiomyocytes [2] and tubular cells of the kidney [3], for example.

The kininogens: the precursors of kinins

The kininogens are single-chain glycoproteins synthesized mainly by the liver. Their molecular mass allows for differentiation of two human forms of kininogens: high-molecular weight kininogen (HK, 115 kD) and low-molecular weight kininogen (LK, 6.8 kD) which derive from a single hepatic gene (K gene) that yields two mRNAs by alternative splicing [4, 5]. Both kininogens possess a common multidomain COOH-terminal heavy chain, a different NH₂-terminal light chain and a kinin-forming moiety bridging the two. HK circulates in plasma at a concentration of approximately 90 μ g/ml [6]. Through its amino-terminal light chain, HK is a coagulation cofactor [7]. In fact, it is complexed to prekallikrein (PK) and factor XI and by a histidine rich domain, it binds to negative surfaces [8, 9]. The function of the light chain of LK is still unknown [4].

The kininogenases: the kinin releasing enzymes

Kininogens release their kinin moiety when hydrolyzed by specific and non specific kininogenases. Plasma and tissue kallikreins are specific kininogenases. In man, the tissue kallikrein gene family has three members, the hRKALL, hGK-1 and PSA genes, clustered on chromosome 19. The protein coded by hRKALL, the true tissue kallikrein or hK1, is the only one known to hydrolyze kininogens to any significant physiological extent [10, 11]. It is synthesized as a inactive proenzyme in different tissues, like the kidney. Tissue kallikrein releases Lys-BK from both kininogens; LK however is its preferential substrate.

Plasma kallikrein is synthesised and secreted by hepatocytes as a precursor known as plasma prekallikrein. The single gene coding for this proenzyme is found on chromosome 4 [12]. Prekallikrein is a single chain glycoprotein that circulates in plasma bound to the light chain of HK. Catalytic hydrolysis of the Arg³⁷¹-Ile³⁷² bond leads to the formation of the active plasma kallikrein which consists in a two-chain serine proteinase molecule held together by a disulfide bridge [13]. Plasma kallikrein releases BK from HK by hydrolysis of Lys-Arg and Arg-Ser bonds. LK is a poor substrate for plasma kallikrein [14].

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The contact system of plasma

The contact system of plasma consists in 3 proenzymes (factor XII and XI of the coagulation and plasma PK) and one cofactor, HK. The presence of a negatively charged surface allows for binding to factor XII and HK (which circulates complexed with PK and factor XI) leading to the auto-activation of factor XII into XIIa which in turn transforms PK into the active serine protease which releases BK from HK. The nature of the negatively charged surfaces susceptible to activate this system *in vitro* has been reviewed recently [7]; however, none of these compounds has been shown to be of a significant physiological relevance.

Another mechanism has been proposed to explain the local release of BK *in vivo*: it involves the endothelial cells. Two different groups have recently reported that endothelium cells are susceptible to bind HK and factor XII in a specific way [15, 16]. This binding involves the same receptor and is zinc-dependent, it has been identified as the COOH-terminal domain of the receptor for the C1q complement factor (gC1qR) [17]. Besides endothelial cells, interaction between the contact system and neutrophils and platelets has also been shown, it involves different potential binding sites [7].

BK: the prototype of kinins

In 1949, Rocha e Silva et al. reported that the incubation of dog plasma globulins with the venom extract of *Bothrops jararaca* or trypsin leads to the production of an active molecule capable of the slow and delayed contraction of guinea pig ileum. This group was to call this biologically active molecule BK [18]. BK and its analogs with a carboxy-terminal Arg stimulate B2 receptors. Kininase I, a generic name for different carboxypeptidases, transform B2 agonists into their desArg metabolites that also belong to the family of kinins but stimulate B1 receptors [19].

Kinin receptors

In mammals, the biological activities of kinins are mediated by two distinct receptors, termed B1 and B2. The B1/B2 classification relies on rank order of potency of kinin analogs [20]. Both B1 and B2 receptors have been cloned [21]; they are cell-surfaced, G-protein coupled receptors of the seventransmembrane domained family. These two receptors show a 35 % homology, mostly located in the seventh transmembrane region. They are primarily linked to phospholipase $C-\beta$ activation, with hydrolysis of phosphatidylinositol and consequent intracellular Ca²⁺ mobilization by inositol 1,4,5triphosphate (IP₃). In endothelial cells, the enhancement of cytosolic Ca²⁺ leads to an activation of arachidonic acid metabolism through phospholipase A₂ and an increase in nitric oxide formation via the calcium-calmodulin-dependent NOsynthase. Endothelial prostaglandin and NO exert many of the pharmacological effects of kinins via adenosine monophosphate (cAMP) and guanosine monophosphate (cGMP) formation such as vascular smooth muscle cell relaxation, antiproliferative and anti-ischaemic effects [22, 23].

