Available online at www.sciencedirect.com

SCIENCE DIRECT®

European Journal of Pharmacology 500 (2004) 467–485

www.elsevier.com/locate/ejphar

Review

Putative roles of kinin receptors in the therapeutic effects of angiotensin 1-converting enzyme inhibitors in diabetes mellitus

Réjean Couture[a,*], Jean-Pierre Girolami[b]

[a]*Département de Physiologie, Faculté de Médecine, Université de Montréal, C.P. 6128, Succursale centre-ville, Montréal, Québec, Canada H3C 3J7*
[b]*Inserm U 388, Institut Louis Bugnard, CHU Rangueil, Toulouse Cedex 4, France*

Accepted 1 July 2004
Available online 26 August 2004

Abstract

The role of endogenous kinins and their receptors in diabetes mellitus is being confirmed with the recent developments of molecular and genetic animal models. Compelling evidence suggests that the kinin B_2 receptor is organ-protective and partakes to the therapeutic effects of angiotensin 1-converting enzyme inhibitors (ACEI) and angiotensin AT_1 receptor antagonists. Benefits derive primarily from vasodilatory, antihypertensive, antiproliferative, antihypertrophic, antifibrotic, antithrombotic and antioxidant properties of kinin B_2 receptor activation. Mechanisms include the formation of nitric oxide and prostacyclin and the inhibition of NAD(P)H oxidase activity involving classical and novel signalling pathways. Kinin B_2 receptor also ameliorates insulin resistance by increasing glucose uptake and supply, and by inducing glucose transporter-4 translocation either directly or through phosphorylation of insulin receptor. The kinin B_1 receptor, which is induced by the cytokine network, growth factors and hyperglycaemia, mediates hyperalgesia, vascular hyperpermeability and leukocytes infiltration in diabetic animals. However, emerging data highlight reno- and cardio-protective effects mediated by kinin B_1 receptor under chronic ACEI therapy in diabetes mellitus. Thus, the Janus-faced of kinin receptors needs to be taken into account in future drug development. For instance, locally acting kinin B_1/B_2 receptor agonists if used in a safe therapeutic window may represent a more rationale strategy in the prevention and management of diabetic complications. Because kinin B_2 receptor antagonists may further increase insulin resistance, the persisting dogma that restricts the development of kinin receptor analogues to antagonists (that is still relevant to abrogate pain and inflammation) needs to be revisited.

Keywords: Angiotensin 1-converting enzyme; Bradykinin; Diabetes mellitus; Kinin B_1 receptor; Kinin B_2 receptor; Oxidative stress

Contents

* Corresponding author. Tel.: +1 514 343 7060; fax: +1 514 343 2111.
E-mail address: rejean.couture@umontreal.ca (R. Couture).

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.07.045

1. Introduction

The World Health Organisation has estimated that there will be around 300 million of clinically diagnosed type 2 diabetes worldwide by the year 2025. This represents a 42% increase in the developed countries and a 170% increase in the developing countries (King et al., 1998; Gorus et al., 2004). The epidemic of diabetes mellitus is associated with a wide variety of long-term devastating complications that contribute to the increased mortality and morbidity of the disease. As depicted in Fig. 1, these complications can be divided into macrovascular complications including myocardial infarction, stroke, artherosclerosis, hypertension and large-vessel occlusive disease, and microvascular complications that include nephropathy, polyneuropathy and retinopathy (Feldman, 2003). Compelling evidence suggests a causal link between hyperglycaemia and the development of these clinical complications (Way et al., 2001; Brownlee, 2001). In spite that several therapies are successfully used to control glycaemia, these complications occur in 20–30% of type 1 diabetic patients (10% of the diabetic population) and type 2 diabetic patients (90% of the diabetic population) (Feldman, 2003; Zimmet, 2003). These complications are at present irreversible and lead to chronic and further end-stage diseases in addition to consuming a disproportionate share of total health care expenditures.

Currently available therapeutic strategies involved in the management and prevention of diabetes complications include glycaemia control either with insulin (diabetes of type 1) or antidiabetic drugs and antihypertensive agents, particularly those blocking the renin-angiotensin system. More novel strategies to influence vasoactive hormone action or to inhibit various metabolic pathways such as the oxidative stress cascade are under development. Angiotensin 1-converting enzyme inhibitors (ACEI) provide unique therapeutic benefits to reduce both microvascular and macrovascular complications in diabetes and appear to improve insulin sensitivity and glucose metabolism (McFarlane et al., 2003). In addition to interrupting the renin-angiotensin system, kinins are most likely involved in the beneficial effects of ACEI in the treatment of diabetes. Our review will focus on these recent developments and put emphasis on the role of kinins which aim not only to control the glycaemia but also the side effects occurring in diabetes.

2. Complications associated with diabetes mellitus

2.1. Diabetic nephropathy

Diabetic nephropathy is a major and irreversible complication of diabetes representing 30% of all new cases of end-stage of renal failure. It occurs as the results of a deleterious interaction between metabolic and haemodynamic factors, including glucose dependent pathways and arterial hypertension pathways (Cooper, 2001; Davis et al., 2004). The early changes, summarized in Fig. 2, include increases of the kidney size, glomerular volume and kidney functions mainly associated with glomerular hyperfiltration. That initial and transient step is followed by the development of mesangial cell proliferation and hypertrophy, accumulation of glomerular extracellular matrix and increased urinary albumin excretion. Established diabetic nephropathy is clinically characterized by proteinuria, hypertension, glomerulosclerosis (hyperplasia and hypertrophy of mesangial cells, excessive matrix (collagen and fibronectin deposit)) and progressive renal insufficiency. Until recently most of the studies have focused on the initial early events of the pathological mechanisms. Growing evidence has emerged and supports the involvement of several growth factors and cytokines in the development of diabetic nephropathy.

High glucose-induced extracellular matrix expansion in the renal glomerulus has been extensively investigated using cultured mesangial cells and results show that the cytokine transforming growth factor β (TGF-β) plays a central role. Synthesis of TGF-β is directly stimulated by oxidative stress. The activation of TGF-β receptor II induces the synthesis of matrix components, mainly different forms of collagen and fibronectin. Blockade of TGF-β accumulation

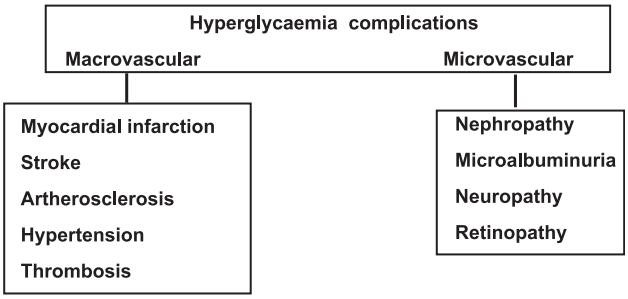

Fig. 1. Schematic classification of the main vascular complications associated with the progression of diabetic mellitus.

or blockade of its receptor prevents extracellular matrix synthesis (Ha et al., 1997; Heilig et al., 1997; Ziyadeh and Han, 1997; Ha and Kim, 1999).

2.2. Diabetic neuropathy

Neuropathy, an early clinical sign of diabetes affecting sensory and autonomic peripheral functions, is found in about 30–50% of diabetic patients of type 2 (Dickinson et al., 2002; Singleton et al., 2003; Feldman, 2003). Identified as neurovascular disease within the diabetes population which experienced pain (mainly in the lower limbs and feet) and autonomic dysfunction (particularly erectile dysfunction and altered cardiac vagal response), neuropathy derives from hyperglycaemia-induced oxidative stress that leads to decreased nerve conduction velocity, endoneural blood flow and nerve growth factors, and to increased low-density lipoprotein oxidation (Baynes, 1991; Dickinson et al., 2002; Singleton et al., 2003; Feldman, 2003). Lipid peroxidation in cell membrane causes oxidative damage in the myelin sheath surrounding the nerve. Typical symptoms of diabetic neuropathic pain include burning and lancinating pain, allodynia, paraesthesia and hyperaesthesia, aching, cramping and tingling, nocturnal exacerbation (Benbow and MacFarlane, 1999). Peripheral neuropathy and peripheral vascular disease associated with microvascular and macrovascular lesions represent major aetiological factors involved in the development of diabetic foot ulceration and lower limb amputation that occur in about 15% of people with diabetes and which remain the commonest reason for diabetes-related hospitalisation (Dickinson et al., 2002; Feldman, 2003).

2.3. Diabetic retinopathy

Blindness is one of the most feared complications of diabetes. Diabetic retinopathy is the commonest cause of new cases of legal blindness in Europe as in North America in the age group 30 to 70–74 years. Diabetic retinopathy is due to microangiopathy affecting the retinal precapillary arterioles, capillaries, and venules. Clinical trials suggest that glycaemic control and stricter control of hypertension can lower the incidence and prevent the progression of retinopathy and loss of vision associated with diabetes (Klein, 1996; Grassi, 2003; Aiello, 2003).

3. Oxidative stress as a consequence of hyperglycaemia

Oxidative stress has been considered to be a common pathogenic factor of diabetic complications and thus appears a target for therapeutic treatments. Inhibition of oxidative stress blocks the manifestations of the disease (Ha and Kim, 1999). Hyperglycaemia-induced oxidative stress plays a major role in extracellular matrix expansion since high glucose induced collagen secretion by mesangial cells is blocked by antioxydants (Trachtman et al., 1993; Trachtman, 1994). Tissue exposure to hyperglycaemia results in increased production of reactive oxygen species. The global term reactive oxygen species includes oxygen radicals such as superoxide anion ($O_2^{\bullet -}$), alkoxyl ($RO^{\bullet}$), peroxyl ($ROO^{\bullet}$), hydroxyl radicals ($OH^{\bullet}$), peroxynitrite ($ONOO^{-}$), and non-radical derivatives of oxygen, namely hydrogen peroxide (H_2O_2) and ozone (O_3). The level of reactive oxygen species is the balance between the production via reactive oxygen species generating systems and the degradation through antioxidant defence. In diabetes, antioxidant defences are blunted whereas the generating systems are stimulated (Dickinson et al., 2002; Hodgkinson et al., 2003). An experimental model of intracellular antioxidant enzyme deficiency displays an

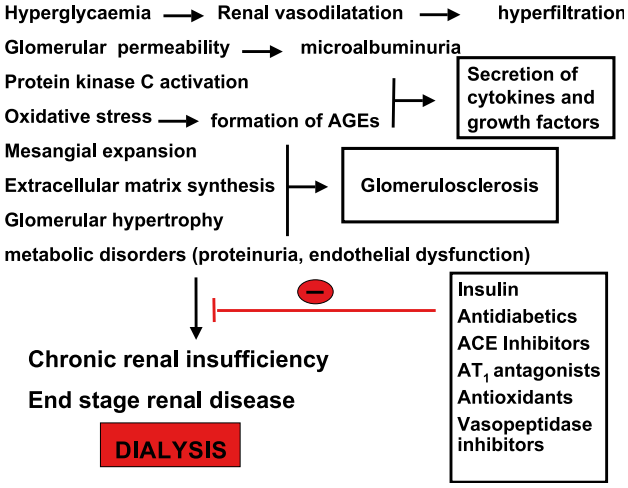

Fig. 2. Sequential renal events linking hyperglycaemia to chronic renal insufficiency and available therapeutic treatments (indicated by –). The early events are the induction of vasodilatation and the subsequent glomerular hyperfiltration. This results in alteration of glomerular permeability as detected by microalbuminuria. Then, increased intracellular glucose concentration activates the cascade of protein kinase C (PKC) and the formation of reactive oxygen species and advanced glycation end products (AGEs) resulting in cytokines and growth factors synthesis leading to progressive matrix accumulation. In spite of various therapeutic treatments, diabetic patients are the major group undergoing dialysis.

increase in vascular oxidant stress, with resulting endothelial dysfunction (Forgione et al., 2002). Induction of reactive oxygen species formation can result from different additive mechanisms. These mechanisms include direct intracellular effect of glucose in cells subjected to increase glucose uptake during hyperglycaemia (renal, retinal and some nervous cells) and indirect effect via the extracellular formation of advanced glycation end products (AGEs) (Fig. 3).

In cells, where hyperglycaemia induces increase in glucose uptake, the rise in glucose concentration leads to activation of intracellular pathways including aldose reductase (Windebank and Feldman, 2001), protein kinase C (PKC), nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase (Kitada et al., 2003), mitochondrial electron-transport chain (Brownlee, 2001). Activation of all these pathways leads to over production of reactive oxygen species and intracellular formation of AGEs with associated toxic effects. In addition to these direct intracellular effects, glucose and particularly fructose and sorbitol react non-enzymatically with proteins, lipids, and nucleic acids to produce AGEs in the extracellular medium, which in turn induce reactive oxygen species generation (Ceriello, 1999; Singh et al., 2001; Dickinson et al., 2002). One of the main toxic extracellular AGEs being glycated albumin that decrease plasma antioxidant defence (Himmelfarb and McMonagle, 2001). Endothelial reactive oxygen species can also be generated during hyperglycaemia by peroxidation of glucose and low-density lipoproteins and by dysregulation of transition metals that serve as catalysts for autoxidation (Baynes, 1991; Cameron et al., 2001). Ischemia can also accelerate reactive oxygen species formation by decreasing mitochondrial efficiency and by reperfusion injury (Singleton et al., 2003).

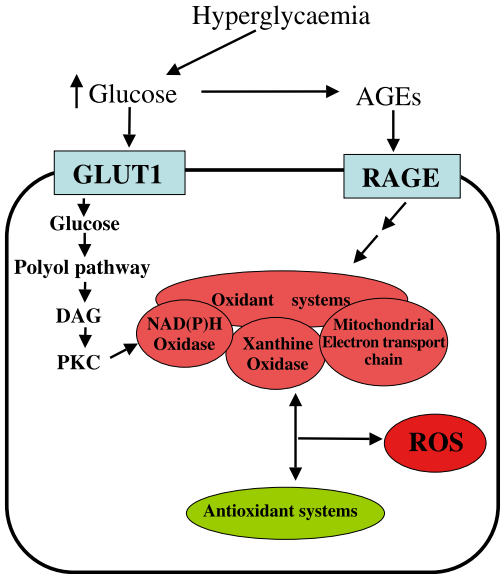

Fig. 3. Schematic representation of the mechanisms responsible for the formation of reactive oxygen species (ROS) in glucose sensitive cells expressing the glucose transporter GLUT1. Increase in extracellular glucose concentration is associated with increase in glucose uptake via an upregulation of the expression of GLUT1 and the formation of advanced glycation end products (AGEs). Increase in intracellular glucose activates protein kinase C (PKC) while AGEs bind to specific receptors (RAGE). Activation of PKC and RAGE synergistically stimulates oxidant systems resulting in the formation of ROS.

AGEs interact with specific receptors termed RAGE resulting in enhanced reactive oxygen species production which in turn stimulate transcription factors such as the transcriptional nuclear factor (NF-kB) and cytokines formation mainly TGF-β which play a central role in the development of renal hypertrophy and accumulation of extracellular matrix.

In diabetic nephropathy, a renal accumulation of AGEs is observed (Suzuki et al., 1999; Tanji et al., 2000; Forbes et al., 2002; Nangaku et al., 2003). Both reactive oxygen species and AGEs are directly neurotoxic and cause axonal degeneration (Windebank and Feldman, 2001; King, 2001). It is now clear that the formation of AGEs is a very important early step in the initiation of deleterious cascades leading to diabetic complications and therefore controlling AGEs formation and action can be an efficient therapy to reduce the progression of diabetes in peripheral tissues.

