Kinins are important peptide mediators of a diverse range of physiological and pathological functions of the cardiovascular system. The kinin peptides exert their effects by selective activation of two distinct G-protein coupled receptors termed B₁ and B₂. The principal kinin peptides involved in the acute regulation of cardiovascular function during normal physiology are bradykinin (BK) and Lys-BK which produce their effects via activation of B₁ receptors. The B₁ receptor is activated by the des-Arg kinin metabolites namely des-Arg²BK and Lys-des-Arg⁹BK, the synthesis of which are increased during inflammation. The B₁ receptor, which is not constitutively expressed, is induced in various pathologies relating to inflammation. Recent investigations into the molecular mechanisms of B₁ receptor induction and their distribution and function in the cardiovascular system have shown that following an inflammatory stimulus the B₁ receptor is induced and may play an important role in modulation of cardiovascular function. This review summarises recent studies on B₁ receptor expression and function in the cardiovascular system and discusses the role of these receptors in regulation of circulatory homeostasis and their potential as therapeutic targets. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: G-proteins; Infection/inflammation; Receptors; Signal transduction

1. Introduction

The kinin peptides, particularly bradykinin (BK), Lys-BK (kallidin) and their biologically active des-Arg⁹ metabolites are the functional components of the kallikrein–kinin system. Kinins are important mediators of a diverse range of physiological and pathological responses of the cardiovascular system. The physiological actions of this system are produced by two endogenous kinins, BK and Lys-BK, formed by proteolytic cleavage of high- and low-molecular-weight kininogens (HMWK and LMWK) by plasma or tissue kallikrein (PK or TK), respectively. BK and Lys-BK are metabolised and deactivated by kininase I or kininase II (also known as angiotensin converting enzyme). The activity of kininase I is of particular relevance to this review in that it produces kinin metabolites without the C-terminal arginine residue, des-Arg²BK (DABK) and Lys-des-Arg⁹BK (Lys-DABK) from BK and Lys-BK, respectively. Whilst these des-Arg⁹ metabolites are largely inactive in normal conditions, in certain immuno-pathological situations they produce responses characteristic of inflammation including vasodilation, oedema and leukocyte recruitment within the microcirculation.

The kinins mediate their effects via the selective activation of kinin receptors of which there are two types, B₁
and B₂. The B₂ receptor is constitutively expressed and mediates the majority of the acute vascular actions of BK [1]. In contrast, the B₁ receptor is generally absent from normal tissue but following an inflammatory insult, receptor expression is induced in a variety of cell types including vascular smooth muscle cells (VSMC), endothelial cells (EC) and fibroblasts (see below). The activity of the kinins suggests that they may be involved in inflammatory cardiovascular disease, and the inducibility of the kinin B₁ receptor makes it an exciting potential therapeutic target in such pathological conditions. This review will address the role of B₁ receptors in the physiology and pathophysiology of the cardiovascular system and will highlight the therapeutic potential of agents that interact with this system.

2. The kinin B₁ receptor: an inducible G-protein-coupled receptor (GPCR)

The B₁ receptor was first defined as mediating the contractile effect of kinins in the rabbit isolated aorta [2]. Regoli and Barabé [3] later suggested the existence of two types of kinin receptor in 1980 based on differential in vitro tissue reactivity to the endogenous agonists DABK and BK. The order of agonist potency at B₁ receptors was shown to be DABK > Tyr(Me)²BK > BK, with a reverse order at the B₂ receptor (i.e. BK > Tyr(Me)²BK > DABK) [3]. This profile is determined by the discriminating nature of the C-terminal arginine of B₂ receptor selective agents, that is absent in B₁ receptor selective compounds. The selectivity of the kinin peptides is further determined at the receptor by differences in a single position in the third transmembrane domain of the human B₁ and B₂ receptors [4]. The reader is referred to recent excellent reviews discussing kinin receptor ligands in greater detail [5,6].

In 1992, Phillips et al. [7] demonstrated the expression of both B₁ and B₂ receptors in Xenopus oocytes injected with mRNA from NG108-15, rat uterus, and human fibroblast cell line WI38. Structural analysis revealed that the receptors are encoded by distinct mRNA [8]. The human B₁ receptor gene was subsequently cloned from human embryonic lung fibroblasts [9] and was shown to be a member of the 7-transmembrane domain GPCR family. The mouse [10], rat [11] and rabbit [12] B₁ receptors display functional and structural homology with the human receptor. The rabbit receptor shows greatest homology with the human receptor whilst homology with the rodent receptors is relatively low. Interestingly this difference in homology is demonstrated by differences in preferred agonists; Lys-DABK in humans and rabbits and DABK in rodents [5]. This selectivity of Lys-DABK for the human B₁ receptor depends on interaction between the peptide N-terminal 1-lysine and the fourth extracellular domain of the human B₁ receptor [13].