The B2 receptor is constitutive in a number of different cell types, it responds to stimulation with a strong, but short signal and immediately undergoes a rapid loss of functional responses, receptor internalization and sequestration, ligand dissociation and, upon long-term stimulation, its own mRNA and protein down-regulation [22, 24, 25].

In contrast to B2 receptors, B1 receptors are inducible: growth factors and cytokines like IL-1 β , IL-2, IL-8 or bacterial lipopolysaccharides strongly up-regulate B1 receptor expression [19], via the inflammatory transcription factor, nuclear factor κ B (NF- κ B) binding site [26, 27]. The B1 receptor is a non-internalizing receptor.

The metallopeptidases: key enzymes in the metabolism of BK (Figure 1)

Several peptidases collectively termed kininases are susceptible to rapidly degrade kinins. Their nature and properties have been extensively reviewed. From our results [28–31] and those of other laboratories [32], 5 metallopeptidases seem to be particularly important in the metabolism of BK: angiotensin-converting enzyme (ACE, kininase II), neutral endopeptidase 24.11 (NEP), aminopeptidase P (APP), carboxypeptidase N and carboxypeptidase M (kininase I). These five enzymes all require zinc at their catalytic site; four are membrane-bound single-chain glycoproteins, carboxypeptidase N being a soluble tetrameric complex.

Angiotensin-converting enzyme

Angiotensin-converting enzyme (ACE) is the metallopeptidase which has the highest affinity for BK ($K_m = 0.18 \ \mu M$) [33]. ACE hydrolyses BK by cleaving carboxyterminal dipeptides to sequentially yield BK₁₋₇ and BK₁₋₅ [33, 34]. Knowing that the affinity of ACE for BK is about 100 times higher than for angiotensin I, ACE could be considered a kininase rather than an angiotensinase [32]. Moreover, ACE also inactivates desArg⁹BK, cleaving the carboxyterminal Ser⁶-Pro⁷-Phe⁸ tripeptide [35]. ACE has been shown to play an important metabolic role not only at endothelium [29] but also at the cardiomyocyte [30] and plasma level [28].

The molecular cloning and sequencing of cDNA for human ACE has been reported by the group of Soubrier et al. [36].

Interestingly, ACE is characterized by a I/D polymorphism associated with serum ACE activity [37]. Subjects homozigous for the D allele have a mean serum ACE level nearly twice as high for the I allele, while heterozygous have intermediate activities. The DD-ACE genotype has been implicated in the pathogenesis of cardiovascular disorders. Some authors have hypothesized that this association between DD-ACE genotype and cardiovascular diseases could be attributed to an increased formation of angiotensin II (reviewed in [38]). We have reported that the DD genotype influences the plasma metabolism of BK, in fact BK half-life was significantly de-



Figure 1. Bradykinin metabolism and its relationship with two other vasoactive mediators: angiotensin and natriuretic peptides. ACE, angiotensin-converting enzyme; AI, angiotensin I; AII, angiotensin II; ANP, atrial natriuretic peptide; APP, aminopeptidase P; AT₁, angiotensin II; type I receptor; AT₂, angiotensin II type I receptor; BK, bradykinin; BNP, brain natriuretic peptide; CNP, C-natruretic peptide; NEP, neutral endopeptidase 24.11; NPR-A, natriuretic peptide receptor type A; NPR-B, natriuretic peptide receptor type B.

creased in the plasma of DD genotype subjects when compared to the plasma of II genotype subjects [39].

Neutral endopeptidase 24.11

Neutral endopeptidase 24.11 (NEP) inactivates BK by cleaving the COOH-terminal Phe⁸-Arg⁹ dipeptide [40] and Phe⁵-Ser⁶-Pro⁷ tripeptide, yielding the inactive BK₁₋₄ metabolite [41]. This latter metabolite can also be obtained by the catalytic action of NEP on desArg⁹BK [41]. The affinity of NEP for BK is lower than that of ACE [40]. NEP is encoded by the 3q21-27 locus of human chromosome 3 [42, 43] and has a large tissue distribution [44]. A high NEP activity has been detected on the membranes of endothelium and of cardiomyocytes, but also and mostly in the brush border membrane in the kidney [45]. In plasma, unlike ACE, NEP does not play a significant role in the metabolism of kinins [28].