In this respect several recent reports indicate that ACEI inhibit the formation of AGEs and oxidative stress, and improve renal damage in diabetic rat models (de Cavanagh et al., 2001; Forbes et al., 2002; Miyata et al., 2002, Miyata and van Ypersele de Strihou, 2003; Nangaku et al., 2003). Chronic treatment with ACEI increases enzymatic and non-enzymatic antioxidant defences in mouse tissues (de Cavanagh et al., 1997) and restores the deficiency of several circulating antioxidant systems in chronic hemodialysis patients (de Cavanagh et al., 1999). It seems that ACEI may represent a “magic bullet” against vascular oxidative stress, a beneficial effect not achieved by the radical scavenging antioxidant vitamin E (Münzel and Keaney, 2001). Traditionally, ACEI have been identified as inhibitors of angiotensin II formation. Angiotensin II causes vasoconstriction, mitogenic and pro-fibrotics effects. In addition to these known effects, ACEI prevent the degradation of kinins which exert vasodilator, antithrombotic and antiproliferative effects through the formation of nitric oxygen (NO), prostaglandins and endothelium-derived hyperpolarizing factor. Moreover, ACEI may interact with the NADPH oxidase system to act as antioxydants.

3.1. A central role of NAD(P)H oxidases in reactive oxygen species generation

Activation of NAD(P)H oxidase by protein kinase C produces the predominant source of reactive oxygen species in the vasculature that lead to diabetic complications and numerous cardiovascular diseases (Kitada et al., 2003; Feldman, 2003; Griendling and FitzGerald, 2003; Cai et al., 2003). Several stimuli are known to activate NAD(P)H

oxidases such as cytokines, thrombin, tyrosine kinases, mechanical forces, hyperglycaemia and angiotensin II via AT_1 receptor signalling (Münzel and Keaney, 2001; Cai et al., 2003; McFarlane et al., 2003). Thus, the inhibition of angiotensin AT_1 receptor or the formation of angiotensin II with ACEI will target oxidative stress at its source by preventing the formation of superoxide anion and other reactive oxygen species that occurred following NAD(P)H activation. Moreover, ACEI enhance the formation of NO through kinins accumulation and abrogate a number of downstream effects resulting from the activation of NAD(P)H oxidase and the subsequent formation of reactive oxygen species (increased cell proliferation, reducted NO bioactivity, lipid peroxidation). NO is also known to inhibit the activity of NAD(P)H oxidase, thereby reducing the formation of reactive oxygen species (Lee et al., 2000a,b). Hyperglycaemia increases aldose reductase activity that contribute to NAD(P)H depletion (Tesfamariam, 1994; Singleton et al., 2003). Because NAD(P)H is required for generation of NO from L-arginine, the depletion of NAD(P)H also leads to reduced NO formation. A central role of NAD(P)H oxidase was also shown in AGE-RAGE-mediated generation of reactive oxygen species activation (Wautier et al., 2001).

3.2. Endothelial dysfunction

In endothelial cells, NO plays an important role in vasodilatation and detoxification of reactive oxygen species. NO contains an unpaired electron and may react with superoxide radical anion to form inactive nitrite. NO is therefore a superoxide radical anion scavenger (Tesfamariam, 1994) that can also inhibit the formation of AGEs (Asahi et al., 2000). NO is synthesized by NO synthase in vascular endothelial cells (eNOS) in response to insulin, bradykinin, shear stress and other stimuli. NO diffuses to the underlying vascular smooth muscle cells to cause relaxation via the formation of cGMP resulting from the activation of the soluble guanylate cyclase. Failure of vasodilatation secondary to NO consumption during neutralization of free radicals generated by hyperglycaemia or the inhibition of its synthesis may result in tissue ischemia, hypertension and atherosclerosis (Singleton et al., 2003). AGEs downregulate the expression of eNOS by increasing the rate of mRNA degradation (Rojas et al., 2000). Disruption of vascular NO signalling in eNOS knockout mice or the inhibition of eNOS activity, ultimately leads to a state of insulin resistance (Shankar et al., 2000). Thus, endothelial dysfunction of micro and macro vessels are associated with the pathogenesis of diabetes (De Vriese et al., 2000).

3.3. The role of glucose transporters in glucose-dependent oxidative stress

The cellular response to glucose is tissue specific and depends on the expression of numerous glucose transporters (GLUTs) in the plasma membrane (Heilig et al., 1997). The more common responses of glucose transporters to high glucose exposure are to downregulate their expression as a protecting feedback against the toxic effect of excess glucose. This is the case for GLUT-4, an insulin-dependent glucose transporter located in skeletal muscle and adipose tissue, which is down regulated during hyperglycaemia and that leads to insulin resistance (Heilig et al., 1997). However, glucose demonstrates a potent cytotoxic effect on mesangial, retinal and neuronal cells. These cells are very sensitive to glucose because they express mainly the glucose transporter GLUT-1, an insulin-independent glucose transporter, which is directly up-regulated by extracellular glucose concentration (Heilig et al., 1997, 2001). An early effect of high glucose concentration in mesangial cells is the rapid influx of glucose and subsequent activation of protein kinase C isoforms, polyol pathway, diacylglycerol and TGF-β (Heilig et al., 1997; Ha and Kim, 1999). These early steps induced by high glucose exposure also involve rapid activation of mitogen-activated protein kinase (MAP kinase) isoforms (Cellier et al., 2003). The activation of these different pathways causes excessive synthesis and release of extracellular matrix, leading to glomerulosclerosis and renal failure in diabetes. In this respect, antisense GLUT-1 protects mesangial cells from glucose induction of GLUT-1 and fibronectine expression (Heilig et al., 2001). Likewise, diabetic vascular complications, including basement membrane thickening, extracellular matrix deposition, increased vascular permeability, vascular blood flow impairment and neovascularization, are mediated by the diacylglycerol-PKC signal transduction pathway activation during hyperglycaemia (Way et al., 2001). This is in keeping with the finding that insulin signalling in vascular tissues through MAP kinase pathway is selectively preserved in the state of insulin resistance (Jiang et al., 1999).

4. The kallikrein-kinin system

Kinins namely bradykinin and kallidin (Lys-BK) are among the most potent pro-inflammatory vasoactive peptides generated during tissue injury and noxious stimulation. They are also neuromediators of neuronal pathways involved in the central autonomic control of blood pressure and in the regulation of nociception (Couture and Lindsey, 2000). As depicted in Fig. 4, bradykinin and kallidin are generated following the proteolytic cleavage of their respective precursors, high molecular weight kininogen and low molecular weight kininogen, by plasma and tissue serine proteases named kallikreins (Bhoola et al., 1992). These peptides undergo rapid metabolic degradation by amino-, carboxy- and endopeptidases found in tissues and biological fluids. The most physiologically relevant enzymes are kininase I (carboxypeptidase N from plasma and carboxypeptidase M from cell membrane), which remove the COOH-terminal Arg from kinins to produce

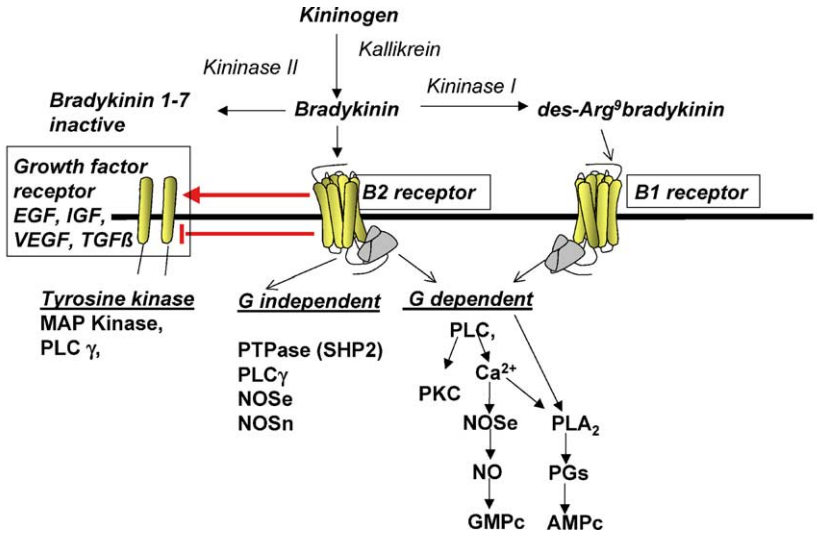

Fig. 4. Organisation of the kallikrein-kinin system. Kinins act through the activation of two G-protein coupled receptors denoted as B_1 and B_2 receptors. However, activation of the B_2 receptor has been associated with the recruitment of G-protein independent pathways and trans-activation or trans-inhibition of growth factor receptor.

the active metabolites des-Arg^9-bradykinin and des-Arg^{10}-kallidin; neutral endopeptidase 24.11 (enkephalinase) and kininase II (also named ACE), which act as dipeptidyl carboxypeptidases to remove the COOH-terminal dipeptide, Phe^8-Arg^9. Moreover, endopeptidase 24.15 and kininase II cleave the COOH-terminal dipeptide Ser^6-Pro^7 of bradykinin (1–7) to produce bradykinin (1–5), which is the final metabolite of bradykinin and des-Arg^9-bradykinin. Kallidin and des-Arg^{10}-kallidin can be transformed into bradykinin and des-Arg^9-bradykinin by aminopeptidase activity (Kuoppala et al., 2000; Campbell, 2000; Couture and Lindsey, 2000). A novel ACE (termed ACE2) has recently been found in human heart, kidney and testis (Donoghue et al., 2000). This carboxypeptidase is a zinc metalloprotease which is not inhibited by typical ACE inhibitors and does not hydrolyse bradykinin but cleaves des-Arg-bradykinin and neurotensin, and converts angiotensin I to angiotensin (1–9) and angiotensin II to angiotensin (1–7) (Donoghue et al., 2000; Turner et al., 2002; Tikellis et al., 2003). ACE2 protein and mRNA in the renal tubules of 24 weeks streptozotocin diabetic rats were reduced (Tikellis et al., 2003). Thus, the pathophysiological role of ACE2 in diabetes deserves further investigation.

Kinins exert their biological effects through the activation of two transmembrane G-protein-coupled receptors (Gαq and Gαi), denoted as kinin B_1 and B_2 receptors (Regoli et al., 2001). Whereas the kinin B_2 receptor is constitutive and activated by the parent molecules (bradykinin and kallidin), the kinin B_1 receptor is generally underexpressed in normal tissues and is activated by the C-terminal kininase 1 metabolites, des-Arg^9-bradykinin and des-Arg^{10}-kallidin. The induction and increased expression of kinin B_1 receptor occur following tissue injury or after treatment with bacterial endotoxins, growth factors or cytokines such as interleukin-1β and tumor necrosis factor-α (Marceau et al., 1998). The induction of kinin B_1 receptor by cytokines is controlled by MAP kinase and NF-κB (Larrivée et al., 1998; Ni et al., 1998; Schanstra et al., 1998; Campos et al., 1999; Sardi et al., 1999). A role for NO was also reported in the induction of kinin B_1 receptor by heat stress in the rat (Lagneux et al., 2000). Sequence analysis of human and rat kinin B_1 receptor gene has revealed the presence of a transcriptional regulatory site for NF-κB in the promotor region (Bachvarov et al., 1996; Ni et al., 1998). Signal transduction pathways and mechanisms regulating the expression of kinin B_1 and B_2 receptors have been discussed in recent seminal reviews (Prado et al., 2002; Blaukat, 2003). Highly potent kinin B_1 and B_2 receptor antagonists are currently available to prevent the deleterious effects of kinins in pain, inflammation and cancer (Regoli et al., 2001; Gougat et al., 2004; Stewart, 2004).

4.1. Bradykinin: antiproliferative and antihypertrophic and remodelling properties

Kinins have been shown to regulate cell proliferation of a wide variety of cultured cells including fibroblasts, arterial smooth muscle cells and mesangial cells. A review of these studies demonstrates that the effects of kinins are complex as stimulation and inhibition have been reported depending on the experimental conditions. In general, both kinin B_1 and B_2 receptor agonists induce a weak mitogenic effect of quiescent cells, whereas they may inhibit mitogenesis stimulated by growth factors. These opposite effects are consistent with the stimulation of a dual signalling pathway. Whereas the classical activation of G protein-dependent pathways has been associated with the promitogenic effects of kinins (Alric et al., 1999; Bascands et al., 2003), inhibition of cell proliferation involves less classical pathways and may result from various mechanisms, including

NOS activation and a direct protein–protein interaction between the kinin B_2 receptor and a protein-tyrosine phosphatase which does not require G-protein activation (Duchêne et al., 2002a,b).

Bradykinin prevents angiotensin II-induced hypertrophy of rat cardiomyocytes in the presence of endothelial cells via NO and cGMP production (Ritchie et al., 1998; Rosenkranz et al., 2000). This antihypertrophic effect of BK was blunted in diabetic rat heart (Rosenkranz et al., 2003). Ventricular hypertrophy and age-dependent cardiac failure occur in kinin B_2 receptor knockout (B_2 KO) mice (Maestri et al., 2003). It has also been reported that bradykinin could reduce fibronectin and collagen gene expression in various cells and tissues such as cardiac fibroblasts via the NO/cGMP pathway and prostacyclin (Gallagher et al., 1998; Kim et al., 1999). Recently, it was reported that transgenic expression of the human tissue kallikrein gene prevents cardiac fibrosis and left ventricular dysfunction via a kinin B_2 receptor-dependent pathway in rat diabetic cardiomyopathy (Tschöpe et al., 2004b). Kinin B_2 KO mice and transgenic rats expressing increased endogenous bradykinin were used to demonstrate that the kinin B_2 receptor reduces renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction via a cascade involving the activation of plasminogen activators and metalloproteinase-2 enzymes (Schanstra et al., 2002). However, a potential role of bradykinin and kinin B_2 receptors in the antifibrotic effects of ACEI has not been confirmed in B_2 KO mice using the same animal model of accelerated renal fibrosis (Schanstra et al., 2003a).

The differential effects of kinins on renal function and morphology can be related to the activation of different signalling pathways, namely the activation of phospholipase C (PLC) and MAP kinases. Hence, in addition to being vasoactive peptides, kinins can be considered as modulators of growth factors. For instance, activation of kinin B_2 receptors by bradykinin reduces the stimulation of MAP kinases induced by trophic factors, named insulin-like growth factor-1, platelet-derived growth factor-BB, vascular endothelial growth factor (IGF-1, PDGF-BB, VEGF) and hyperglycaemia in isolated rat renal glomeruli; this effect of bradykinin involves the activation of a protein tyrosine phosphatase (Cellier et al., 2002, 2003). Bradykinin also inhibits the epidermal growth factor-induced phosphorylation of its receptors in epithelial cell line A431 via stimulation of a protein tyrosine phosphatase (Graness et al., 2000).

5. Rationale suggesting a role for kinins in diabetes

5.1. Clinical and experimental evidence

Clinical reports showed either increased (Mayfield et al., 1984) or decreased (Pelikanova et al., 1998) urinary kallikrein excretion in poorly controlled insulin-dependent diabetic subjects, and decreased in type 2 diabetics with nephropathy (Baba et al., 1986). Higher circulating levels of high and low molecular weight kininogens and prekallikrein were found in type 1 diabetic rats (Rothschild et al., 1999), yet myocardial and renal kallikrein gene expression were reduced (Jaffa et al., 1997; Tschöpe et al., 1999). Increased renal production of kinins may contribute to hyperfiltration in early insulin-dependent diabetes mellitus as blockade of kinin B_2 receptors reduces the higher glomerular filtration rate and renal vasodilatation in streptozotocin-diabetic rats (Jaffa et al., 1995), albeit this conclusion was not supported by others (Bank et al., 1988; Komers and Cooper, 1995). Renal bradykinin was found increased in severe hyperglycaemic streptozotocin-diabetic rats. Although this seems to affect to a minor degree glomerular haemodynamics, kinins are partly involved in the antiproteinuric action of ACEI at this stage of diabetic nephropathy (Tschöpe et al., 2003). This beneficial effect of ACEI associated with increasd bradykinin contrasts somehow with the reduction of renal excretion of proteins, nitrites and kallikrein under kinin B_2 receptor inhibition with an antagonist in diabetic-streptozotocin mice (Zuccollo et al., 1996).