3. B₁ receptor regulation: mechanisms of induction

The low homology (36%) between the B₁ and B₂ receptors suggests that both receptors may be components of very different regulatory systems [14]. One important example of this is the differential regulation of their expression. The inducibility of the B₁ receptor was first reported by Regoli et al., [2] who described a time- and protein synthesis-dependent appearance of contractile reactivity to DABK in rabbit isolated aorta following 2–3 h of tissue incubation in physiological buffer [15]. This is due to de novo synthesis of B₁ receptor since the response is absent in tissues treated with inhibitors of RNA transcription, translation or of protein maturation [5].

The stimulus for post-isolation B₁ receptor induction in these in vitro studies is unclear but may be related to the trauma of isolating vessels ex vivo. B₁ receptor upregulation occurs, in vitro and in vivo, under the control of specific cytokines released in situations of trauma and stress, including interleukin (IL)-1β and tumour necrosis factor (TNF)-α [16–18]. Additionally, studies in vitro show that certain cytokines and growth factors (e.g. IL-1β, IL-2, interferon-γ, epidermal growth factor and oncostatin) increase the rate at which a B₁ receptor-mediated response develops as a consequence of tissue isolation and incubation [15,17–21]. This upregulation is again due to de novo protein synthesis and is sensitive to glucocorticoids [17,22]. Of all the cytokines IL-1β has been shown to be the optimal inducer of B₁ receptor expression in various cell types of several species in vitro [18,23] including human embryo lung fibroblasts. In these cells IL-1β upregulates B₁ receptor mRNA expression at both a transcriptional and post-transcriptional level [24,25]. In addition, agents that stimulate the synthesis of these cytokines, in particular bacterial lipopolysaccharide (LPS) and tumour necrosis factor also lead to functional B₁ receptor expression when administered either in vitro or in vivo [16,18,26]. B₁ receptor induction also occurs following heat stress, another immunopathological stimulus [27].

The induction of functional B₁ receptor-mediated responses is associated with B₁ receptor mRNA and protein expression. This was first shown in the rat isolated heart, where in vitro perfusion with IL-1β promoted B₁ receptor induction at both the molecular (mRNA expression) and functional level (coronary vasodilation) [18]. This inducibility to IL-1β has also been demonstrated in vivo for the first time in our laboratory [28] (see below).

Studies attempting to identify the molecular mechanisms involved in B₁ receptor induction implicate the inflammatory transcription factor, nuclear factor κB (NF-κB). Interestingly NF-κB is not only involved in mediating certain B₁ receptor effects but also receptor induction [24,29,30]. Accordingly, NF-κB binding domains [24,29] have been identified in the promoter region of the B₁ receptor gene and IL-1β and TNFα-induced B₁ receptor expression is directly related to NF-κB activation [5].
Additionally, it has been proposed that B₂ receptor activation and consequent desensitisation may be a direct stimulus for B₁ receptor induction since B₂ receptor agonists also cause NF-κB activation [31,32].

Apart from differential expression profiles, kinin receptors also display important differences in their susceptibility to desensitisation. When activated by an agonist, B₂ receptors undergo desensitisation and internalisation [33–35] a characteristic accounting for the rapid reversibility of its biological effects in vitro. Conversely, B₁ receptors, once induced, are not internalised or desensitised [20,33–35]. This difference may be explained by the presence of a large C-terminal loop in the B₂ receptor containing Ser and Tyr residues, typical phosphorylation sites [36,37]. In addition, Cys324 in the cytoplasmic carboxyl terminus of the B₂ receptor appears to play an integral role in agonist-induced internalisation. Replacement of the cytoplasmic carboxyl terminus of the B₂ receptor starting from Cys324, with that of the B₁ receptor (beginning at Cys330) greatly reduced ligand internalisation without significantly altering ligand binding affinity or coupling efficiency. In contrast, the corresponding replacement in the B₁ receptor led to an increase of ligand internalisation without altering affinity or coupling. These results indicate that the cytoplasmic carboxyl terminus of the human B₂ receptor contains sequences that are necessary and sufficient to permit rapid ligand-induced sequestration of human kinin receptors and internalisation of their agonists [34]. This differential susceptibility to desensitisation would support the hypothesis that an integrated system develops from B₂ receptor-mediated acute inflammation to a sustained B₁ receptor-mediated chronic, or at least prolonged, inflammatory response. Thus one could speculate that B₂ receptors are unlikely to be involved in sub-acute and chronic inflammatory conditions, whereas B₁ receptors are better equipped to mediate the development and progression of a chronic inflammatory response.