The kininase I

Kininase I is a generic name for carboxypeptidases, mainly carboxypeptidases N (CPN) and M (CPM), which transform BK into its active metabolite: desArg⁹BK [46].

Aminopeptidase P

Aminopeptidase P (APP) specifically cleaves peptides with a penultimate proline at the aminoterminal end and can thereby remove the N-terminal Arg from BK and des Arg⁹BK [47]. In human plasma, APP is the main degrading pathway of des Arg⁹BK [48].

Different experiments in our laboratory showed that the relative importance of these metallopeptidases in the metabolism of BK and desArg⁹BK depends not only in the biological milieu (plasma, endothelium, cardiomyocytes) but also on the pathophysiological background (diabetes, myocardial infarction or left ventricular hypertrophy for example). From the different experimental data reported in the literature and summarized here, it appears that BK is generated locally at the tissue level where it exerts its pharmacological activity before being rapidly inactivated by different peptidases which limit the B1 or B2 activity at the site of formation. Kinins must then be considered as autocrine or paracrine mediators rather than hormones.

Cardiovascular Effects of BK

Besides the fact that BK is the preferential substrate for ACE, different experimental arguments plead for a role of BK in the cardiovascular effects of ACEi. These arguments, mainly of pharmacological nature, are based on the fact that exogenous BK reproduces the *in vitro* and *in vivo* experimental models the pharmacological effects of ACEi, these effects being suppressed by icatibant (HOE 140), a B2 receptor antagonist.

Experimental evidence for a role of BK in the effects of ACEi

Cell models

Endothelial cells, as cardiomyocytes, release BK *in vitro* and the nM concentration of the B2 agonist measured in the supernatant is potentiated by a preincubation of the cells with an ACEi [49]. The formation of NO and PGI₂ in cultured bovine endothelial cells is increased by exogenous BK and/or an ACEi, this effect being suppressed by the B2 antagonist, icatibant [50]. Also, exogenous BK as well as an ACEi reduces CK release and the sarcolemnal damage induced by hypoxemia in neonatal myocytes; this effect is inhibited by N^G-monomethyl-L-arginine monoacetate (L-NMMA) or an inhibitor of the guanylate cyclase [51]. An angiotensin II (ANGII) antagonist had no protective effect in this *in vitro* model. Knowing that ACEi inhibit BK degradation, these results consequently suggest that these drugs act through the local kallikrein-kinin system in endothelial and cardiomyocytic cells by enhancing the autocrine/paracrine cardioprotective effects of the B2 agonist.

BK and the heart

In vitro models of ischaemia reperfusion

ACEi and exogenous BK have, in experimental models of total or partial ischaemia-reperfusion in isolated working rat hearts, the same cardioprotective effect mediated by B2 receptors. They improve cardiodynamic and metabolic parameters decreasing the severe ventricular arrhythmias and increasing the left ventricular pressure, the dp/dtmax and the coronary flow. They also increase the myocardial concentrations of glycogen, ATP and creatine phosphate [52]. ACEi have also been shown to increase BK [53] and desArg⁹BK [54] in the cardiac effluent during the reperfusion period. Moreover, comparative studies with BK and ramiprilat in isolated working rat hearts with postischaemic reperfusion arrythmias show an almost identical pattern of changes in cardiodynamics and metabolism, even in low concentrations (reviewed in [23]).

Like adenosine or acetylcholine [55], exogenous BK has also been shown to have a preconditioning effect in a model of isolated rat heart [23, 56], these specific effects of the exogenous B2 agonist have also been confirmed *in vivo* in the human heart [57].

In vivo animal models

A study on dogs in the late 1960s was the first to show that kinins administered locally and systemically increased the coronary blood flow and improved myocardial metabolism [58]. In 1970, an activation of the plasma kallikrein-kinin system during myocardial ischaemia was shown [59]. These different data raised the hypothesis that kinins released during an ischaemic episode might constitute a compensatory cardioprotective effect [23].

ACEi and BK separately were also shown to significantly reduce infarct size in dogs [23] and in rabbits [56]; this effect was abolished by the coadministration of icatibant. Furthermore, myocardial tissue injury evoked by neutrophil mediated release of free radicals through platelet-activating factor is reduced by BK as well as by ACEi [60].

Studies on bovine or porcine coronary artery rings showed that ACEi induced endothelium-dependent relaxation could not be observed in non-flow conditions [61] indicating that a shear-stress is needed for the ACEi to exert their effects on the coronary flow.