The recent development of molecular and genetic models permitted to address in a more specific manner the participation of endogenous kinins and their receptors in diabetes. Tissue kallikrein deficient mice are unable to generate significant levels of kinins in most tissues and develop cardiac and vascular abnormalities despite normal blood pressure (Meneton et al., 2001; Trabold et al., 2002). Another study has however reported that mice lacking the kallikrein gene are hypertensive (Kim et al., 1995). Human kallikrein gene delivery attenuated hypertension, cardiac and renal abnormalities in animal models of hypertension (Wang et al., 1995; Chao et al., 1998; Yayama et al., 1998) and reduced insulin resistance and hyperinsulinemia in fructose-induced hypertension and type 2 diabetes (Zhao et al., 2003). This is keeping with the causal link between a genetically determined modest increase in ACE gene function and the development of nephropathy, proteinuria and renal injuries (mainly glomerular hypertrophy) in diabetic mice (Huang et al., 2001).

Although evidence suggests that tissue kallikrein is the main kinin-generating enzyme in vivo (Meneton et al., 2001), plasma pre-kallikrein may represent a risk marker for hypertension and nephropathy in type 1 diabetic patients as elevation of pre-kallikrein levels was associated with increased blood pressure and macroalbuminuria (Jaffa et al., 2003).

High glucose concentration increased the expression of the kinin B_2 receptor in rat vascular smooth muscle cells and this effect was prevented by inhibition of PKC activity (Christopher et al., 2001). Moreover, kinin B_2 receptors, PKC and the oxidative stress were involved in the prevention of high glucose-mediated suppression of human aortic endothelial cell proliferation by ACEI (Yasunari et al., 2003). Kinin B_2 receptors play a significant role in the control of regional blood flows and vascular resistances in the

coronaries and kidneys as documented in B_2 KO mice (Trabold et al., 2002). Studies conducted in B_2 KO mice have shown that bradykinin interacts with the renin-angiotensin system by stimulating the renin gene expression (Yosipiv et al., 2001; Imig et al., 2003) and by neutralizing the vasoconstrictor activity of angiotensin II through the release of NO (Cervenka et al., 2001). B_2 KO mice develop salt-sensitive hypertension and mineralocorticoid-induced hypertension (Alfie et al., 1997; Madeddu et al., 1997; Emanueli et al., 1998; Cervenka et al., 1999). Endothelin-1 and angiotensin II are probably involved in the mechanism that leads to hypertension caused by a high-salt diet in B_2 KO mice (Brochu et al., 2002). Furthermore, B_2 KO mice exhibited a reduced renal nitrite excretion and glomerular cGMP content associated with a reduced glomerular capillary surface area, indicating that kinins influence glomerular trophicity (Schanstra et al., 2003b).

5.2. Genetic markers

Additional evidence of a link between the kallikrein-kinin system and diabetes comes from polymorphism studies. One polymorphism in exon 3 of the kinin B_1 receptor promoter was proposed as a marker of prognostic significance for the preservation of renal function in patients with a history of end-stage renal failure. It was hypothesized that the prevalence of the C allele determines an over-expression of the kinin B_1 receptor which could confer a nephroprotective effect by increasing tissue effects of endogenous kinins (Bachvarov et al., 1998). In another study, no significant difference in the kinin B_1 receptor-699C allele frequency was observed between control and patients with type 1 diabetes and microalbuminuria or patients with type 2 diabetes and nephropathy (Knigge et al., 2000). Interestingly, common variation in kinin B_1 and B_2 receptors genes (kinin B_1 receptor-699G and kinin B_2 receptor (+9) alleles) increases human cardiovascular risk associated with hypertension, an effect not identified amongst those homozygous for the kinin B_2 receptor (−9) or kinin B_1 receptor-699C alleles (Dhamrait et al., 2003). In a study of 49 type 1 and 112 type 2 diabetic patients, a polymorphic variant located in exon 1 (+/−) of the kinin B_2 receptor gene was associated with increased urinary albumin to creatinine ratio and serum creatinine levels. Also the (+) allele of kinin B_2 receptor exon 1 polymorphism was associated with lower albumin/creatinine values in these patients, suggesting that this polymorphism represents a susceptibility marker for nephropathy progression in diabetic patients (Maltais et al., 2002). Although kinin B_1 receptor G^{-699} C and kinin B_2 receptor $C^{181}T$ polymorphisms were not associated with microalbuminuria or overt nephropathy in Caucasian type 2 diabetic patients, kinin B_2 receptor $C^{181}T$ polymorphism was associated with significantly lower systolic and diastolic blood pressure (Zychma et al., 2003). Also, the kinin B_2 receptor promotor C^{-58} allele was found to be associated with essential hypertension in populations of Japanese and African-Americans (Mukae et al., 1999; Gainer et al., 2000).

An insertion/deletion polymorphism of the ACE gene is found in type 2 diabetes in which a strong association was evidenced with the DD genotype (Feng et al., 2002). The DD genotype is strongly associated with increased plasma or serum ACE levels and elevated kinin degradating capacity (Rigat et al., 1990). Moreover, this DD genotype is associated with an elevated frequency of glomerulopathy lesions in type 2 diabetes (Solini et al., 2002).

5.3. Relationship between kinins and insulin

Plasma levels of high and low molecular-weight kininogens and pre-kallikrein were increased in streptozotocin-diabetic rats; this effect was normalized by insulin and suggests a direct modulatory interaction between bradykinin and insulin and/or their receptors (Rothschild et al., 1999). Maximum glucose uptake, insulin sensitivity index, and insulin clearance were reduced in kininogen-deficient rats (Damas et al., 1999), and gene therapy with human tissue kallikrein normalized hypertension, whole body glucose tolerance and insulin resistance in hypertensive and diabetic rats (Xiong et al., 1995; Zhao et al., 2003).

While insulin modulates renal kallikrein production, activation, and excretion (Jaffa et al., 1987, 1992), bradykinin increases the release of insulin from pancreatic β cells through the increase of intracellular calcium in response to hyperglycaemia (Yang and Hsu, 1997; Damas et al., 1999). Bradykinin increases the glucose uptake in cultured adipocytes (Isami et al., 1996) and in skeletal muscle of the human forearm (Dietze et al., 1996). In Zucker rats, a model of resistance to insulin and intolerance to glucose, chronic treatment with bradykinin improves the tolerance to glucose in all tissues (Henriksen et al., 1998). These data and others suggest that locally released bradykinin can regulate the uptake and availability of glucose in target tissues independently of the release of insulin (Rett et al., 1990). In B_2 KO mice, a resistance to insulin occurs further suggesting a stimulatory role for this receptor in the sensitivity to insulin. It is also known that the up-regulation of kinin B_1 receptor in B_2 KO mice cannot assume the metabolic function of the missing kinin B_2 receptor (Duka et al., 2001).

Acute and chronic treatments with captopril improve significantly the transport of glucose in skeletal muscle induced by insulin in obese Zucker rats (Henriksen and Jacob, 1995), diabetic dogs and in non-insulin dependent diabetic patients through kinin B_2 receptors (Uehara et al., 1994). Captopril and bradykinin also reverse insulin resistance in aging rats by modulating the early steps of insulin signalling in the liver and muscle (Carvalho et al., 1997). Selective antagonists of the kinin B_2 receptor decrease glucose uptake and insulin sensitivity and abolish the improvement in insulin sensitivity produced by ACEI (Uehara et al., 1994; Tomiyama et al., 1994; Kohlman et al., 1995; Henriksen et al., 1996, 1999).

The presence of kinin B_2 receptor and its mRNA was demonstrated on the surface of skeletal muscle cells by immunohistochemistry, binding and RT-PCR (reverse transcriptase-polymerase chain reaction) (Figueroa et al., 1996; Rabito et al., 1996; Miyata et al., 1998). Through kinin B_2 receptors, bradykinin potentiates the insulin-induced glucose uptake by upregulating the insulin receptor tyrosine kinase activity which stimulates phosphorylation of insulin receptor and its cytosolic receptor substrate-1 (IRS-1) which, in turn, potentiates the translocation of GLUT-4 in skeletal muscle (Miyata et al., 1998) and adipocytes (Isami et al., 1996; McCarty, 2003). Bradykinin can also directly trigger GLUT-4 translocation and increase glucose uptake via an insulin-independent pathway in cardiac and skeletal muscles (Rett et al., 1996; Kishi et al., 1998). This has some bearing on glucose transport in skeletal muscles which is believed to be facilitated by bradykinin locally released from contracting muscles during physical exercise. It has been shown that ACEI improve insulin resistance by increasing glucose uptake in type 2 diabetic mice and rats partly through enhancement of the bradykinin-NO system and consequently GLUT-4 translocation in skeletal muscles (Henriksen et al., 1999; Shiuchi et al., 2002).

Therefore, the beneficial effects of ACEI and bradykinin in diabetes involve several mechanisms including the improvement of insulin resistance (Fig. 5) through increasing glucose uptake, especially in skeletal muscles, and the prevention of oxidative stress and the production of extracellular matrix in glucose sensitive cells (retina, neurons and kidneys) as shown in Fig. 6.

5.4. Mechanisms underlying the benefical effects of bradykinin

Whereas bradykinin is associated with inflammation, compelling evidence suggests that bradykinin and its kinin B_2 receptors can be of benefit value in the treatment of diabetes mellitus by reducing the oxidative stress. Bradykinin may interfere with the oxidative stress in different ways: (1) In streptozotocin-induced diabetic rats, a strong glomerular accumulation of 4-hydroxynonenal protein derivatization, an index of oxidative stress, has been observed (Cellier et al., 2003). The increase of this marker was prevented by insulin but also by chronic treatment with ACEI, an effect which was prevented by a kinin B_2 receptor antagonist. (2) Bradykinin is able to reduce some oxidative index such as plasma levels of hydrogen peroxide and malondialdehyde and to increase antioxydative enzyme activity, namely superoxide dismutase, catalase and glutathione peroxidase in streptozotocin-induced acute hyperglycaemia in rats (Mikrut et al., 2001). (3) Bradykinin can reduce plasma levels of glucose either by increasing glucose supply to skeletal muscles following vasodilatation or by increasing glucose uptake by stimulating GLUT-4 translocation either directly or via the insulin pathway (Miyata et al., 1998; Kishi et al., 1998). Bradykinin-induced increased blood flow may also help to increase oxygen supply, the wash out of reactive oxygen species and glucose auto-oxidation. (4) Bradykinin can facilitate the release of insulin (Yan and Hsu, 1997; Damas et al., 1999). (5) Bradykinin can stimulate the glycolytic enzymes, phosphofructokinase and pyruvate dehydrogenase, that would reduce hyperglycaemia (Dietze et al., 1984; Begum et al., 1985). (6) Bradykinin induces NO formation which is a potent superoxide radical anion scavenger that reduces the formation of AGEs and reactive oxygen species (Tesfamariam, 1994; Asahi et al., 2000). The production of superoxide anion mediated by

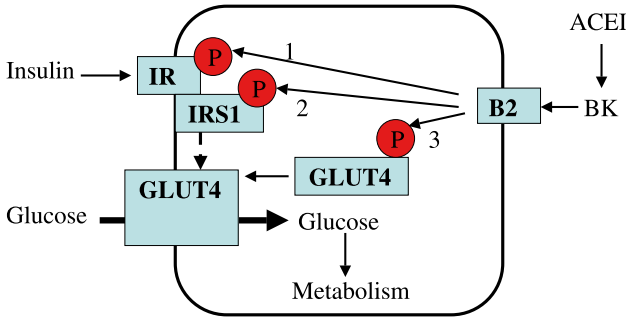

Fig. 5. Schematic representation of the mechanisms involved in the improvement of insulin resistance by activation of the kinin B_2 receptor (B2): (1 and 2) stimulation of insulin receptor (IR) and insulin receptor substrate 1 (IRS1) tyrosine phosphorylation; (3) stimulation of glucose transporter 4 (GLUT4). These insulin mimicking effects of BK have been shown in various tissues such as liver, skeletal muscle, fibroblasts and adipocytes and result in the increase of glucose uptake.

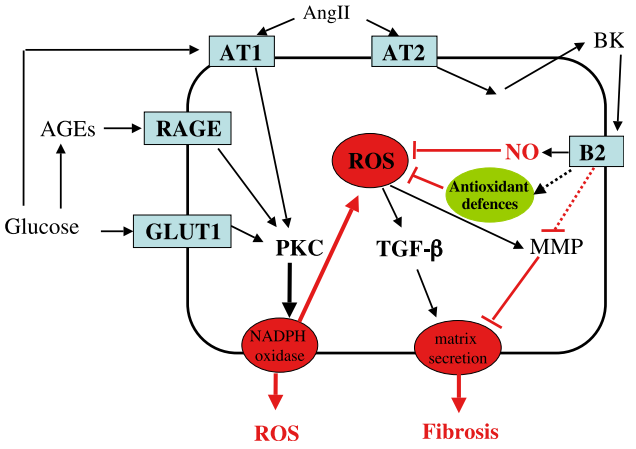

Fig. 6. Schematic representation of putative mechanisms involving angiotensin (AngII) receptors (AT1 and AT2) and bradykinin (BK) receptors (B2) on stimulation and reduction of oxidative stress during hyperglycaemia. Many reports support an oxidative effect of AT_1 receptor activation, yet emerging evidence suggests that B_2 receptors could play an antioxidant role. Recent data also indicate that angiotensin II-induced AT_2 receptor-dependent effects are mediated by B_2 receptor activation. Glucose, both directly via GLUT1 and indirectly via RAGE and AT_1 activation, increases the intracellular formation of reactive oxygen species (ROS). BK through B_2 receptor activation produces nitric oxide (NO), a potent scavenger of ROS, and possibly acts on other antioxidant defences. BK also inhibits metalloproteases (MMP), but it is presently unknown whether this effect is direct or results from ROS reduction.

increased angiotensin II-induced activation of NAD(P)H oxidase was inhibited by bradykinin in dog coronary microcirculation (Kinugawa et al., 2003).

In addition to be involved in the therapeutic effect of ACEI, bradykinin can also partake to the beneficial effects of angiotensin AT_1 receptor antagonists which are used as alternative therapy to prevent the deleterious effects of angiotensin II in cardiovascular diseases and diabetes mellitus (Schiffrin and Touyz, 2003; Ravera et al., 2003). Blockade of angiotensin AT_1 receptors causes elevation in the plasma level of angiotensin II in men (Christen et al., 1991), and induces the activation of angiotensin AT_2 receptors that leads to vasodilatation and hypotension through the release of bradykinin and subsequently NO from vascular endothelium (Gohlke et al., 1998; Tsutsumi et al., 1999; Sosa-Canache et al., 2000; Abadir et al., 2003). At another level of interaction, angiotensin II increases the expression of vascular kinin B_2 receptors through the activation of angiotensin AT_{1A} receptors and the MAP kinase pathway (Tan et al., 2004). Conversely, angiotensin AT_1 receptor overexpression reduced kinin B_1 receptor expression while angiotensin AT_1 receptor inhibition further increased kinin B_1 receptor expression, thereby contributing to the cardioprotective effect of angiotensin AT_1 blockers in myocardial infarction (Tschöpe et al., 2004a). These findings further highlight multiple interactions between angiotensin II and kinin receptors on cardiovascular functions (Tschöpe et al., 2002).