4. Synthesis of B₁ receptor endogenous ligands: the kallikrein–kinin system

The synthesis of kinins is determined by the activity of the kallikrein–kinin system that is comprised of two separate pathways differentiated by their location: the plasma and tissue systems [5]. The various elements of the kallikrein–kinin system have been reviewed in detail elsewhere (see Bhoola et al. [1]; Kaplan et al. [38]). In brief, the substrates for kinin synthesis are the multi-domain proteins known as kininogens of which there are three types: high molecular weight kininogen (HMWK), low molecular weight kininogen (LMWK) and T-kininogen. The kininogens contain the nine amino acid peptide sequence for BK (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg.). HMWK, the precursor of BK, is a circulating protein in the plasma system, whereas LMWK, the precursor for Lys-BK, is distributed in tissues, fibroblasts and other structural cells within connective tissue [1]. T-kininogen is the rodent equivalent of human HMWK [1]. The human kininogen gene has been mapped to chromosome 3 (3q26-3qter) [39] that codes, via alternative splicing, for the expression of both HMWK and LMWK.

Kallikreins are the enzymes that cleave kininogens and liberate kinins. Plasma kallikrein (PK) releases BK from HMWK [40]; a process that is upregulated during an inflammatory insult such as ischaemia–reperfusion (I/R) injury [41]. There is also evidence that HMWK adsorbed on extracellular proteins of Streptococcus pyogenes, an important pathogen in ‘sepsis’ can release BK in the presence of prekallikrein [42] thus implicating kinin generation in the pathophysiology of this disease. Tissue kallikreins (TK) are a family of serine proteases closely related to PK and are highly effective in the generation of biologically active kinins. Human TK preferentially releases the decapeptide Lys-BK from kininogens, as found in the nasal secretions of subjects with allergic or viral rhinitis [43]. Human TK is widely expressed in many tissue types including glandular and duct cells, as well as in neutrophils [44], cultured VSMCs, colonic goblet cells, and renal distal tubules and collecting ducts [45–48].

4.1. Kinin metabolism

The kinins are metabolised by several different enzymes, but the two most relevant with regard to the deactivation of BK are kininase I and kininase II. BK exhibits a very short half-life (10–50 s) in blood plasma in vitro and in vivo [49]. Kininase II, otherwise known as angiotensin I converting enzyme (ACE), is the most efficient and the major mechanism for BK inactivation [50], removing the C-terminal dipeptide from BK or Lys-BK and generating biologically inactive fragments. Assays for BK-like peptides have shown that kininase II accounts for between 40 and 75% of the hydrolysis of exogenous synthetic BK by serum or cardiac membrane preparations of humans, rabbits or rats [49,51]. Kininase II is predominantly located on the surface of the luminal membrane of ECs and is therefore in a prime location for the inactivation of circulating BK.

Other peptidases including aminopeptidase P and neutral endopeptidase (NEP) also play an important role in kinin metabolism in vivo. Aminopeptidase P is responsible for up to 30% of total BK metabolism in rat lung and coronary circulation [52,53]. NEP, also a membrane-bound peptidase, located in high concentration on leukocyte membranes [50,54] cleaves two bonds in BK [55] and is responsible for 10–20% of BK inactivation [1]. The NEP homologue endothelin converting enzyme, located at the surface of EC and SMCs can also metabolise BK as efficiently as it metabolises big endothelin [56,57].

Kininase I enzymes (otherwise known as Arg carboxypeptidases) play a lesser role in the deactivation of BK.
being responsible for less than 10% of total BK metabolism [49]. However, kininase I activity is of particular importance, since this enzyme is responsible for the generation of the des-Arg9 kinins. Under normal conditions B1 receptors are absent and these fragments remain functionally ‘silent’ and it is only following situations where these receptors have been induced (see above) that des-Arg9 metabolites show activity. Kininase I is composed of the arginine carboxypeptidases, carboxypeptidase N in the plasma and carboxypeptidase M in tissues (predominantly membrane-bound and widely distributed, including in the microvasculature [50,54]). The half-life of DABK is 4- to 12-fold higher than that of BK under comparable experimental conditions [49,51] and this may explain why the in vivo concentration of DABK is consistently higher than that of BK. Therefore, it appears that, whilst the synthesis of DABK is not considerable its half life endows it with a much greater capacity to accumulate than BK. Interestingly, blocking the competing kininase II pathway with enalaprilat improves the conversion of BK to DABK [49,51]. The techniques used to determine the above kinetics are limited by the fact that they only measured kinin metabolism in normal, non-inflammatory tissue/cells. It is possible that the formation of des-Arg9 kinins is greater at inflammatory sites than in plasma or normal tissue (see below).