BK and hypertension

BK clearly contributes to the acute antihypertensive action of ACEi in animals suffering from a renin-dependent hypertension [62, 63]. However, the coadministration of icatibant to spontaneous hypertensive rats (SHR) receiving ACEi did not affect the antihypertensive action of the ACEi, indicating that endogeneous kinins do not seem to participate in the antihypertensive actions of ACEi in a non-renin-dependent hypertension model [64]. The reasons for the absence of contribution of kinins in this model of hypertension is related to the pathophysiology of this hypertension model, where only normal to low plasma renin are found [23].

ACEi and atherosclerosis

The results of studies on the role of ACEi in atherosclerosis are conflicting and depend on the experimental model. For example, ACEi have been shown to prevent a loss of endothelial function due to a long term atherogenic diet in rabbits [23, 65] whereas only losartan, an ANGII receptor antagonist, and not ramipril (via a putative BK mediated mechanism) attenuated atherosclerosis in an apoE deficient mouse model [66, 67].

BK and left ventricular hypertrophy (LVH)

The beneficial effects of ACEi on LVH during the post-MI period have been studied mainly in rats [68] with a normal KKKS. In kininogen-deficient Brown-Norway rats however, ramipril did not reduce infarct size [69], showing that an intact KKKS is needed in order for the ACEi to exert their beneficial cardioprotective effects, and that these effects are mediated by the potentiation of BK rather than by inhibition of ANGII formation [69, 70]. Moreover, studies on knockout mice that show a partial or a total deficiency of the B₂ receptor are prone to develop LV hypertrophy or decompensated hypertrophy and failure respectively, clearly establishing the important role of kinins in the preservation in myocardial structure and function [71].

A one year prevention study in rats showed that both the antihypertensive dose of an ACEi and the dose which had no effect on blood pressure had prevented LVH [72]. This protective effect was still present after 6 months of treatment cessation.

Metabolic Effects of BK

Glucose metabolism

ACEi are known to improve whole-body insulin-mediated glucose disposal. In animal models of insulin resistance, both acute and chronic administration of ACEi with a sulfhydryl or non-sulfhydryl group improve insulin sensitivity *in vivo* by a mechanism that could involve BK [73, 74]. BK has been shown to have insulinomimetic properties [75, 76] and could modulate glucose metabolism in peripheral tissues. In experimental models of insulin and non-insulin dependent diabetes, ACEi and exogenously perfused BK enhance insulin sensitivity, potentiating the insulin-dependent glucose uptake by a B2 receptor dependent mechanism. Bradykinin also enhances GLUT4 translocation through the increase of insulin receptor tyrosine kinase in primary adipocytes [77], further evidence for the role of bradykinin in glucose homeostasis.

Renal function

Tissue kallikrein and kininogens are present at the tubular level in the kidney. The local kinin production is of functional importance in the control of renal blood flow and of natriuresis and diuresis. Moreover, acting on the pre and post glomerular arterioles, BK increases the renal blood flow (reviewed in [13]).

NEP and ACE are the main brush border peptidases responsible for the local degradation of BK, NEP being the major kininase in human urine [78]. ACEi treatment significantly attenuates the development of renal disease, like progressive glomerulosclerosis and proteinuria in experimental models of reduced renal mass and diabetes mellitus. Clinical studies have confirmed that the use of ACEi allows renal protection in insulin and non-insulin dependant diabetes, and in progressive chronic renal disease due to other causes. The combined risks of death, dialysis and transplantation are, in fact, decreased significantly in diabetics treated with ACEi. These beneficial effects are generally attributed to a decreases synthesis of ANGII; however, knowing that ACE is more a kininase than an angiotensinase, it can be assumed that a least part of the beneficial effects of these widely used agents can be linked to kinins.

Clinical Evidence for a Role of BK in the Pharmacological Effects of ACEi

It is well-known that ACEi have been successfully used in the treatment of cardiovascular diseases such as left ventricular dysfunction. In patients who have experienced an acute myocardial infarction, inhibition of ACE significantly reduces the risk of further myocardial infarction, and unstable angina pectoris [79, 80]. Captopril, compared with placebo, was shown to decrease the incidence of ventricular extrasystoles and ventricular fibrillation in patients with acute MI [81]. Furthermore, a study on patients with congestive heart failure showed that 3 months therapy with perindopril improved endothelial function of peripheral resistance vessels [82]. ACEi also proved to attenuate myocardial stunning [83] and the effect of sympathetic stimulation on overall coronary vasomotor tone [84], to have anti-ischaemic properties [79], to have antithrombotic properties, to diminish cardiac hypertrophy and to decrease cardiac enlargement [85]. Human data are however lacking to clearly establish a positive effect of ACE inhibition on atherosclerosis [85]. The HOPE study showed that ramipril was beneficial in a broad range of patients without evidence of left ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events [86]. The authors also observed a marked reduction in the incidence of complications related to diabetes and new cases of diabetes.