6. Crosstalk between kinin B_2 receptors and ACE?

Studies in isolated cells overexpressing ACE and kinin B_2 receptors and in intact vessel preparations suggest that ACEI potentiate bradykinin by inhibiting kinin B_2 receptor desensitization, via a mechanism involving PKC and phosphatases (Benzing et al., 1999; Marcic et al., 1999; Marcic and Erdös, 2000). However, several comprehensive studies using various intact isolated vessel preparations/perfused organs and ACE-resistant bradykinin analogues have not confirmed such crosstalk between ACE and kinin B_2 receptors. It was concluded that bradykinin potentiation by ACEI is only a matter of metabolism that can be explained on the basis of ACE-kinin B_2 receptor co-localization on the cell membrane affecting the concentration of bradykinin in the vicinity of the receptor (Dendorfer et al., 2001; Gobeil et al., 2002; Tom et al., 2002, 2003). Thus, the hypothetical concept of a direct physical interaction between ACE and the kinin B_2 receptor that may be influenced by ACEI is not universally accepted at this time.

7. Cardiovascular function of kinin B_1 receptor

In B_2 KO mice, kinin B_1 receptor becomes overexpressed and takes over some of the haemodynamic properties of the missing kinin B_2 receptor such as vasodilatation and hypotension associated with ACEI (Duka et al., 2001). It contributes to vasodilatation by inhibiting a vasoconstricting product of the arachidonic acid cascade acting via the PGH_2/thromboxane A_2 receptor (Duka et al., 2003). When constitutively expressed or induced under experimental conditions, kinin B_1 receptors generally mediate vasodilatation and hypotension to improve perfusion and preserve nutrition and oxygenation of vital organs. Indeed, des-Arg^9-bradykinin induced hypotension and vasodilatation in conductance and resistance coronary vessels via the activation of the constitutive canine kinin B_1 receptor (Nakhostine et al., 1993; Lamontagne et al., 1996; Bélichard et al., 1996; Su et al., 2000). An hypotension mediated by kinin B_1 receptor activation was also found in rabbits (Regoli et al., 1981; Drapeau et al., 1991), rats (Oh-ishi et al., 1996; Nicolau et al., 1996), pigs (Schmid et al., 1998) and Green monkeys (deBlois and Horlick, 2001) pre-treated with the endotoxin lipopolysaccharide, a well established approach to induce and up-regulate peripheral kinin B_1 receptors. Intriguingly, however, a paradoxical study has reported hypertensive responses to intravenous des-Arg^9-bradykinin in transgenic mice overexpressing kinin B_1 receptors (Ni et al., 2003). The reason of this discrepancy is not known but may be related to the genetic background of the genetically manipulated kinin B_1 receptor mice.

7.1. Status of the kinin B_1 receptor in diabetes: positive and negative outcomes

Several stimuli are susceptible to trigger the induction of kinin B_1 receptor in diabetes. For instance, type 1 diabetes is associated with the overproduction of pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin-1β, resulting from the autoimmune destruction of the insulin-producing β-cells in the pancreatic islets of Langerhans (Hussain et al., 1996; Rabinovitch, 1998; Rabinovitch and Suarez-Pinzon, 1998). Kinin B_1 receptor can also be induced by hyperglycaemia and the oxidative stress associated with diabetes which are known to activation the NF-kB pathway (Couture et al., 2001; Vianna et al., 2003).

Kinin B_1 receptors are induced and overexpressed in several organs of the streptozotocin-diabetic rats where they mediate several biological functions of kinins, namely the spinal autonomic control of blood pressure and nociception (Cloutier and Couture, 2000; Couture et al., 2001) and vasodilatation of retinal microvessels (Abdouh et al., 2003). In isolated renal glomeruli from streptozotocin-diabetic rats, the kinin B_1 receptor participates in the reducing effect of ACEI on hyperglycaemia-induced MAP-kinase activation, suggesting a protective effect of the kinin B_1 receptor in renal glomerulosclerosis (Mage et al., 2002). Another beneficial effect of the kinin B_1 receptor would be its ability to increase renal blood flow (Lortie et al., 1992).

The induction of kinin B_1 receptor in diabetes was also associated with unwanted syndromes of the disease, namely pain hypersensitivity and thermal hyperalgesia (Couture et

al., 2001; Gabra and Sirois, 2002, 2003a,b; Gabra et al., 2003), increased vascular permeability and inflammation (Campos et al., 2001; Simard et al., 2002), including mononuclear and polymorphonuclear leukocyte migration (Vianna et al., 2003). Overexpression of kinin B_1 receptors in transgenic mice induces susceptibility to inflammation (Ni et al., 2003) while B_1 KO mice display deficit in behavioural tests to thermal and chemical nociceptive stimuli, and reduced inflammatory responses (Pesquero et al., 2000).

Increased in vascular permeability may also be beneficial by providing a provisional scaffold for migrating endothelial cells. Interestingly enough, kinin B_1 receptor activation promotes neovascularization and angiogenesis by reducing apoptosis and stimulating endothelial cell proliferation via the NOS pathway in the absence of inflammatory reaction (Hu and Fan, 1993; Emanueli et al., 2000, 2001, 2002a,b; Emanueli and Madeddu, 2001; Morbidelli et al., 1998; Parenti et al., 2001). These studies suggested a role for the kinin B_1 receptor in post-ischaemic healing. This is in agreement with the up-regulation of kinin B_1 receptor gene expression by ischaemia in skeletal muscle and myocardium (Tschöpe et al., 2000; Emanueli et al., 2001) and on human vascular tissues in atheromatous disease (Raidoo et al., 1997). Although angiogenesis and the kinin B_1 receptor are strongly regulated by hypoxia and acidosis, the natural angiogenic responses to ischaemia are compromised by the impairment in the spontaneous surge of growth factors in diabetes and atherosclerosis (Emanueli and Madeddu, 2001). Thus, vasodilatation and neovascularization afforded by kinin B_1 receptor agonists may have a significant therapeutic potential in the treatment of peripheral ischaemic diseases such as diabetes by improving perfusion and maintaining nutrition and oxygenation of tissues. Kinin B_1 receptor activation may represent a new avenue to prevent feet amputation in diabetic patients by reversing microvascular insufficiency which represent a major cause of end-organ failure in diabetes. Conversely, kinin B_1 receptor antagonists may have promising values in the treatment of excessive vascular growth and angiogenesis occurring in cancer and chronic inflammatory diseases. In this respect, a new and orally active non-peptide kinin B_1 receptor antagonist has recently been disclosed by Sanofi-Synthelabo (Gougat et al., 2004).

7.2. Induction of kinin B_1 receptors by ACEI

Functional kinin B_1 receptors were induced and up-regulated in vascular and renal tissues of normotensive rats and B_2 KO mice (Marin-Castano et al., 2002), and in the spinal cord and aorta of spontaneously hypertensive rats (Ongali et al., 2003; Duguay et al., 2004) under chronic ACE inhibition. However, when administered acutely (24–48 h), ACEI failed to induce kinin B_1 receptors (Marceau et al., 1999). Kinin B_1 receptors contribute to the hypotensive effect of ACEI in rats (Marin-Castano et al., 2002) and to the increased forearm blood flow (vasodilatation) associated with chronic ACEI therapy in patients with heart failure (Witherow et al., 2001). Thus, endogenous kinins can participate through kinin B_1 receptors to the benefit ACEI therapy in patients with heart failure by restoring the reduced cardiac reserve following systemic vasodilatation. This is consistent with the vasodilatation reported in conductance and resistance coronary vessels, and also with the reduction of peripheral resistance induced by stimulation of the constitutive canine kinin B_1 receptor (Nakhostine et al., 1993; Lamontagne et al., 1996; Bélichard et al., 1996; Su et al., 2000). Another cardioprotective action of the kinin B_1 receptor is the inhibition of ventricular arrhythmias attributed to a decrease of noradrenaline release at reperfusion in the rat ischaemic heart (Chahine et al., 1993).

Despite the kinin B_1 receptor appears to play a protective role in cardiovascular and renal functions, the real contribution of these receptors to the benefit of ACEI therapy in diabetes deserves further investigation. Intriguingly, it has been claimed that part of the therapeutic efficacy of ACEI is due to direct stimulation of kinin B_1 receptors (Ignjatovic et al., 2002a,b). However, this concept has been critically challenged and not confirmed in several tissue systems and in cell line stably expressing kinin B_1 receptors (Fortin et al., 2003). An unwanted effect is also attributed to kinin B_1 receptors, namely angioedema in susceptible patients treated with ACEI (Blais et al., 1999; Molinaro et al., 2002).

8. Perspectives

It is becoming clear that the formation of AGEs is a very important early step in the initiation of deleterious cascades leading to diabetic complications and therefore controlling AGEs formation and action can be an efficient therapy to reduce the progression of diabetes in peripheral tissues. An increasing number of reports demonstrate reduction of oxidative stress by anti-hypertensive agents such as ACEI and angiotensin AT_1 blockers, suggesting additive mechanisms with the haemodynamic control. Combination therapy with ACE and AGE inhibition offers superior renoprotective effects when compared with either monotherapy in the diabetic spontaneously hypertensive rat (Davis et al., 2004). Several recent reports show that endogenous bradykinin plays a pivotal role, through kinin B_1 and/or B_2 receptors, in the mechanism of the cardio- and renoprotective actions not only of ACEI (Witherow et al., 2001; Marin-Castano et al., 2002; Zhou et al., 2003; Pawluczyk et al., 2004) but also of angiotensin AT_1 blockers (Walther et al., 2002; Yokota et al., 2003; Tschöpe et al., 2004a). As locally increased concentration of bradykinin by ACEI and angiotensin AT_2 receptor stimulation (under angiotensin AT_1 receptor blockade) affords cardioprotective and nephroprotective effects, selective kinin B_2 receptor agonists (and in some circumstances kinin B_1 receptor agonists) may represent promising therapeutic agents in the treatment of various cardiovascular disorders and diabetes mellitus. Indeed activation of kinin receptors are associated with both

Table 1
Summary of positive and negative effects of peripheral kinin receptors in diabetes mellitus

	B_1 receptors	B_2 receptors
Positive effects	Neovascularisation	Antioxidant (NO)
	Angiogenesis	Antihypertension
	Vasodilatation/hypotension	Vasodilatation/hypotension
	Antiischemia	Antiischemia
	Reno- and cardioprotection under ACEI therapy	Reno- and cardioprotection under ACEI therapy
	Antiarrhythmia	Decrease insulin resistance
		Increase glucose uptake (GLUT-4 translocation)
		Increase glucose supply
		Antiproliferation
		Antihypertrophia
		Antifibrosis
		Antithrombosis
Negative effects	Chronic pain/inflammation	Acute pain/inflammation
	Hyperalgesia	Hyperalgesia
	Angioedema under ACEI	Oedema
	Vascular hyperpermeability	Vascular hyperpermeability
	Leukocytes infiltration	Rhinitis
	Cough	Arthritis
		Asthma

positive and negative effects as summarized in Table 1. Thus a balance between the dual beneficial and pro-inflammatory effects of bradykinin in clinical situations remain a major challenge, and a safe therapeutic window remains to be determined. However, recent data suggest that the vasodilatation, anti-proliferative and anti-fibrotic effects of bradykinin could be mediated by distinct signalling pathways. Therefore, the possibility to define specific agonists of these distinct pathways open new challenge, i.e. kinin B_2 receptor agonists devoid of inflammatory/pain effect. Several long-acting non-peptide B_2 receptor agonists were recently made available (Asano et al., 1998, Amblard et al., 1999, Sawada et al., 2004a,b) and provide promising tools for this new approach. Moreover, angiotensin AT_2 receptor activation and angiotensin (1–7) facilitate the release of bradykinin and NO (Wiemer et al., 2002; Abadir et al., 2003; Kurisu et al., 2003; Hannan et al., 2003; Tom et al., 2003; Soares de Moura et al., 2004), angiotensin AT_2 receptor agonists and mimetic compounds at the putative angiotensin (1–7) receptor (Wiemer et al., 2002) may have important clinical value. These unexplored therapeutic targets still remain unanswered questions.

The kinin B_1 receptor represents a promising target in the treatment of various diabetic complications, including hyperalgesia, neuropathy, retinopathy and nephropathy. Since kinin receptors are Janus-faced receptors, these data also raise the puzzling question whether or not an agonist rather than an antagonist should be used in the treatment of diabetic complications (Heitsch, 2003). Whereas the induced kinin B_1 receptor exhibits nephro and cardioprotective effects and neovascularization that can reverse ischaemia and vascular angiopathy, this receptor also participates to hyperalgesia and inflammatory processes that could be better treated with the use of kinin B_1 receptor antagonists. Further insights in clinical settings are urgently needed to define a more conclusive therapeutic approach. More challenging would be to deliver locally kinin B_1 receptor agonists/antagonists or kinin B_1 receptor gene to switch on or switch off a specific function in a selected target organ in order to prevent unwanted systemic and/or central effects.

Recent studies have shown that dual inhibition of ACE and neutral endopeptidase 24.11 with so-called vasopeptidase inhibitors (omapatrilat, AVE7688) is more effective than ACEI alone to ameliorate type 2 diabetic nephropathy, whole-body and myocardial insulin resistance in rat, and to improve both symptoms and prognosis in congestive heart failure patients (Rouleau et al., 2000; Wang et al., 2003; Schäfer et al., 2004a). Blockade of both enzymes has a greater protective effect on bradykinin metabolism than ACE inhibition alone in human heart membranes (Blais et al., 2000). Most probably vasopeptidase inhibitors also prevent the degradation of other vasoactive peptides which can improve the endothelial dysfunction by re-establishing the generation of NO mediated by receptor activation (d'Uscio et al., 2001; Schäfer et al., 2004b). Thus, the next decade promises to be one of great discovery and hope that might improve the care for patients with diabetes.

Acknowledgements

This work was supported by grants from the Canadian Institutes of Health Research (MOP-14379) to RC, INSERM U388 to J-PG and INSERM-FRSQ program to RC and J-PG.

References

Abadir, P.M., Carey, R.M., Siragy, H.M., 2003. Angiotensin AT_2 receptors directly stimulate renal nitric oxide in bradykinin B_2-receptor-null mice. Hypertension 42, 600–604.

Abdouh, M., Khanjari, A., Abdelazziz, N., Ongali, B., Couture, R., Hasséssian, H.M., 2003. Early upregulation of kinin B_1 receptors in retinal microvessels of the streptozotocin-diabetic rat. Br. J. Pharmacol. 140 (1), 33–40.

Aiello, L.M., 2003. Perspectives on diabetic retinopathy. Am. J. Ophthalmol. 136 (1), 122–135.

Alfie, M.E., Sigmon, D.H., Pomposiello, S.I., Carretero, O.A., 1997. Effect of high salt intake in mutant mice lacking bradykinin-B_2 receptors. Hypertension 29, 483–487.

Alric, C., Pecher, C., Bascands, J.-L., Girolami, J.-P., 1999. Effect of bradykinin on tyrosine kinase and phosphatase activities and cell proliferation in mesangial cells. Immunopharmacology 45 (1–3), 57–62.

Amblard, M., Daffix, I., Bedos, P., Berge, G., Pruneau, D., Paquet, J.L., Luccarini, J.M., Bélichard, P., Dodey, P., Martinez, J., 1999. Design and synthesis of potent bradykinin agonists containing a benzothiazepine moiety. J. Med. Chem. 42 (20), 4185–4192.