4.2. Kallikrein–kinin system during injury and inflammation

All the necessary components required for kinin synthesis are not only present but elevated at sites of inflammation. In models of sepsis and myocardial I/R injury, the levels of detectable des-Arg9 kinins are increased 2 to 4-fold [41,58]. This elevation may be due to several factors including the possibility that plasma protein extravasation, at sites of inflammation, will provide substrate (HMWK) and enzyme (PK) for enhanced BK synthesis [59]. Additionally, during an inflammatory response the activity of the kallikrein–kinin system is enhanced by activation of the tissue kallikrein–kinin pathway [14]. Firstly, levels of LMWK are elevated by inflammatory cytokines [60]. Secondly, not only is TK present in and secreted from neutrophils, which are normally present, neutrophil elastase and mast cell tryptase, also present at sites of inflammation [62]. Other enzymes that may also catalyse kinin formation are 5.1. Kinin B1 receptor distribution and function in the cardiovascular system

B1 receptor expression has been demonstrated in a variety of blood vessels, both veins and arteries, in several species. Expression has also been described in cardiac tissue and in the central nervous system. Thus, the major systems involved in the regulation of cardiovascular homeostasis have the capacity to express these receptors. Table 1 summarises the distribution of this receptor, with expression in ECs and VSMCs of several vessels ranging from large elastic arteries and veins to small muscular arteries. B1 receptors are present on the ECs and VSMCs of the tunica media in the renal, femoral, carotid, coronary, vertebral, basilar and pericallosal arteries. The ECs of the large elastic pulmonary artery contain both B1 and B2 receptors. In the ECs and VSMCs of arterioles, B2 receptor immunolabelling is more intense than that observed for B1 receptors. Only B2 receptor immunoreactivity was detected on the ECs of the large veins and in the aorta [65] (see Table 1 for further details).

Studies attempting to identify the cell signalling pathways involved in B1 receptor activity show some heterogeneity. Bovine pulmonary artery ECs synthesise prostaglandins in response to B1 receptor activation [66,67]. In bovine aortic (BA) and rat microvascular coronary (RMC) ECs B1 receptor activation results in intracellular accumulation of guanosine-3’,5’-cyclic monophosphate (cGMP) [68,69] and is associated with B1 receptor mRNA expression in RMC ECs, human umbilical vein (HUV) ECs but paradoxically not in BAECs [70]. B1 receptor-mediated vascular effects generally involve protein kinase C activation and calcium release [20,71] leading to the promotion of phosphoinositide hydrolysis by phospholipase C or arachidonic acid release by phospholipase A2 [72].
### Table 1
Kinin B<sub>1</sub> receptor distribution and function in the cardiovascular system