Several evidences plead for a role of BK in the cardiovascular effects of ACEi in humans [87]; in fact, the edema/ hyperemia reaction observed when BK is injected into the human dermis as well as the hypotensive effect of intravenously or intra-arterially injected BK in humans are potentiated by oral ACEi [88–91].

BK and the endothelium function

The Trial on Reversing Endothelial Dysfunction (TREND) [92] showed that in the quinapril-treated group, the initial vasoconstrictor response to intracoronary infusion of acetylcholine (an endothelium-dependent vasodilator) was dramatically reduced and partly normalized towards a vasodilator response, whereas no change was observed in the placebo-treated group. This beneficial response to ACE inhibition would be explained by the reduction in ANGII but also by an increase in BK [91]. These data confirm that BK participates in the vascular effects of ACEi by exerting a continuous vasodilating effect on coronary resistance artery tone [85].

Alterations in endothelial function occur in many conditions such as coronary artery disease [93] or congestive heart failure [91, 94] and NO plays an important role in this respect. Also, isolated human coronary resistance microvessels actively generate kinins to stimulate the production of NO and local administration of BK receptor antagonists in the human coronary circulation in vivo causes vasoconstriction and impairs flow-dependent vasodilation which is mediated by NO [95]. Increased catabolism of NO is considered a primary factor in promoting endothelial dysfunction and is dependent on the redox state of the endothelium. ACEi may then influence the endothelial dysfunction by reducing the levels of ANGII, which enhances the formation of free radical superoxide anions, affecting the redox state and the bioavailability of NO [85]. This is particularly true in disorders like diabetes which are associated with an increase in circulating oxygen derived free radicals causing an endothelial dysfunction [96]. Moreover, alterations in the rate of production of kinins within the vascular wall, as well as impairment of endothelial reactivity to these peptides, are associated with

risk factors for coronary heart disease such as hypertension, diabetes and hypercholesterolaemia [97]. Kinins then seem, through the direct or indirect activation of endothelial cells, to be important regulators of both vasomotion and vascular wall/blood cell interactions [98].

The antithrombotic properties of ACEi can be explained via 2 mechanisms: on one hand, a reduction in ANGII which enhances risks for thrombosis by induction of the plasminogen activator inhibitor-1 (PAI-1) [99] and on the other hand potentiation of BK which is an important stimulus for endothelial tissue-type plasminogen activator (tPA) secretion [100].

BK and the hypotensive effects of ACEi

A 1998 study on 20 normotensive and 7 hypertensive subjects measured the contribution of BK to the haemodynamic, endocrine and renal responses to short-term ACE inhibition by comparing the effects of captopril, captopril plus icatibant, losartan and placebo [101]: this study showed that BK contributes substantially to the hypotensive effects of ACE inhibition given that coadministration of icatibant decreased the average response to blood pressure to captopril by 53 %. The decrease in blood pressure after the administration of an ACEi and icatibant combined was similar to that after the administration of losartan. These authors and others have attributed this difference between the ACEi and the AT₁ blocker to BK.

BK and the anti-ischaemic effects of ACEi

Kinins are also probably involved in the short-term anti-ischaemic effects of ACEi in stable, exercise-induced angina by increasing coronary flow with a reduction in circulating ANGII [85]. A 1999 study on 30 patients with coronary artery disease undergoing an angioplasty (PTCA) demonstrated that pretreatment with BK preconditions human myocardium against ischaemia, just as effectively as ischaemic preconditioning [58]. Pretreatment with BK may then be a useful prophylactic measure in patients undergoing PTCA who are at risk for complications.

BK and the anti-hypertrophic effects of ACEi

Two large clinical trials have failed to show an effect of longterm ACE inhibition on coronary artery restenosis after coronary angioplasty [102, 103]: in these studies, cilazapril did not prevent long-term (6 months) narrowing of the coronary segment undergoing angioplasty. Several explanations have been proposed, including the dose of the ACEi, the timing of administration and also the fact that angioplasty may damage the vascular endothelial lining so severely that no pharmacological agent can be expected to solve the problem [85].