Asahi, K., Ichimori, K., Nakazawa, H., Izuhara, Y., Inagi, R., Watanabe, T., Miyata, T., Kurokawa, K., 2000. Nitric oxide inhibits the

formation of advanced glycation end products. Kidney Int. 58 (4), 1780–1787.
Asano, M., Hatori, C., Sawai, H., Johki, S., Inamura, N., Kayakiri, H., Satoh, S., Abe, Y., Inoue, T., Sawada, Y., Mizutani, T., Oku, T., Nakahara, K., 1998. Pharmacological characterization of a nonpeptide bradykinin B_2 receptor antagonist, FR165649, and agonist, FR190997. Br. J. Pharmacol. 124 (3), 441–446.
Baba, T., Murabayashi, S., Ishizaki, T., Ido, Y., Aoyagi, K., Takebe, K., 1986. Renal kallikrein in diabetic patients with hypertension accompanied by nephropathy. Diabetologia 29 (3), 162–167.
Bachvarov, D.R., Hess, J.F., Menke, J.G., Larrivée, J.F., Marceau, F., 1996. Structure and genomic organization of the human B1 receptor gene for kinins (BDKRB1). Genomics 33, 374–381.
Bachvarov, D.R., Landry, M., Pelletier, I., Chevrette, M., Betard, C., Houde, I., Bergeron, J., Lebel, M., Marceau, F., 1998. Characterization of two polymorphic sites in the human kinin B1 receptor gene: altered frequency of an Allele in patients with a history of end-stage renal failure. J. Am. Soc. Nephrol. 9, 598–604.
Bank, N., Lahorra, M.A., Aynedjian, H.S., Schlondorff, D., 1988. Vasoregulatory hormones and the hyperfiltration of diabetes. Am. J. Physiol. 254 (2 Pt2), F202–F209.
Bascands, J.-L., Schanstra, J.P., Couture, R., Girolami, J.-P., 2003. Les récepteurs de la bradykinine: de nouveaux rôles physio-pathologiques. Médecine/Sciences 19 (11), 1093–1100.
Baynes, J.W., 1991. Role of oxidative stress in development of complications in diabetes. Diabetes 40, 405–412.
Begum, N., Tepperman, H.M., Tepperman, J., 1985. Studies on the possible involvement of prostaglandins in insulin generation of pyruvate dehydrogenase activator. Diabetes 34 (1), 29–37.
Bélichard, P., Loillier, B., Paquet, J.L., Luccarini, J.M., Pruneau, D., 1996. Haemodynamic and cardiac effects of kinin B_1 and B_2 receptor stimulation in conscious instrumented dogs. Br. J. Pharmacol. 117 (7), 1565–1571.
Benbow, S.J., MacFarlane, I.A., 1999. Painful diabetic neuropathy. Baillière's Clin. Endocrinol. Metab. 13 (2), 295–308.
Benzing, T., Fleming, I., Blaukat, A., Müller-Esterl, W., Busse, R., 1999. Angiotensin-converting enzyme inhibitor ramiprilat interferes with the sequestration of the B_2 kinin receptor within the plasma membrane of native endothelial cells. Circulation 99, 2034–2040.
Bhoola, K.D., Figueroa, C.D., Worthy, K., 1992. Bioregulation of kinins: kallikreins, kininogens, and kininases. Pharmacol. Rev. 44, 1–80.
Blais Jr., C., Rouleau, J.L., Brown, N.J., Lepage, Y., Spence, D., Munoz, C., Friborg, J., Geadah, D., Gervais, N., Adam, A., 1999. Serum metabolism of bradykinin and des-Arg9-bradykinin in patients with angiotensin-converting enzyme inhibitor-associated angioedema. Immunopharmacology 43 (2–3), 293–302.
Blais, C.Jr., Fortin, D., Rouleau, J.L., Molinaro, G., Adam, A., 2000. Protective effect of omapatrilat, a vasopeptidase inhibitor, on the metabolism of bradykinin in normal and failing human hearts. J. Pharmacol. Exp. Ther. 295 (2), 621–626.
Blaukat, A., 2003. Structure and signalling pathways of kinin receptors. Andrologia 35 (1), 17–23.
Brochu, I., Labonté, J., Bkaily, G., D'Orléans-Juste, P., 2002. Role of endothelin receptors in the hypertensive state of kinin B2 knockout mice subjected to a high-salt diet. Clin. Sci. 103 (Suppl. 48), 380S–384S.
Brownlee, M., 2001. Biochemistry and molecular cell biology of diabetic complications. Nature 414 (6865), 813–820.
Cai, H., Griendling, K.K., Harrison, D.G., 2003. The vascular NAD(P)H oxidases as therapeutic targets in cardiovascular diseases. Trends Pharmacol. Sci. 24 (9), 471–478.
Cameron, N.E., Eaton, S.E., Cotter, M.A., Tesfaye, S., 2001. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia 44, 1973–1988.
Campbell, D.J., 2000. Towards understanding the kallikrein-kinin system: insights from measurement of kinin peptides. Braz. J. Med. Biol. Res. 33, 665–677.
Campos, M.M., Souza, G.E.P., Calixto, J.B., 1999. In vivo B1 kinin-receptor upregulation. Evidence for involvement of protein kinases and nuclear factor κB pathways. Br. J. Pharmacol. 127, 1851–1859.
Campos, M.M., Cabrini, D.A., Cardozo, A.H., Rae, G.A., Toro, J.H., Calixto, J.B., 2001. Changes in paw oedema triggered via bradykinin B(1) and B(2) receptors in streptozotocin-diabetic rats. Eur. J. Pharmacol. 416 (1–2), 169–177.
Carvalho, C.R.O., Thirone, A.C.P., Gontijo, J.A.R., Velloso, L.A., Saad, M.J.A., 1997. Effect of captopril, losartan, and bradykinin on early steps of insulin action. Diabetes 46, 1950–1957.
Cellier, E., Duchêne, J., Pécher, C., Alric, C., Bascands, J.-L., Schanstra, J.P., Girolami, J.-P., 2002. B_2 receptor activation reduces Erk1 and Erk2 phosphorylation induced by insulin-like growth factor-1, platelet-derived growth factor-BB, and high glucose in rat isolated glomeruli. Can. J. Physiol. Pharm. 80, 341–345.
Cellier, E., Mage, M., Duchêne, J., Pécher, C., Couture, R., Bascands, J.-L., Girolami, J.P., 2003. Bradykinin reduces growth factor-induced glomerular ERK1/2 phosphorylation. Am. J. Physiol. Renal Physiol. 284, F282–F292.
Ceriello, A., 1999. Hyperglycaemia: the bridge between non-enzymatic glycation and oxidative stress in the pathogenesis of diabetic complications. Diabetes Nutr. Metab. 12, 42–46.
Cervenka, L., Harrison-Bernard, L.M., Dipp, S., Primrose, G., Imig, J.D., El-Dahr, S.S., 1999. Early onset salt-sensitive hypertension in bradykinin B_2 receptor null mice. Hypertension 34, 176–180.
Cervenka, L., Maly, J., Karasova, L., Simova, M., Vitko, S., Hellerova, S., Heller, J., El-Dahr, S.S., 2001. Angiotensin II-induced hypertension in bradykinin B_2 receptor knockout mice. Hypertension 37 (3), 967–973.
Chahine, R., Adam, A., Yamaguchi, N., Gaspo, R., Regoli, D., Nadeau, R., 1993. Protective effects of bradykinin on the ischaemic heart: implication of the B_1 receptor. Br. J. Pharmacol. 108 (2), 318–322.
Chao, J., Zhang, J.J., Lin, K.F., Chao, L., 1998. Human kallikrein gene delivery attenuates hypertension, cardiac hypertrophy, and renal injury in Dahl salt-sensitive rats. Hum. Gene Ther. 9, 21–31.
Christen, Y., Waeber, B., Nussberger, J., Porchet, M., Borland, R.M., Lee, R.J., Maggon, K., Shum, L., Timmermans, P.B., Brunner, H.R., 1991. Oral administration of DuP 753, a specific angiotensin II receptor antagonist, to normal male volunteers. Inhibition of pressor response to exogenous angiotensin I and II. Circulation 83 (4), 1333–1342.
Christopher, J., Velarde, V., Zhang, D., Mayfield, D., Mayfield, R.K., Jaffa, A.A., 2001. Regulation of B_2-kinin receptors by glucose in vascular smooth muscle cells. Am. J. Physiol. Heart Circ. Physiol. 280 (4), H1537–H1546.
Cloutier, F., Couture, R., 2000. Pharmacological characterization of the cardiovascular responses elicited by kinin B_1 and B_2 receptor agonists in the spinal cord of streptozotocin-diabetic rats. Br. J. Pharmacol. 130, 375–385.
Cooper, M.E., 2001. Interaction of metabolic and haemodynamic factors in mediating experimental diabetic nephropathy. Diabetologia 44 (11), 1957–1972.
Couture, R., Lindsey, C.J., 2000. Brain kallikrein-kinin system: from receptors to neuronal pathways and physiological functions. In: Quirion, R., Björklund, A., Hökfelt, T. (Eds.), Handbook of Chemical Neuroanatomy, Peptide Receptors, Part I, vol. 16. Elsevier Science B.V., Amsterdam, The Netherlands, pp. 241–300.
Couture, R., Harrisson, M., Vianna, R.M., Cloutier, F., 2001. Kinin receptors in pain and inflammation. Eur. J. Pharmacol. 429, 161–176.
Damas, J., Bourdon, V., Lefebvre, P.J., 1999. Insulin sensitivity, clearance and release in kininogen-deficient rats. Exp. Physiol. 84 (3), 549–557.
Davis, B.J., Forbes, J.M., Thomas, M.C., Jerums, G., Burns, W.C., Kawachi, H., Allen, T.J., Cooper, M.E., 2004. Superior renoprotective effects of combination therapy with ACE and AGE inhibition in the diabetic spontaneously hypertensive rat. Diabetologia 47, 89–97.
deBlois, D., Horlick, R.A., 2001. Endotoxin sensitization to kinin B(1) receptor agonist in a non-human primate model: haemodynamic and pro-inflammatory effects. Br. J. Pharmacol. 132 (1), 327–335.

de Cavanagh, E.M., Fraga, C.G., Ferder, L., Inserra, F., 1997. Enalapril and captopril enhance antioxidant defenses in mouse tissues. Am. J. Physiol. 272 (2 Pt2), R514–R518.

de Cavanagh, E.M., Ferder, L., Carrasquedo, F., Scrivo, D., Wassermann, A., Fraga, C.G., Inserra, F., 1999. Higher levels of antioxidant defenses in enalapril-treated versus non-enalapril-treated hemodialysis patients. Am. J. Kidney Dis. 34 (3), 445–455.

de Cavanagh, E.M., Inserra, F., Tobli, J., Stella, I., Fraga, C.G., Ferder, L., 2001. Enalapril attenuates oxidative stress in diabetic rats. Hypertension 38 (5), 1130–1136.

Dendorfer, A., Reissmann, S., Wolfrum, S., Raasch, W., Dominiak, P., 2001. Potentiation of kinin analogues by ramiprilat is exclusively related to their degradation. Hypertension 38, 142–146.

De Vriese, A.S., Verbeuren, T.J., Van de Voorde, J., Lameire, N.H., Vanhoutte, P.M., 2000. Endothelial dysfunction in diabetes. Br. J. Pharmacol. 130 (5), 963–974.

Dhamrait, S.S., Payne, J.R., Li, P., Jones, A., Toor, I.S., Cooper, J.A., Hawe, E., Palmen, J.M., Wootton, P.T.E., Miller, G.J., Humphries, S.E., Montgomery, H.E., 2003. Variation in bradykinin receptor genes increases the cardiovascular risk associated with hypertension. Eur. Heart J. 24, 1672–1680.

Dickinson, P.J., Carrington, A.L., Frost, G.S., Boulton, A.J.M., 2002. Neurovascular disease, antioxidants and glycation in diabetes. Diabetes Metab. Res. Rev. 18, 260–272.

Dietze, G., Maerker, E., Lodri, C., Schifman, R., Wicklmayr, M., Geiger, R., Fink, E., Boettger, I., Fritz, H., Mehnert, H., 1984. Possible involvement of kinins in muscle energy metabolism. Adv. Exp. Med. Biol. 167, 63–71.

Dietze, G.J., Wicklmayr, M., Rett, K., Jacob, S., Henriksen, E.J., 1996. Potential role of bradykinin in forearm muscle metabolism in humans. Diabetes 45 (Suppl. 1), S110–S114.

Donoghue, M., Hsieh, F., Baronas, E., Godbout, K., Gosselin, M., Stagliano, N., Donovan, M., Woolf, B., Robison, K., Jeyaseelan, R., Breitbart, R.E., Acton, S., 2000. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. Circ. Res. 87 (5), E1–E9.

Drapeau, G., deBlois, D., Marceau, F., 1991. Hypotensive effects of Lys-des-Arg9-bradykinin and metabolically protected agonists of B_1 receptors for kinins. J. Pharmacol. Exp. Ther. 259 (3), 997–1003.

Duchêne, J., Schanstra, J., Cellier, E., Bascands, J.-L., Girolami, J.-P., 2002a. Le récepteur B_2 de la bradykinine: voie alternative et antiproliférative. Néphrologie 23 (1), 39–41.

Duchêne, J., Schanstra, J.P., Pecher, C., Pizard, A., Susini, C., Esteve, J.-P., Bascands, J.-L., Girolami, J.P., 2002b. A novel protein-protein interaction between a G protein-coupled receptor and the phosphatase SHP-2 is involved in bradykinin-induced inhibition of cell proliferation. J. Biol. Chem. 277 (43), 40375–40383.

Duguay, D., Sarkissian, S.D., Kouz, R., Ongali, B., Couture, R., deBlois, D., 2004. Kinin B_2 receptor is not involved in enalapril-induced apoptosis and regression of hypertrophy in spontaneously hypertensive rat aorta: possible role of B_1 receptor. Br. J. Pharmacol. 141 (4), 728–736.

Duka, I., Shenouda, S., Johns, C., Kintsurashvili, E., Gavras, I., Gavras, H., 2001. Role of the B_2 receptor of bradykinin in insulin sensitivity. Hypertension 38, 1355–1360.

Duka, I., Duka, A., Kintsurashvili, E., Johns, C., Gavras, I., Gavras, H., 2003. Mechanisms mediating the vasoactive effects of the B_1 receptors of bradykinin. Hypertension 42, 1021–1025.

d'Uscio, L.V., Quaschning, T., Burnett, Jr. J.C., Luscher, T.F., 2001. Vasopeptidase inhibition prevents endothelial dysfunction of resistance arteries in salt-sensitive hypertension in comparison with single ACE inhibition. Hypertension 37 (1), 28–33.

Emanueli, C., Madeddu, P., 2001. Targeting kinin receptors for the treatment of tissue ischaemia. Trends Pharmacol. Sci. 22 (9), 478–484.

Emanueli, C., Fink, E., Milia, A.F., Salis, M.B., Conti, M., Demontis, M.P., Madeddu, P., 1998. Enhanced blood pressure sensitivity to deoxycorticosterone in mice with disruption of bradykinin B_2 receptor gene. Hypertension 31, 1278–1283.

Emanueli, C., Zacheo, A., Minasi, A., Chao, J., Chao, L., Salis, M.B., Stacca, T., Straino, S., Capogrossi, M.C., Madeddu, P., 2000. Adenovirus-mediated human tissue kallikrein gene delivery induces angiogenesis in normoperfused skeletal muscle. Arterioscler. Thromb. Vasc. Biol. 20 (11), 2379–2385.

Emanueli, C., Minasi, A., Zacheo, A., Chao, J., Chao, L., Salis, M.B., Straino, S., Tozzi, M.G., Smith, R., Gaspa, L., Bianchini, G., Stillo, F., Capogrossi, M.C., Madeddu, P., 2001. Local delivery of human tissue kallikrein gene accelerates spontaneous angiogenesis in mouse model of hindlimb ischemia. Circulation 103 (1), 125–132.

Emanueli, C., Salis, M.B., Pinna, A., Stacca, T., Milia, A.F., Spano, A., Chao, J., Chao, L., Sciola, L., Madeddu, P., 2002. Prevention of diabetes-induced microangiopathy by human tissue kallikrein gene transfer. Circulation 106 (8), 993–999.

Emanueli, C., Salis, M.B., Stacca, T., Pintus, G., Kirchmair, R., Isner, J.M., Pinna, A., Gaspa, L., Regoli, D., Cayla, C., Pesquero, J.B., Bader, M., Madeddu, P., 2002. Targeting kinin B_1 receptor for therapeutic neovascularization. Circulation 105, 360–366.