<table>
<thead>
<tr>
<th>Species/vessel/ effect in vivo</th>
<th>Location of receptor expression</th>
<th>Functional effect</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
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<tr>
<td>Aorta</td>
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<tr>
<td>Pulmonary artery</td>
<td>EC</td>
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<tr>
<td>Femoral artery</td>
<td>EC/VSM&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Renal artery</td>
<td>EC/VSM</td>
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<tr>
<td>Carotid artery</td>
<td>EC/VSM</td>
<td>nd</td>
<td></td>
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<tr>
<td>Coronary artery</td>
<td>EC/VSM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Vasodilation</td>
<td>Endo+/NO</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>EC/VSM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>nd</td>
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<tr>
<td>Basilar artery</td>
<td>EC/VSM</td>
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</tr>
<tr>
<td>Pericallosal artery</td>
<td>EC/VSM</td>
<td>nd</td>
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<tr>
<td>Femoral vein</td>
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<tr>
<td>Pulmonary vein</td>
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<tr>
<td>Renal vein</td>
<td>–</td>
<td>nd</td>
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<tr>
<td>Muscular arteriole</td>
<td>EC/VSM</td>
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<td>Umbilical artery</td>
<td>nd</td>
<td>Vasoconstriction</td>
<td>nd</td>
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<tr>
<td>Umbilical vein</td>
<td>EC</td>
<td>Vasoconstriction</td>
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<tr>
<td>Rabbit</td>
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<tr>
<td>Aorta</td>
<td>VSM</td>
<td>Vasoconstriction</td>
<td>Endo−, IP, AA</td>
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<tr>
<td>Mesenteric vein</td>
<td>nd</td>
<td>Vasoconstriction</td>
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<td>Mesenteric artery</td>
<td>VSM</td>
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<td>IP, AA</td>
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<tr>
<td>Mesenteric artery</td>
<td>nd</td>
<td>Vasodilation</td>
<td>Endo+−/−, PG</td>
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<td>Endo+, NO</td>
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<td>Endo−, PG</td>
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<td>nd</td>
<td>Vasodilation</td>
<td>Endo+, NO</td>
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<tr>
<td>Blood pressure</td>
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<td>Hypotension</td>
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<td>Rat</td>
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<tr>
<td>Portal vein</td>
<td>nd</td>
<td>Vasoconstriction</td>
<td>PG</td>
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<tr>
<td>Perfused kidney</td>
<td>nd</td>
<td>Vasoconstriction</td>
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<tr>
<td>coronary circulation</td>
<td>nd</td>
<td>Vasodilation</td>
<td>Endo+, PG</td>
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<tr>
<td>Blood pressure</td>
<td>nd</td>
<td>Hypotension</td>
<td>cGMP</td>
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<td>Cat</td>
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<tr>
<td>Pulmonary bed</td>
<td>nd</td>
<td>Vasoconstriction</td>
<td>Catecholamines</td>
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<td>nd</td>
<td>Vasodilation</td>
<td>NO</td>
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<tr>
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<td>nd</td>
<td>Vasodilation</td>
<td>NO</td>
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<td>Dog</td>
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<tr>
<td>Renal artery</td>
<td>nd</td>
<td>Vasodilation</td>
<td>Endo−, PG</td>
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<tr>
<td>Blood pressure</td>
<td>nd</td>
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<td>Cow</td>
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<tr>
<td>Coronary artery</td>
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<td>Vasodilation</td>
<td>Endo+, NO</td>
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<tr>
<td>Pulmonary artery</td>
<td>EC</td>
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<td>IP, AA, NO, PG</td>
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<tr>
<td>Aorta</td>
<td>EC</td>
<td>nd</td>
<td>PG, cGMP</td>
</tr>
</tbody>
</table>

<sup>a</sup>EC, endothelial cell; VSM, vascular smooth muscle; –, absence of immunoreactive labelling; nd, not determined; Endo+, endothelium-dependent; Endo−, endothelium-independent; NO, nitric oxide; PG, prostaglandin; IP, inositol phosphate; AA, arachadonic acid; cGMP, cyclic guanosine-3’,5’-cyclic monophosphate. See text for references.

<sup>b</sup>Blood vessels with atheromatous disease.

#### 5.1.1. B<sub>1</sub> receptor-mediated vasoconstriction

B<sub>1</sub> receptor ligands cause vasoconstriction of a range of blood vessels including rabbit aorta [2,71,73] rabbit mesenteric vein [74], pig renal vein [75] and human umbilical artery [76] and vein [22,77,78] (see Table 1). More recently vascular B<sub>1</sub> receptors have been identified in the rat isolated perfused kidney, activation of which lead to vasoconstriction [79]. B<sub>1</sub> receptor-mediated contraction
of vascular smooth muscle is generally not dependent on an intact endothelium and involves a direct co-operation between protein kinase C and calcium release [20,35,71,80]. However, in the feline pulmonary vascular bed the vasoconstrictor response to DABK is mediated by the release of catecholamines and subsequent activation of α-adrenergic receptors [81] whereas prostaglandin-dependent constriction is observed in rat portal vein [82].

5.1.2. B₁ receptor-mediated vasodilation

B₁ receptor-mediated vasodilator responses are usually an endothelium-dependent phenomenon as is the case in the rat coronary circulation [18], bovine [83], porcine [84] and human coronary arteries [85] and in rabbit mesenteric [86] and carotid arteries [87]. In the large part this endothelium-dependency can be attributed to activation of eNOS and subsequent release of vasodilator NO as demonstrated using NOS inhibitors in a wide range of blood vessels including the rabbit carotid [87], bovine [83] porcine [84] and human [85] coronary arteries [81] (see Table 1). B₁ receptor-mediated vasorelaxation in these latter studies [81,84,87,88] was not sensitive to cyclooxygenase inhibition and hence is unlikely to involve prostaglandin release. In contrast, B₁ receptor-mediated vasodilation of the rat coronary circulation [18] and rabbit mesenteric artery [86,89] involves the release of eicosanoids, in particular prostacyclin [18].