Vasopeptidase Inhibitors

Definition

Vasopeptidase inhibitors (VPIs) are single molecules that simultaneously inhibit the activity of NEP and ACE with similar nanomolar inhibitory constants. These molecules not only affect BK and ANGII metabolism but also the natriuretic peptides [104]. Simultaneous inhibition of ACE and NEP therefore constitutes an interesting approach, allowing the vasodilation induced by the ANP to last through inhibition of ANGII generation.

Omapatrilat is the first of this new class of drugs. In our laboratory, we have shown a protective effect of omapatrilat on BK degradation not only at endothelium, but also at the cardiomyocyte level (Dumoulin, unpublished data, 2000). This effect however depends on the pathophysiological background such as myocardial infarction, left ventricular hypertrophy and diabetes [30].

Clinical results

The first question raised by the VPIs was the comparison of the *in vivo* inhibition over 24 hours of ACE by a single oral dose of VPI with that of a single dose of a selective ACEi. A 1999 study [105] on 9 normotensive, mild sodium-depleted healthy male volunteers showed a similar 24 hour in vivo ACE inhibition. This point is important because in order to compare the hemodynamic, hormonal and tissue effects of a dual VPI with those of an ACEi, a similar degree of ACE inhibition must be achieved. This study also showed an increase in the urinary ANP after the VPI administration, as well as a blockade of the plasma ANP decrease usually induced by ACEi. Moreover, the ACEi and the VPI demonstrated the same pattern of changes in plasma ANGII levels over time showing that neutral-endopeptidase had no detectable influence on endogenous plasma ANGII clearance when ACE was also inhibited. The VPI significantly increased urinary sodium excretion compared with placebo and ACEi in those experimental conditions of sodium depletion. Another study on 573 patients suffering from different stages of congestive heart failure, compared the effects of omapatrilat, the first VPI agent, with those of lisinopril on exercise tolerance in patients with congestive heart failure. This study also examined side effects of the treatments, effects on death rate, and worsening events for worsening heart failure [106]. Omapatrilat did not improve exercise tolerance compared with the ACEi lisinopril. However, an improvement in the exercise tolerance is not necessarily associated with improved survival. On the other hand, clinical endpoints related to survival or any comorbid event for worsening heart failure were improved with omapatrilat, this improvement being consistent with studies on cardiomyopathic hamsters [107] and studies in the dog [108, 109]. These changes associated with omapatrilat seem to be the result of differences in the circulating neurohormones such as natriuretic peptides, nitric oxide and prostaglandins rather than a change in the ventricle function. Finally, there were fewer patients given omapatrilat with more renal deterioration than those given lisinopril, suggesting a protective effect of the natriuretic peptides [110]. A large-scale phase III study (4420 patients) is now being conducted to compare the effects of omapatrilat and enalapril in patients with heart failure (OVERTURE trial).

Concerning the antihypertensive actions of omapatrilat, clinical trials comparing this agent with placebo showed a remarkable decrease in diastolic as well as in systolic blood pressure [111]. A 1999 study on afro-american subjects and in subjects over 65 years of age was conducted in order to compare omapatrilat and lisinopril: a dose of 40 mg of omapatrilat was shown to be more effective in decreasing systolic and diastolic pressure compared to a 20 mg dose, in the afro-american group [112]. In the group of patients over 65 years old, lisinopril and omapatrilat decreased the diastolic pressure to the same extent, whereas omapatrilat provoked a more important reduction of the systolic blood pressure. Omapatrilat was also compared to amlodipine and lisinopril together in a study in which the patients suffered from different stages of hypertension: once again, omapatrilat was shown to be superior to the 2 other agents in reducing blood pressure [113].

Conclusions and Perspectives

From this brief review of the literature, it appears that much experimental evidence, mainly of pharmacological nature, indicate a role for BK in the beneficial cardiovascular effects of ACEi. The main goals for future studies are to determine the role of endogenous kinins (BK and/or desArg⁹BK) in the cardiovascular effects of ACEi in experimental models. This will be possible with the development of highly sensitive and specific methods for the quantification of the endogenous mediators in relation with their specific B1 or B2 activities. We must also show the role of endogenous kinins in relation with clinical parameters. Only then could we reconcile the known proinflammatory activities of endogenous kinins with their putative cardioprotective effects, these latter effects being dependent on the concentration of peptides [114, 115], as well as on a polymorphism of the metallopeptidases responsible for their metabolism.

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