Feldman, E.L., 2003. Oxidative stress and diabetic neuropathy: a new understanding of an old problem. J. Clin. Invest. 111, 431–433.

Feng, Y., Niu, T., Xu, X., Chen, C., Li, Q., Qian, R., Wang, G., Xu, X., 2002. Insertion/deletion polymorphism of the ACE gene is associated with type 2 diabetes. Diabetes 51, 1986–1988.

Figueroa, C.D., Dietze, G., Esterl, W., 1996. Immunolocalization of bradykinin B_2 receptors on skeletal muscle cells. Diabetes 45 (Suppl. 1), 24–28.

Forbes, J.M., Cooper, M.E., Thallas, V., Burns, W.C., Thomas, M.C., Brammar, G.C., Lee, F., Grant, S.L., Burrell, L.A., Jerums, G., Osicka, T.M., 2002. Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy. Diabetes 51 (11), 3274–3282.

Forgione, M.A., Weiss, N., Heydrick, S., Cap, A., Klings, E.S., Bierl, C., Eberhardt, R.T., Farber, H.W., Loscalzo, J., 2002. Cellular glutathione peroxidase deficiency and endothelial dysfunction. Am. J. Physiol. Heart Circ. Physiol. 282 (4), H1255–H1261.

Fortin, J.-P., Gobeil Jr., F., Adam, A., Regoli, D., Marceau, F., 2003. Do angiotensin-converting enzyme inhibitors directly stimulate the kinin B_1 receptor? Am. J. Physiol. Heart Circ. Physiol. 285, H277–H282.

Gabra, B.H., Sirois, P., 2002. Role of bradykinin B_1 receptors in diabetes-induced hyperalgesia in streptozotocin-treated mice. Eur. J. Pharmacol. 457, 115–124.

Gabra, B.H., Sirois, P., 2003a. Beneficial effect of chronic treatment with the selective bradykinin B_1 receptor antagonists, R-715 and R-954, in attenuating streptozotocin-diabetic thermal hyperalgesia in mice. Peptides 24, 1131–1139.

Gabra, B.H., Sirois, P., 2003b. Kinin B_1 receptor antagonists inhibit diabetes-induced hyperalgesia in mice. Neuropeptides 37, 36–44.

Gabra, B.H., Couture, R., Sirois, P., 2003. Dualité fonctionnelle des récepteurs des kinines en physiopathologie. Médecine/Sciences 19 (11), 1101–1110.

Gainer, J.V., Brown, N.J., Bachvarova, M., Bastien, L., Maltais, I., Marceau, F., Bachvarov, D.R., 2000. Altered frequency of a promoter polymorphism of the kinin B2 receptor gene in hypertensive African-Americans. Am. J. Hypertens. 13, 1268–1273.

Gallagher, A.M., Yu, H., Printz, M.P., 1998. Bradykinin-induced reductions in collagen gene expression involve prostacylin. Hypertension 32 (1), 84–88.

Gobeil, F., Hallé, S., Blais, P.-A., Regoli, D., 2002. Studies on the angiotensin-converting enzyme and the kinin B_2 receptor in the rabbit jugular vein: modulation of contractile response to bradykinin. Can. J. Physiol. Pharm. 80, 151–161.

Gohlke, P., Pees, C., Unger, T., 1998. AT2 receptor stimulation increases aortic cyclic GMP in SHRSP by a kinin-dependent mechanism. Hypertension 31 (1 Pt2), 349–355.

Gorus, F.K., Weets, I., Couck, P., Pipeleers, D.G., 2004. Epidemiology of type 1 and type 2 diabetes. The added value of diabetes registries for

conducting clinical studies: the Belgian paradigm. Acta Clin. Belg. 59 (1), 1–13.

Gougat, J., Ferrari, B., Sarran, L., Planchenault, C., Poncelet, M., Maruani, J., Alonso, R., Cudennec, A., Croci, T., Guagnini, F., Urban-Szabo, K., Martinolle, J.-P., Soubrié, P., Finance, O., Le Fur, G., 2004. SSR240612, a new non-peptide antagonist of the bradykinin B_1 receptor. Biochemical and pharmacological characterization. J. Pharmacol. Exp. Ther. 309 (2), 661–669.

Graness, A., Hanke, S., Boehmer, F.D., Presek, P., Liebmann, C., 2000. Protein-tyrosine-phosphatase-mediated epidermal growth factor (EGF) receptor-transinactivation and EGF receptor-independent stimulation of mitogen-activated protein kinase by bradykinin in A431 cells. Biochem. J. 347, 441–447.

Grassi, G., 2003. Diabetic retinopathy. Minerva Med. 94 (6), 419–435.

Griendling, K.K., FitzGerald, G.A., 2003. Oxidative stress and cardiovascular injury: Part I. Basic mechanisms and in vivo monitoring of ROS. Circulation 108 (16), 1912–1916.

Ha, H., Kim, K.H., 1999. Pathogenesis of diabetic nephropathy: the role of oxidative stress and protein kinase C. Diabetes Res. Clin. Pract. 45, 147–151.

Ha, H., Lee, S.H., Kim, K.H., 1997. Effects of rebamipide in a model of experimental diabetes and on the synthesis of transforming growth factor-beta and fibronectin, and lipid peroxidation induced by high glucose in cultured mesangial cells. J. Pharmacol. Exp. Ther. 281 (3), 1457–1462.

Hannan, R.E., Davis, E.A., Widdop, R.E., 2003. Functional role of angiotensin II AT_2 receptor in modulation of AT_1 receptor-mediated contraction in rat uterine artery: involvement of bradykinin and nitric oxide. Br. J. Pharmacol. 140 (5), 987–995.

Heilig, C.W., Brosius, F.C., Henry, D.N., 1997. Glucose transporters of the glomerulus and the implications for diabetic nephropathy. Kidney Int. 52 (Suppl. 60), S-91–S-99.

Heilig, C.W., Kreisberg, J.I., Freytag, S., Murakami, T., Ebina, Y., Guo, L., Heilig, K., Loberg, R., Qu, X., Jin, Y., Henry, D., Brosius, F.C., 2001. Antisense GLUT-1 protects mesangial cells from glucose induction of GLUT-1 and fibronectin expression. Am. J. Physiol. Renal Physiol. 280 (4), F657–F666.

Heitsch, H., 2003. The therapeutic potential of bradykinin B2 receptor agonists in the treatment of cardiovascular disease. Expert Opin. Investig. Drugs 12 (5), 759–770.

Henriksen, E.J., Jacob, S., 1995. Effect of captopril on glucose transport activity in skeletal muscle of obese Zucker rats. Metabolism 44, 267–272.

Henriksen, E.J., Jacob, S., Agustin, H.J., Dietze, G.J., 1996. Glucose transport activity in insulin resistant rat muscle: effects of ACE inhibitors and bradykinin antagonism. Diabetes 45 (Suppl. 1), S125–S128.

Henriksen, E.J., Jacob, S., Fogt, D.L., Dietze, G.J., 1998. Effects of chronic bradykinin administration on insulin action in an animal model of insulin resistance. Am. J. Physiol. 275, R40–R45.

Henriksen, E.J., Jacob, S., Kinnick, T.R., Youngblood, E.B., Schmit, M.B., Dietze, G.J., 1999. ACE inhibition and glucose transport in insulin resistant muscle: roles of bradykinin and nitric oxide. Am. J. Physiol. 277 (1 Pt2), R332–R336.

Hodgkinson, A.D., Bartlett, T., Oates, P.J., Millward, B.A., Demaine, A.G., 2003. The response of antioxidant genes to hyperglycemia is abnormal in patients with type 1 diabetes and diabetic nephropathy. Diabetes 52 (3), 846–851.

Himmelfarb, J., McMonagle, E., 2001. Albumin is the major plasma protein target of oxidant stress in uremia. Kidney Int. 60 (1), 358–363.

Hu, D.E., Fan, T.P., 1993. [Leu^8]des-Arg^9-bradykinin inhibits the angiogenic effect of bradykinin and interleukin-1 in rats. Br. J. Pharmacol. 109 (1), 14–17.

Huang, W., Gallois, Y., Bouby, N., Bruneval, P., Heudes, D., Belair, M.-F., Krege, J.H., Meneton, P., Marre, M., Smithies, O., Alhenc-Gelas, F., 2001. Genetically increased angiotensin 1-converting enzyme level and renal complications in the diabetic mouse. Proc. Natl. Acad. Sci. U. S. A. 98, 13330–13334.

Hussain, M.J., Peakman, M., Gallati, H., Lo, S.S., Hawa, M., Viberti, G.C., Watkins, P.J., Leslie, R.D., Vergani, D., 1996. Elevated serum levels of macrophage-derived cytokines precede and accompany the onset of IDDM. Diabetologia 39 (1), 60–69.

Ignjatovic, T., Tan, F., Brovkovych, V., Skidgel, R.A., Erdös, E.G., 2002a. Activation of bradykinin B_1 receptor by ACE inhibitors. Int. Immunopharmacol. 2 (13–14), 1787–1793.

Ignjatovic, T., Tan, F., Brovkovych, V., Skidgel, R.A., Erdös, E.G., 2002b. Novel mode of action of angiotensin I converting enzyme inhibitors: direct activation of bradykinin B_1 receptor. J. Biol. Chem. 277 (19), 16847–16852.

Imig, J.D., Zhao, X., Orengo, S.R., Dipp, S., El-Dahr, S.S., 2003. The bradykinin B_2 receptor is required for full expression of renal COX-2 and renin. Peptides 24, 1141–1147.

Isami, S., Kishikawa, H., Araki, E., Uechara, M., Kaneko, K., Shirotani, T., Todaka, M., Ura, S., Motoyoshi, S., Matsumoto, K., Miyamura, N., Shichiri, M., 1996. Bradykinin enhances GLUT4 translocation through the increase of insulin receptor tyrosine kinase in primary adipocytes: evidence that bradykinin stimulates the insulin signalling pathway. Diabetologia 39 (4), 412–420.

Jaffa, A.A., Miller, D.H., Bailey, G.S., Chao, J., Margolius, H.S., Mayfield, R.K., 1987. Abnormal regulation of renal kallikrein in experimental diabete effects of insulin on prokallikrein synthesis and activation. J. Clin. Invest. 80 (6), 1651–1659.

Jaffa, A.A., Chai, K.X., Chao, J., Chao, L., Mayfield, R.K., 1992. Effects of diabetes and insulin on expression of kallikrein and renin genes in the kidney. Kidney Int. 41, 789–795.

Jaffa, A.A., Rust, P.F., Mayfield, R.K., 1995. Kinin, a mediator of diabetes-induced glomerular hyperfiltration. Diabetes 44 (2), 156–160.

Jaffa, A.A., Vio, C., Velarde, V., LeRoith, D., Mayfield, R.K., 1997. Induction of renal kallikrein and renin gene expression by insulin and IGF-I in the diabetic rat. Diabetes 46 (12), 2049–2056.

Jaffa, A.A., Durazo-Arvizu, R., Zheng, D., Lackland, D.T., Srikanth, S., Garvey, W.T., Schmaier, A.H., 2003. Plasma prekallikrein: a risk marker for hypertension and nephropathy in type 1 diabetes. Diabetes 52 (5), 1215–1221.

Jiang, Z.Y., Lin, Y.W., Clemont, A., Feener, E.P., Hein, K.D., Igarashi, M., Yamauchi, T., White, M.F., King, G.L., 1999. Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (fa/fa) rats. J. Clin. Invest. 104 (4), 447–457.

Kim, H.S., Krege, J.H., Kluckman, K.D., Hagaman, J.R., Hodgin, J.B., Best, C.F., Jennette, J.C., Coffman, T.M., Maeda, N., Smithies, O., 1995. Genetic control of blood pressure and the angiotensinogen locus. Proc. Natl. Acad. Sci. U. S. A. 92, 2735–2739.

Kim, N.N., Villegas, S., Summerour, S., Villarreal, F.J., 1999. Regulation of cardiac fibroblast extracellular matrix production by bradykinin and nitric oxide. J. Mol. Cell. Cardiol. 31 (2), 457–466.

King, R.H., 2001. The role of glycation in the pathogenesis of diabetic polyneuropathy. J. Clin. Pathol. Mol. Pathol. 54, 400–408.

King, H., Aubert, R.E., Herman, W.H., 1998. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 21 (9), 1414–1431.

Kinugawa, S., Post, H., Kaminski, P.M., Zhang, X., Xu, X., Huang, H., Recchia, F.A., Ochoa, M., Wolin, M.S., Kaley, G., Hintze, T.H., 2003. Coronary microvascular endothelial stunning after acute pressure overload in the conscious dog is caused by oxidant processes. Circulation 108, 2934–2940.

Kishi, K., Muromoto, N., Nakaya, Y., Miyata, I., Hagi, A., Hayashi, H., Ebina, Y., 1998. Bradykinin directly triggers GLUT4 translocation via an insulin independent pathway. Diabetes 47 (4), 550–558.

Kitada, M., Koya, D., Sugimoto, T., Isono, M., Araki, S., Kashiwagi, A., Haneda, M., 2003. Translocation of glomerular p47phox and p67phox by protein kinase C-beta activation is required for oxidative stress in diabetic nephropathy. Diabetes 52 (10), 2603–2614.

Klein, R., 1996. Diabetic retinopathy. Annu. Rev. Public Health 17, 137–158.

Knigge, H., Bluthner, M., Bruntgens, A., Sator, H., Ritz, E., 2000. G(−699)/C polymorphism in the bradykinin-1 receptor gene in patients with renal failure. Nephrol. Dial. Transplant. 15 (5), 586–588.

Kohlman Jr., O., Neves, F., de, A., Ginoza, M., Taveres, A., Cezareti, M.L., Zanella, M.T., Ribeiro, A.B., Gavras, I., Gavras, H., 1995. Role of bradykinin in insulin sensitivity and blood pressure regulation during hyperinsulinemia. Hypertension 25, 1003–1007.

Komers, R., Cooper, M.E., 1995. Acute renal hemodynamic effects of ACE inhibition in diabetic hyperfiltration: role of kinins. Am. J. Physiol. 268 (4 Pt2), F588–F594.

Kuoppala, A., Lindstedt, K.A., Saarinen, J., Kovanen, P.T., Kokkonen, J.O., 2000. Inactivation of bradykinin by angiotensin-converting enzyme and by carboxypeptidase N in human plasma. Am. J. Physiol. Heart Circ. Physiol. 278, H1069–H1074.

Kurisu, S., Ozono, R., Oshima, T., Kambe, M., Ishida, T., Sugino, H., Matsuura, H., Chayama, K., Teranishi, Y., Iba, O., Amano, K., Matsubara, H., 2003. Cardiac angiotensin II type 2 receptor activates the kinin/NO system and inhibits fibrosis. Hypertension 41, 99–107.

Lagneux, C., Godin-Ribuot, D., Demenge, P., Ribuot, C., 2000. Nitric oxide and its role in the induction of kinin B_1-receptors after heat stress in the rat. Immunopharmacology 48, 43–49.

Lamontagne, D., Nakhostine, N., Couture, R., Nadeau, R., 1996. Mechanisms of kinin B_1-receptor-induced hypotension in the anesthetized dog. J. Cardiovasc. Pharmacol. 28 (5), 645–650.

Larrivée, J.-F., Bachvarov, D.R., Houle, F., Landry, J., Huot, J., Marceau, F., 1998. Role of the mitogen-activated protein kinases in the expression of the kinin B_1 receptors induced by tissue injury. J. Immunol. 160, 1419–1426.

Lee, C., Miura, K., Liu, X., Zweier, J.L., 2000a. Biphasic regulation of leukocyte superoxide generation by nitric oxide and peroxynitrite. J. Biol. Chem. 275 (50), 38965–38972.