In some vessels, B₁ receptor-mediated vasodilation is endothelium-independent and this has been attributed to prostaglandin activity, e.g. in rabbit coeliac and mesenteric artery [90,91]. This functional and mechanistic diversity of B₁ receptor-mediated vascular reactivity may be related to species and/or regional variation and/or due to differences in local sensitivity to vasodilator mediators. B₁ receptors are positively coupled to phospholipase A₂ and thereby cause arachidonic acid release [35,72,80]. Despite this ability to elevate prostaglandin synthesis it is clear that functional responses depend entirely upon local prostaglandin sensitivity. For example, B₁ receptor stimulation causes prostaglandin synthesis and contraction of RASMC however the latter response is not blocked by indomethacin [71] a scenario repeated in bovine vascular tissue [92,93,67,83]. Indeed, the rabbit aorta does not relax in response to PGI₂ or PGE₂ [94]. In contrast, these prostaglandins produce potent vasodilation in rabbit mesenteric and coeliac arteries and rat coronary circulation [94–97], tissues in which B₁ receptor activation induces PGI₂ secretion [98,18] and a prostaglandin synthesis-dependent relaxant response. Taken together, not all endothelium-independent B₁ receptor-mediated relaxant responses are mediated by prostaglandins, despite the observations that prostaglandins are consistently released in response to B₁ receptor activation. This is possibly linked to the absence of specific prostaglandin receptors.

With few exceptions, it would seem that B₁ receptor activation consistently produces constrictor responses in veins and dilator responses in arteries. This pattern of reactivity is in line with a pro-inflammatory role of the B₁ receptor; i.e. arterial/arteriolar dilation associated with venuconstriction would lead to increased hydrostatic pressure thus enhancing plasma protein extravasation and the associated inflammatory events. Whilst this is an attractive hypothesis the observation that B₁ receptor activation does cause contraction of some arteries suggests that B₁ receptor-mediated control of vascular tone is a complex and still unresolved process.

5.2. Myocardial effects

The expression of kinin receptors by cardiomyocytes and cardiac conduction tissue has been demonstrated [99,100]. B₁ receptors are also expressed on sympathetic fibres in myocardial tissue the activation of which enhances noradrenaline outflow [101–103]. In contrast, other studies have shown that B₁ receptor activation reduces sympathetic outflow and this effect has been linked to the proposed protective activity of des-Arg³-kinins in I/R injury [101]. B₂ receptor activation results in a prostaglandin-independent negative chronotropic effect in the canine sinus node [99]. Both B₁ and B₂ receptor stimulation can prolong the action potential duration in rat ventricular muscle [100] and this has been suggested to be a possible explanation for the anti-arrhythmic activity of the kinins.

5.3. Control of blood pressure

B₁ receptor-mediated hypotensive responses have been demonstrated and characterised in the rabbit [16], rat [18], pig [104], and dog [105]. The mechanism of this effect may be explained by the profile of reactivity within the vasculature, i.e. arterial dilation and venuconstriction. However, a reduction in heart rate was also observed in conjunction with the hypotensive effect of intravenously administered B₁ receptor agonists in the rabbit [106]. The authors suggest that early decreases in mean arterial pressure induced following B₁ receptor activation are due to the acute decreases in peripheral vascular resistance, presumably as a consequence of arterial dilation. However, the sustained hypotensive response was associated with a decrease in cardiac output attributed to decreases in cardiac contractility and heart rate. The B₁ receptor-mediated hypotensive response is generally only observed following an inflammatory stimulus e.g. endotoxin treatment, however some studies suggest that the hypotensive response occurs in ‘normal’ animals [105]. This may be an example of species variation, but is more likely to be associated with pre-existing infection [107].