Lee, C.I., Liu, X., Zweier, J.L., 2000b. Regulation of xanthine oxidase by nitric oxide and peroxynitrite. J. Biol. Chem. 275 (13), 9369–9376.

Lortie, M., Regoli, D., Rhaleb, N.E., Plante, G.E., 1992. The role of B_1- and B_2-kinin receptors in the renal tubular and hemodynamic response to bradykinin. Am. J. Physiol. 262, R72–R76.

Madeddu, P., Varoni, M.V., Palomba, D., Emanueli, C., Demontis, M.P., Glorisoso, N., Dessi-Fulgheri, P., Sarzani, R., Anania, V., 1997. Cardiovascular phenotype of a mouse strain with disruption of bradykinin B_2-receptor gene. Circulation 96, 3570–3578.

Maestri, R., Milia, A.F., Salis, M.B., Graiani, G., Lagrasta, C., Monica, M., Corradi, D., Emanueli, C., Madeddu, P., 2003. Cardiac hypertrophy and microvascular deficit in kinin B2 receptor knockout mice. Hypertension 41 (5), 1151–1155.

Mage, M., Pécher, C., Neau, E., Cellier, E., Dos Reiss, M.L., Schanstra, J.P., Couture, R., Bascands, J.-L., Girolami, J.-P., 2002. Induction of B_1 receptors in streptozotocin diabetic rats: possible involvement in the control of hyperglycemia-induced glomerular Erk 1 and 2 phosphorylation. Can. J. Physiol. Pharm. 80, 328–333.

Maltais, I., Bachvarova, M., Maheux, P., Perron, P., Marceau, F., Bachvarov, D., 2002. Bradykinin B_2 receptor gene polymorphism is associated with altered urinary albumin/creatinine values in diabetic patients. Can. J. Physiol. Pharm. 80, 323–327.

Marceau, F., Hess, J.F., Bachvarov, D.R., 1998. The B_1 receptors for kinins. Pharmacol. Rev. 50 (3), 357–386.

Marceau, F., Larrivée, J.F., Bouthillier, J., Bachvarova, M., Houle, S., Bachvarov, D.R., 1999. Effect of endogenous kinins, prostanoids, and NO on kinin B_1 and B_2 receptor expression in the rabbit. Am. J. Physiol. 277 (6 Pt 2), R1568–R1578.

Marcic, B.M., Erdös, E.G., 2000. Protein kinase C and phosphatase inhibitors block the ability of angiotensin I-converting enzyme inhibitors to resensitize the receptor to bradykinin without altering the primary effects of bradykinin. J. Pharmacol. Exp. Ther. 294, 605–612.

Marcic, B.M., Deddish, P.A., Jackman, H.L., Erdös, E.G., 1999. Enhancement of bradykinin and resensitization of its B_2 receptor. Hypertension 33, 835–843.

Marin-Castano, M.E., Schanstra, J.P., Neau, E., Praddaude, F., Pecher, C., Ader, J.L., Girolami, J.P., Bascands, J.L., 2002. Induction of functional bradykinin B(1)-receptors in normotensive rats and mice under chronic angiotensin-converting enzyme inhibitor treatment. Circulation 105 (5), 627–632.

Mayfield, R.K., Margolius, H.S., Levine, J.H., Wohltmann, H.J., Loadholt, C.B., Colwell, J.A., 1984. Urinary kallikrein excretion in insulin-dependent diabetes-mellitus and its relationship to glycemic control. J. Clin. Endocrinol. Metab. 59 (2), 278–286.

McCarty, M.F., 2003. ACE inhibition may decrease diabetes risk by boosting the impact of bradykinin on adipocytes. Med. Hypotheses 60 (6), 779–783.

McFarlane, S.I., Kumar, A., Sowers, J.R., 2003. Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease. Am. J. Cardiol. 91, 30H–37H.

Meneton, P., Bloch-Faure, M., Hagege, A.A., Ruetten, H., Huang, W., Bergaya, S., Ceiler, D., Gehring, D., Martins, I., Salmon, G., Boulanger, C.M., Nussberger, J., Crozatier, B., Gasc, J.-M., Heudes, D., Bruneval, P., Doetschman, T., Ménard, J., Alhenc-Gelas, F., 2001. Cardiovascular abnormalities with normal blood pressure in tissue kallikrein-deficient mice. Proc. Natl. Acad. Sci. U. S. A. 98 (5), 2634–2639.

Mikrut, K., Paluszak, J., Kólik, J., Sosnowski, P., Krauss, H., Grzékowiak, E., 2001. The effect of bradykinin on the oxidative state of rats with acute hyperglycaemia. Diabetes Res. Clin. Pract. 51, 79–85.

Miyata, T., Taguchi, T., Uehara, M., Isami, S., Kishikawa, H., Kaneko, K., Araki, E., Shichiri, M., 1998. Bradykinin potentiates insulin-stimulated glucose uptake and enhances insulin signal through the bradykinin B_2 receptor in dog skeletal muscle and rat L6 myoblasts. Eur. J. Endocrinol. 138, 344–352.

Miyata, T., van Ypersele de Strihou, C., Ueda, Y., Ichimori, K., Inagi, R., Onogi, H., Ishikawa, N., Nangaku, M., Kurokawa, K., 2002. Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: biochemical mechanisms. J. Am. Soc. Nephrol. 13 (10), 2478–2487.

Miyata, T., van Ypersele de Strihou, C., 2003. Angiotensin II receptor blockers and angiotensin converting enzyme inhibitors: implication of radical scavenging and transition metal chelation in inhibition of advanced glycation end product formation. Arch. Biochem. Biophys. 419 (1), 50–54.

Molinaro, G., Cugno, M., Perez, M., Lepage, Y., Gervais, N., Agostoni, A., Adam, A., 2002. Angiotensin-converting enzyme inhibitor-associated angioedema is characterized by a slower degradation of des-arginine^9-bradykinin. J. Pharmacol. Exp. Ther. 303 (1), 232–237.

Morbidelli, L., Parenti, A., Giovannelli, L., Granger, H.J., Ledda, F., Ziche, M., 1998. B1 receptor involvement in the effect of bradykinin on venular endothelial cell proliferation and potentiation of FGF-2 effects. Br. J. Pharmacol. 124 (6), 1286–1292.

Mukae, S., Aoki, S., Itoh, S., Nishio, K., Iwata, T., Ueda, H., Geshi, E., Fuzimaki, T., Katagiri, T., 1999. Promoter polymorphism of the B_2 bradykinin receptor gene is associated with essential hypertension. Jpn. Circ. J. 63, 759–762.

Münzel, T., Keaney, J.F., 2001. Are ACE inhibitors a «magic bullet» against oxidative stress? Circulation 104, 1571–1574.

Nakhostine, N., Ribuot, C., Lamontagne, D., Nadeau, R., Couture, R., 1993. Mediation by B_1 and B_2 receptors of vasodepressor responses to intravenously administered kinins in anaesthetized dogs. Br. J. Pharmacol. 110 (1), 71–76.

Nangaku, M., Miyata, T., Sada, T., Mizuno, M., Inagi, R., Ueda, Y., Ishikawa, N., Yuzawa, H., Koike, H., van Ypersele de Strihou, C., Kurokawa, K., 2003. Anti-hypertensive agents inhibit in vivo the formation of advanced glycation end products and improve renal damage in a type 2 diabetic nephropathy rat model. J. Am. Soc. Nephrol. 14 (5), 1212–1222.

Ni, A., Chao, L., Chao, J., 1998. Transcription factor nuclear factor NF-κB regulates the inducible expression of the human B_1 receptor gene in inflammation. J. Biol. Chem. 273, 2784–2791.

Ni, A., Yin, H., Agata, J., Yang, Z., Chao, L., Chao, J., 2003. Over-expression of kinin B_1 receptors induces hypertensive response to Des-Arg^9-bradykinin and susceptibility to inflammation. J. Biol. Chem. 278 (1), 219–225.

Nicolau, M., Feltrin, M.R., Regoli, D., 1996. Induction of bradykinin B_1 hypotensive receptors in rats by lipopolysaccharide. Can. J. Physiol. Pharm. 74 (3), 337–340.

Oh-ishi, S., Tokumasu, T., Ueno, A., 1996. Induction of a B_1-receptor mediating hypotensive response in young brown Norway rats. Immunopharmacology 33 (1–3), 101–103.

Ongali, B., Buck, H., de, S., Cloutier, F., Legault, F., Regoli, D., Lambert, C., Thibault, G., Couture, R., 2003. Chronic effects of angiotensin-converting enzyme inhibition on kinin receptor binding sites in the rat spinal cord. Am. J. Physiol. Heart Circ. Physiol. 284 (6), H1949–H1958.

Parenti, A., Morbidelli, L., Ledda, F., Granger, H.J., Ziche, M.L., 2001. The bradykinin B_1 receptor promotes angiogenesis by up-regulation of endogenous FGF-2 in endothelium via the nitric oxide synthase pathway. FASEB J. 15, 1487–1489.

Pawluczyk, I.Z., Patel, S.R., Harris, K.P., 2004. The role of bradykinin in the antifibrotic actions of perindoprilat on human mesangial cells. Kidney Int. 65 (4), 1240–1251.

Pelikanova, T., Pinsker, P., Smrckova, I., Stribrna, L., Dryakova, M., 1998. Decreased urinary kallikrein with hyperglycemia in patients with short-term insulin-dependent diabetes mellitus. J. Diabetes Its Complicat. 12 (5), 264–272.

Pesquero, J.B., Araujo, R.C., Heppenstall, P.A., Stucky, C.L., Silva, J.A.Jr., Walther, T., Oliveira, S.M., Pesquero, J.L., Paiva, A.C., Calixto, J.B., Lewin, G.R., Bader, M., 2000. Hypoalgesia and altered inflammatory responses in mice lacking kinin B1 receptors. Proc. Natl. Acad. Sci. U. S. A. 97 (14), 8140–8145.

Prado, G.N., Taylor, L., Zhou, X., Ricupero, D., Mierke, D.F., Polgar, P., 2002. Mechanisms regulating the expression, self-maintenance, and signaling-function of the bradykinin B_2 and B_1 receptors. J. Cell. Physiol. 193, 275–286.

Rabinovitch, A., 1998. An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus. Diabetes Metab. Rev. 14 (2), 129–151.

Rabinovitch, A., Suarez-Pinzon, W.L., 1998. Cytokines and their roles in pancreatic islet beta-cell destruction and insulin-dependent diabetes mellitus. Biochem. Pharmacol. 55 (8), 1139–1149.

Rabito, S.F., Minshall, R.D., Nakamura, F., Wang, L.X., 1996. Bradykinin B_2 receptors on skeletal muscle are coupled to inositol 1,4,5,-trisphosphate formation. Diabetes 45 (Suppl. 1), 29–33.

Raidoo, D.M., Ramsaroop, R., Naidoo, S., Müller-Esterl, W., Bhoola, K.D., 1997. Kinin receptors in human vascular tissue: their role in atheromatous disease. Immunopharmacology 36 (2–3), 153–160.

Ravera, M., Deferrari, L., Ratto, E., Vettoretti, S., Parodi, D., Deferrari, G., 2003. The role of angiotensin II AT_1-receptor antagonists in renal and cardiac protection in type-2 diabetes mellitus. Ital. Heart J. 4 (Suppl. 3), 210–216.

Regoli, D., Marceau, F., Lavigne, J., 1981. Induction of B_1-receptors for kinins in the rabbit by a bacterial lipopolysaccharide. Eur. J. Pharmacol. 71 (1), 105–115.

Regoli, D., Rizzi, A., Perron, S.I., Gobeil, F., 2001. Classification of kinin receptors. Biol. Chem. 382, 31–35.

Rett, K., Wicklmayr, M., Dietze, G.J., 1990. Metabolic effects of kinins: historical and recent developments. J. Cardiovasc. Pharmacol. 15 (Suppl. 6), S57–S59.

Rett, K., Wicklmayr, M., Dietze, G.J., Haring, H.U., 1996. Insulin-induced glucose transporter (GLUT1 and GLUT4) translocation in cardiac muscle tissue is mimicked by bradykinin. Diabetes 45 (Suppl. 1), S66–S69.

Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., Soubrier, F., 1990. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J. Clin. Invest. 86 (4), 1343–1346.

Ritchie, R.H., Schiebinger, R.J., Lapointe, M.C., Marsh, J.D., 1998. Angiotensin II-induced hypertrophy of adult rat cardiomyocytes is blocked by nitric oxide. Am. J. Physiol. 275 (4 Pt 2), H1370–H1374.

Rojas, A., Romay, S., Gonzalez, D., Herrera, B., Delgado, R., Otero, K., 2000. Regulation of endothelial nitric oxide synthase expression by albumin-derived advanced glycosylation and products. Circ. Res. 86 (3), E50–E54.

Rosenkranz, A.C., Dusting, G.J., Ritchie, R.H., 2000. Endothelial dysfunction limits the antihypertrophic action of bradykinin in rat cardiomycytes. J. Mol. Cell. Cardiol. 32 (6), 1119–1126.

Rosenkranz, A.C., Hood, S.G., Woods, R.L., Dusting, G.J., Ritchie, R.H., 2003. B-type natriuretic peptide prevents acute hypertrophic responses in the diabetic rat heart: importance of cyclic GMP. Diabetes 52 (9), 2389–2395.

Rothschild, A.M., Melo, V.L., Reis, M.L., Foss, M.C., Gallo, Jr. L., 1999. Kininogen and prekallikrein increases in the blood of streptozotocin-diabetic rats are normalized by insulin in vivo and in vitro. Naunyn-Schmiedeberg's Arch. Pharmacol. 360 (2), 217–220.

Rouleau, J.L., Pfeffer, M.A., Stewart, D.J., Isaac, D., Sestier, F., Kerut, E.K., Porter, C.B., Proulx, G., Qian, C., Block, A.J., 2000. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. Lancet 356 (9230), 615–620.

Sardi, S.P., Daray, F.M., Errasti, A.E., Pelorosso, F.G., Pujol-Lereis, V.A., Rey-Ares, V., Rogines-Velo, M.P., Rothlin, R.P., 1999. Further pharmacological characterization of bradykinin B1 receptor up-regulation in human umbilical vein. J. Pharmacol. Exp. Ther. 290, 1019–1025.

Schäfer, S., Linz, W., Vollert, H., Biemer-Daub, G., Rütten, H., Bleich, M., Busch, A.E., 2004a. The vasopeptidase inhibitor AVE7688 ameliorates type 2 diabetic nephropathy. Diabetologia 47, 98–103.

Schäfer, S., Steioff, K., Linz, W., Bleich, M., Busch, A.E., Löhn, M., 2004b. Chronic vasopeptidase inhibition normalizes diabetic endothelial dysfunction. Eur. J. Pharmacol. 484, 361–362.

Schanstra, J.P., Bataillé, E., Marin Castaño, M.E., Barascud, Y., Hirtz, C., Pesquero, J.B., Pecher, C., Gauthier, F., Girolami, J.-P., Bascands, J.-L., 1998. The B_1-agonist [des-Arg^{10}]-kallidin activates transcription factor NF-κB and induces homologous upregulation of the bradykinin B_1-receptor in cultured human lung fibroblasts. J. Clin. Invest. 101, 2080–2091.

Schanstra, J.P., Neau, E., Drogoz, P., Arevalo Gomez, M.A., Lopez Novoa, J.M., Calise, D., Pecher, C., Bader, M., Girolami, J.-P., Bascands, J.-L., 2002. In vivo bradykinin B_2 receptor activation reduces renal fibrosis. J. Clin. Invest. 110, 371–379.

Schanstra, J.P., Duchene, J., Desmond, L., Neau, E., Calise, D., Estaque, S., Girolami, J.P., Bascands, J.L., 2003a. The protective effect of angiotensin converting enzyme inhibition in experimental renal fibrosis in mice is not mediated by bradykinin B_2 receptor activation. Thromb. Haemost. 89 (4), 735–740.