A role for B₁ receptors in the central control of blood pressure (BP) has recently been reported. Caligiorne et al. [108] showed that DALBK microinjection into the nucleus tractus solitarii of Wistar Kyoto (WKY) rats prevented the
cardiovascular effects of exogenous BK. Additionally it has been reported that central B, receptor blockade lowers BP in spontaneously hypertensive rats (SHR) but not in normotensive rats [109]. Support for a central rather than peripheral role of B, receptors in hypertension is provided by the fact that in a transgenic rat (mREN2)27 model of hypertension no expression of the B1 receptor was detected in aorta, heart and kidneys [110]. However, it is possible that B1 receptor expression is localised to other vascular beds, not tested, that contribute significantly to peripheral resistance, e.g. the mesenteric vasculature. A role for B1 receptors in the central control of BP was confirmed by Emanueli et al. [111] who demonstrated that intracerebroventricular administration of B1 receptor agonists increases BP in both WKY and SHR. Accordingly, B1 receptor blockade or ‘knock-down’ with antisense oligonucleotides reduced BP in SHR, but not in WKY rats [111]. Furthermore, BP was elevated following central administration of a kininase II inhibitor and this effect was attenuated by central B1 receptor blockade [111]. Together these results suggest that central B1 receptors may play a role in the pathology of essential hypertension. In contrast however, Martins et al. [112] reported that neither DABK nor the B1 receptor antagonist DALBK injected into the fourth cerebral ventricle altered the BP of WKY or SHR [113,114]. Normal regulation of BP however does not appear to involve B1 receptors since B1 receptor KO mice do not display a hyper- or hypertensive phenotype [115]. In contrast, B2 receptor knockouts are predisposed to hypertension [116,117].

5.4. Inflammation and the microcirculation

Many of the effects of peripheral B1 receptor activation are proinflammatory; vasodilation, increased blood flow [106,118], plasma protein extravasation [113,119], activation of leukocyte-endothelial cell interactions [28] and subsequent leukocyte accumulation [120]. B1 receptor-mediated leukocyte recruitment was first demonstrated in our laboratory in 1996 [120]. In this study we showed that neutrophils accumulate in dorsal air pouches of mice when treated locally with IL-1β (4 h). This leukocyte accumulation was partially inhibited by B1 receptor blockade with DALBK, but not by B2 receptor blockade with HOE140. DABK itself also caused leukocyte migration in this model, but only in mice that had been previously treated (24 h) with IL-1β. DABK-induced leukocyte recruitment was inhibited by selective antagonists of the receptors for the neuropeptides substance P and calcitonin gene-related peptide (CGRP) [120] indicating that DABK, directly or indirectly, activates sensory C-fibres to release neuropeptides that, in turn, stimulate leukocyte recruitment. Support for a role for B1 receptors in the cellular component of an inflammatory response was provided in a recent study in which a less specific inflammatory stimulus was used, i.e. sephadex bead-induced pulmonary leukocyte accumulation in guinea pigs was inhibited by B1 receptor antagonism [114]. B1 receptor-mediated leukocyte recruitment has also been demonstrated in a separate study by Vianna and Calixto [113]. In this study intrathoracic injection of DABK produced an inflammatory response characterized by plasma protein extravasation and leukocyte accumulation. In contrast to our study, these effects were observed in ‘normal’ animals suggesting that, in this model, B1 receptors are either constitutively expressed or were already induced. This discrepancy is hard to explain, but may be an example of regional and/or species variation. However, it is more likely associated with a pre-existing inflammatory state (e.g. infection) that would lead to the appearance of pre-formed B1 receptors. Similar to our study, the DABK-induced leukocyte recruitment was inhibited by B1 receptor blockade and by neurokinin and CGRP receptor antagonists [113].

Since our 1996 study we have confirmed our findings and extended them to the microvasculature of mouse mesentery [28]. This investigation has been performed at the level of the leukocyte-endothelial cell interaction in post-capillary venules using the intravital microscopy technique. We demonstrated that B1 receptor activation induces all three phases of the leukocyte recruitment process: cell rolling, adhesion and emigration (Fig. 1). This is in contrast to other agents which display specificity in their action, e.g. histamine which preferentially enhances leukocyte rolling [121]. Additionally, this functional activity was temporally associated with receptor mRNA and protein expression. Modest basal expression of the B1 receptor mRNA was detected in saline injected animals, however, this was not associated with protein expression [28]. It is possible that B1 receptor mRNA is constitutively expressed but an appropriate inflammatory stimulus is required to achieve optimal translation. In this model, DABK-induced effects were independent of B2 receptor activation since experiments using HOE 140 or B2 receptor knockout mice had no effect on the magnitude of the cellular response. As illustrated in Fig. 2, we showed that the DABK-induced leukocyte trafficking responses involved the release of neuropeptides from C fibers, since capsaicin treatment inhibited the responses. Furthermore, mast cells were involved in the response since DABK-induced leukocyte trafficking was reduced following mast cell depletion with compound 48/80 and DABK treatment was shown histologically to induce mast cell degranulation. These findings provide clear evidence that B1 receptors play an important role in the initiation of leukocyte recruitment during an inflammatory response and this effect appears to involve the activation of sensory C fibres and/or mast cells. The exact relationship and sequence of events between the C-fibre- and mast cell-dependent pathways is less clear but certain possibilities are addressed in Fig. 2.