Schanstra, J.P., Duchene, J., Praddaude, F., Bruneval, P., Tack, I., Chevalier, J., Girolami, J.-P., Bascands, J.-L., 2003b. Decreased renal NO excretion and reduced glomerular tuft area in mice lacking the bradykinin B_2 receptor. Am. J. Physiol. Heart Circ. Physiol. 284 (6), H1904–H1908.

Schiffrin, E.L., Touyz, R.M., 2003. Multiple actions of angiotensin II in hypertension: benefits of AT_1 receptor blockade. J. Am. Coll. Cardiol. 42 (5), 911–913.

Schmid, A., Eich-Rathfelder, S., Whalley, E.T., Cheronis, J.C., Scheuber, H.P., Fritz, H., Siebeck, M., 1998. Endogenous B1 receptor mediated hypotension produced by contact system activation in the presence of endotoxemia. Immunopharmacology 40 (2), 131–137.

Shankar, R.R., Wu, Y., Shen, H.Q., Zhu, J.S., Baron, A.D., 2000. Mice with gene disruption of both endothelial and neuronal nitric oxide synthase exhibit insulin resistance. Diabetes 49, 684–687.

Shiuchi, T., Cui, T.-X., Wu, L., Nakagami, H., Takeda-Matsubara, Y., Iwai, M., Horiuchi, M., 2002. ACE inhibitor improves insulin resistance in diabetic mouse via bradykinin and NO. Hypertension 40, 329–334.

Simard, B., Gabra, B.H., Sirois, P., 2002. Inhibitory effect of a novel bradykinin B1 receptor antagonist, R-954, on enhanced vascular permeability in type 1 diabetic mice. Can. J. Physiol. Pharm. 80, 1203–1207.

Singh, R., Barden, A., Mori, T., Beilin, L., 2001. Advanced glycation end-products: a review. Diabetelogia 44, 129–146.

Singleton, J.R., Smith, A.G., Russell, J.W., Feldman, E.L., 2003. Microvascular complications of impaired glucose tolerance. Diabetes 52, 2867–2873.

Soares de Moura, R., Resende, A.C., Emiliano, A.F., Tano, T., Mendes-Ribeiro, A.C., Correia, M.L., De Carvalho, L.C., 2004. The role of bradykinin, AT_2 and angiotensin 1–7 receptors in the EDRF-dependent vasodilator effect of angiotensin II on the isolated mesenteric vascular bed of the rat. Br. J. Pharmacol. 141 (5), 860–866.

Solini, A., Vestra, M.D., Saller, A., Nosadini, R., Crepaldi, G., Fioretto, P., 2002. The angiotensin-converting enzyme DD genotype is associated with glomerulopathy lesions in type 2 diabetes. Diabetes 51, 251–255.

Sosa-Canache, B., Cierco, M., Gutierrez, C.I., Israel, A., 2000. Role of bradykinins and nitric oxide in the AT_2 receptor-mediated hypotension. J. Hum. Hypertens., Suppl. 1, S40–S46.

Stewart, J.M., 2004. Bradykinin antagonists: discovery and development. Peptides 25, 527–532.

Su, J.B., Houel, R., Heloire, F., Barbe, F., Beverelli, F., Sambin, L., Castaigne, A., Berdeaux, A., Crozatier, B., Hittinger, L., 2000. Stimulation of bradykinin B(1) receptors induces vasodilation in conductance and resistance coronary vessels in conscious dogs: comparison with B(2) receptor stimulation. Circulation 101 (15), 1848–1853.

Suzuki, D., Miyata, T., Saotome, N., Horie, K., Inagi, R., Yasuda, Y., Uchida, K., Izuhara, Y., Yagame, M., Sakai, H., Kurokawa, K., 1999. Immunohistochemical evidence for an increased oxidative stress and carbonyl modification of proteins in diabetic glomerular lesions. J. Am. Soc. Nephrol. 10 (4), 822–832.

Sawada, Y., Kayakiri, H., Abe, Y., Mizutani, T., Inamura, N., Asano, M., Hatori, C., Aramori, I., Oku, T., Tanaka, H., 2004. Discovery of the first non-peptide full agonists for the human bradykinin B(2) receptor incorporating 4-(2-picolyloxy)quinoline and 1-(2-picolyl)benzimidazole frameworks. J. Med. Chem. 47 (11), 2853–2863.

Sawada, Y., Kayakiri, H., Abe, Y., Mizutani, T., Inamura, N., Asano, M., Aramori, I., Hatori, C., Oku, T., Tanaka, H., 2004. A new class of nonpeptide bradykinin B(2) receptor ligand, incorporating a 4-amino-quinoline framework. Identification of a key pharmacophore to determine species difference and agonist/antagonist profile. J. Med. Chem. 47 (10), 2667–2677.

Tan, Y., Hutchison, F.N., Jaffa, A.A., 2004. Mechanisms of angiotensin II-induced expression of B2 kinin receptors. Am. J. Physiol. Heart Circ. Physiol. 286 (3), H926–H932.

Tanji, N., Markowitz, G.S., Fu, C., Kislinger, T., Taguchi, A., Pischetsrieder, M., Stern, D., Schmidt, A.M., D'Agati, V.D., 2000. Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. J. Am. Soc. Nephrol. 11 (9), 1656–1666.

Tesfamariam, B., 1994. Free radicals in diabetic endothelial cell dysfunction. Free Radic. Biol. Med. 16 (3), 383–391.

Tikellis, C., Johnston, C.I., Forbes, J.M., Burns, W.C., Burrell, L.M., Risvanis, J., Cooper, M.E., 2003. Characterization of renal angiotensin-converting enzyme 2 in diabetic nephropathy. Hypertension 41 (3), 392–397.

Tom, B., Dendorfer, A., de Vries, R., Saxena, P.R., Danser, A.H.J., 2002. Bradykinin potentiation by ACE inhibitors: a matter of metabolism. Br. J. Pharmacol. 137, 276–284.

Tom, B., Dendorfer, A., Jan Danser, A.H., 2003. Bradykinin, angiotensin-(1–7), and ACE inhibitors: how do they interact? Int. J. Biochem. Cell Biol. 35, 792–801.

Tomiyama, H., Kushiro, T., Abeta, H., Ishii, T., Takahasi, A., Furukawa, L., Asagami, T., Hino, T., Saito, F., Otsuka, Y., Kurumatani, H., Kobayashi, F., Kanmatsuse, K., Kajiwara, N., 1994. Kinins contribute to the improvement of insulin sensitivity during treatment with ACEI. Hypertension 23, 450–455.

Trabold, F., Pons, S., Hagege, A.A., Bloch-Faure, M., Alhenc-Gelas, F., Giudicelli, J.-F., Richer-Giudicelli, C., Meneton, P., 2002. Cardiovascular phenotypes of kinin B_2 receptor- and tissue kallikrein-deficient mice. Hypertension 40, 90–95.

Trachtman, H., 1994. Vitamin E prevents glucose-induced lipid peroxidation and increased collagen production in cultured rat mesangial cells. Microvasc. Res. 47 (2), 232–239.

Trachtman, H., Futterweit, S., Bienkowski, R.S., 1993. Taurine prevents glucose-induced lipid peroxidation and increased collagen production in cultured rat mesangial cells. Biochem. Biophys. Res. Commun. 191 (2), 759–765.

Tschöpe, C., Walther, T., Yu, M., Reinecke, A., Koch, M., Seligmann, C., Heringer, S.B., Pesquero, J.B., Bader, M., Schultheiss, H., Unger, T., 1999. Myocardial expression of rat bradykinin receptors and two tissue kallikrein genes in experimental diabetes. Immunopharmacology 44 (1–2), 35–42.

Tschöpe, C., Heringer-Walther, S., Koch, M., Spillmann, F., Wendorf, M., Leitner, E., Schultheiss, H.P., Walther, T., 2000. Upregulation of bradykinin B_1-receptor expression after myocardial infarction. Br. J. Pharmacol. 129 (8), 1537–1538.

Tschöpe, C., Schultheiss, H.-P., Walther, T., 2002. Multiple interactions between the renin-angiotensin and the kallikrein-kinin systems: role of ACE inhibition and AT_1 receptor blockade. J. Cardiovasc. Pharmacol. 39, 478–487.

Tschöpe, C., Seidl, U., Reinecke, A., Riester, U., Graf, K., Schultheiss, H.-P., Hilgenfeldt, U., Unger, T., 2003. Kinins are involved in the antiproteinuric effect of angiotensin-converting enzyme inhibition in experimental diabetic nephropathy. Int. Immunopharmacol. 3, 335–344.

Tschöpe, C., Spillmann, F., Altmann, C., Koch, M., Westermann, D., Dhayat, N., Dhayat, S., Bascands, J.-L., Gera, L., Hoffmann, S., Schultheiss, H.-P., Walther, T., 2004a. The bradykinin B_1 receptor contributes to the cardioprotective effects of AT_1 blockade after experimental myocardial infarction. Cardiovasc. Res. 61, 559–569.

Tschöpe, C., Walther, T., Koniger, J., Spillmann, F., Westermann, D., Escher, F., Pauschinger, M., Pesquero, J.B., Bader, M., Schultheiss, H.P., Noutsias, M., 2004b. Prevention of cardiac fibrosis and left ventricular dysfunction in diabetic cardiomyopathy in rats by transgenic expression of the human tissue kallikrein gene. FASEB J. 18 (7), 828–835.

Tsutsumi, Y., Matsubara, H., Masaki, H., Kurihara, H., Murasawa, S., Takai, S., Miyazaki, M., Nozawa, Y., Ozono, R., Nakagawa, K., Miwa, T., Kawada, N., Mori, Y., Shibasaki, Y., Tanaka, Y., Fujiyama, S., Koyama, Y., Fujiyama, A., Takahashi, H., Iwasaka, T., 1999. Angiotensin II type 2 receptor overexpression activates the vascular kinin system and causes vasodilation. J. Clin. Invest. 104 (7), 925–935.

Turner, A.J., Tipnis, S.R., Guy, J.L., Rice, G., Hooper, N.M., 2002. ACEH/ACE2 is a novel mammalian metallocarboxypeptidase and a homologue of angiotensin-converting enzyme insensitive to ACE inhibitors. Can. J. Physiol. Pharm. 80 (4), 346–353.

Uehara, M., Kishikawa, H., Isami, S., Kisanuki, K., Ohkubo, Y., Miyamura, N., Miyata, T., Yano, T., Shichiri, M., 1994. Effect of insulin sensitivity of angiotensin converting enzyme inhibitors with or without a sulphydryl group: bradykinin may improve insulin resistance in dogs and humans. Diabetologia 37 (3), 300–307.

Vianna, R.M., Ongali, B., Regoli, D., Calixto, J.B., Couture, R., 2003. Up-regulation of kinin B_1 receptor in the lung of streptozotocin-diabetic rat: autoradiographic and functional evidence. Br. J. Pharmacol. 138 (1), 13–22.

Walther, T., Siems, W.E., Hauke, D., Spillmann, F., Dendorfer, A., Krause, W., Schultheiss, H.P., Tschöpe, C., 2002. AT_1 receptor blockade increases cardiac bradykinin via neutral endopeptidase after induction of myocardial infarction in rats. FASEB J. 16 (10), 1237–1241.

Wang, C., Chao, L., Chao, J., 1995. Direct gene delivery of human tissue

kallikrein reduces blood pressure in spontaneously hypertensive rats. J. Clin. Invest. 95, 1710–1716.

Wang, C.-H., Leung, N., Lapointe, N., Szeto, L., Uffelman, K.D., Giacca, A., Rouleau, J.L., Lewis, G.F., 2003. Vasopeptidase inhibitor omapatrilat induces profound insulin sensitization and increases myocardial glucose uptake in Zucker fatty rats. Circulation 107, 1923–1929.

Wautier, M.P., Chappey, O., Corda, S., Stern, D.M., Schmidt, A.M., Wautier, J.L., 2001. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. Am. J. Physiol. Endocrinol. Metab. 280 (5), E685–E694.

Way, K.J., Katai, N., King, G.L., 2001. Protein kinase C and the development of diabetic vascular complications. Diabet. Med. 18 (12), 945–959.

Wiemer, G., Dobrucki, L.W., Louka, F.R., Malinski, T., Heitsch, H., 2002. AVE 0991, a nonpeptide mimic of the effects of angiotensin-(1–7) on the endothelium. Hypertension 40 (6), 847–852.

Windebank, A., Feldman, E., 2001. Diabetes and the nervous system. In: Aminoff, M. (Ed.), Neurology and General Medicine. Churchill Livingstone, Philadelphia, PA, pp. 341–364.

Witherow, F.N., Helmy, A., Webb, D.J., Fox, K.A.A., Newby, D.E., 2001. Bradykinin contributes to the vasodilator effects of chronic angiotensin-converting enzyme inhibition in patients with heart failure. Circulation 104, 2177–2181.

Xiong, W., Chao, J., Chao, L., 1995. Muscle delivery of human kallikrein gene reduces blood pressure in hypertensive rats. Hypertension 25 (4 Pt2), 715–719.

Yang, C., Hsu, W.H., 1997. Glucose-dependency of bradykinin-induced insulin secretion from the perfused rat pancreas. Regul. Pept. 71 (1), 23–28.

Yasunari, K., Maeda, K., Watanabe, T., Nakamura, M., Asada, A., Yoshikawa, J., 2003. Converting enzyme inhibitor temocaprilat prevents high glucose-mediated suppression of human aortic endothelial cell proliferation. J. Cardiovasc. Pharmacol. 42 (Suppl. 1), S55–S60.

Yayama, K., Wang, C., Chao, L., Chao, J., 1998. Kallikrein gene delivery attenuates hypertension and cardiac hypertrophy and enhances renal function in Goldblatt hypertensive rats. Hypertension 31, 1104–1110.

Yokota, K., Kishida, M., Ogura, T., Suzuki, J., Otsuka, F., Mimura, Y., Takeda, M., Nakamura, Y., Makino, H., 2003. Role of bradykinin in renoprotective effects by angiotensin II type 1 receptor antagonist in salt-sensitive hypertension. Hypertens. Res. 26 (3), 265–272.

Yosipiv, I.V., Dipp, S., El-Dahr, S.S., 2001. Targeted disruption of the bradykinin B(2) receptor gene in mice alters the ontogeny of the renin-angiotensin system. Am. J. Physiol. Renal Physiol. 281 (5), F795–F801.

Zhao, C., Wang, P., Xiao, X., Chao, J., Chao, L., Wang, D.W., Zeldin, D.C., 2003. Gene therapy with human tissue kallikrein reduces hypertension and hyperinsulinemia in fructose-induced hypertensive rats. Hypertension 42 (5), 1026–1033.

Zhou, X., Ono, H., Ono, Y., Frohlich, E.D., 2003. Renoprotective effects of omapatrilat are mediated partially by bradykinin. Am. J. Nephrol. 23 (4), 214–221.

Zimmet, P., 2003. The burden of type 2 diabetes: are we doing enough? Diabetes Metab. 29 (4 Pt), 6S9–6S18.

Ziyadeh, F.N., Han, D.C., 1997. Involvement of transforming growth factor-beta and its receptors in the pathogenesis of diabetic nephrology. Kidney Int. 60, S7–S11.

Zuccollo, A., Navarro, M., Prendes, G.M., Dominguez, A., Catanzaro, O.L., 1996. Effects of HOE 140 on some renal functions in type I diabetic mice. Arch. Physiol. Biochem. 104 (2), 252–254.

Zychma, M.J., Gumprecht, J., Trautsolt, W., Szydlowska, I., Grzeszczak, W., 2003. Polymorphic genes for kinin receptors, nephropathy and blood pressure in type 2 diabetic patients. Am. J. Nephrol. 23, 112–116.