The site of B1 receptor expression is unclear from these studies. There are some in vitro observations suggesting B1
Fig. 1. Intravital video-microscopy images of leukocyte trafficking responses in mouse mesenteric post-capillary venules in vivo in response to (A) saline (0.25 ml, i.p., 2 h), (B) des-Arg<sup>9</sup>bradykinin (30 nmol, i.p., 2 h), (C) des-Arg<sup>9</sup>bradykinin (30 nmol, i.p., 4 h). Mice were anesthetized with diazepam (60 mg/kg s.c.) and Hypnorm® (0.7 mg/kg fentanyl citrate and 20 mg/kg fluanisone i.m). A Zeiss Axioskop FS with a water-immersion objective lens (magnification of ×40; Zeiss) and an eyepiece (×10 magnification; Zeiss) was used to observe the microcirculation. The acquired images were displayed onto a colour video monitor and recorded for subsequent off-line analysis. Mesenteries were superfused with bicarbonate-buffered solution at 37°C. Images reprinted with permission from the Journal of Experimental Medicine.
receptor expression on phagocytic cells and lymphocytes. For instance, human neutrophils secrete elastase in response to BK or Lys-DABK mediated by B<sub>2</sub> and B<sub>1</sub> receptors, respectively [122]. In addition, Lys-DABK causes increased permeability of an endothelial layer maintained in vitro only in the presence of neutrophils [122]. These neutrophils were naïve, non-activated cells hence suggesting that B<sub>1</sub> receptors are constitutively expressed on these cells. Circulating lymphocytes also appear to exhibit a chemokinetic response to kinins via the stimulation of B<sub>1</sub> receptors in vitro [123]. Furthermore, B<sub>1</sub> receptor induction has been shown to occur on T lymphocytes during the course of multiple sclerosis, and when activated mediate a reduction in T-cell migration in vitro [124]. However, in a recent study we showed that DABK had no effect on various parameters of neutrophil function in vitro [120]. At the present time it remains unclear as to whether B<sub>1</sub> receptors are present on leukocytes.

In contrast to the above studies of B<sub>1</sub> receptor-mediated inflammation, B<sub>2</sub> receptors appear to play little role in the cellular component of a vascular inflammatory response. Whilst B<sub>2</sub> receptor-mediated effects such as plasma protein extravasation and adhesion molecule expression have been reported, BK produces no cellular response when injected into the skin [1]. This is confirmed by the observation that very high doses of BK are required to promote leukocyte–endothelial cell interactions in rat mesenteric post-capillary venules; doses 100–500 times higher than that required to promote changes in blood flow [125]. Therefore it appears that B<sub>2</sub> receptors may only have a small role to play in the cellular component of the inflammatory response.

6. Role played by B<sub>1</sub> receptors in pathophysiology of the cardiovascular system

Pathological activation of the kallikrein–kinin system generally occurs during situations of stress such as inflammation or shock (e.g. following a pathogenic or chemical insult). This acute response consists of the activation of PK, leading to BK generation. Release of BK and subsequent activation of B<sub>2</sub> receptors has been suggested to play an important role in acute inflammation and the immediate hypotensive response to endotoxin [1]. However, it now appears that the subsequent formation of des-Arg<sup>9</sup>kinins and induction and activation of B<sub>1</sub> receptors may also play an important role in the pathology of human disease, particularly those diseases in which a vascular inflammatory component exists.
6.1. Sepsis and the kallikrein–kinin system

Sepsis is defined as the systemic inflammatory response syndrome (SIRS) that results from infection and is referred to as ‘septic shock’ when accompanied by hypotension that is unresponsive to fluid therapy [126]. Endotoxins, released from gram-negative bacteria, are thought to play an integral role in the pathogenesis of sepsis. Exposure to gram-negative or gram-positive bacteria, fungi or proteoglycan polysaccharides can trigger the release of inflammatory substances including kallikrein from infiltrating leukocytes, platelets and ECs, as well as directly activating the kallikrein–kinin system leading to increased kinin synthesis [126]. Kinins appear to be particularly important in the pathogenesis of SIRS and sepsis when endotoxin is the critical pathogen [127]. The early peripheral vascular changes accompanying endotoxin shock include a fall in blood pressure. A key feature of endotoxemia is a hypodynamic state which alters the distribution of blood to exchange vessels in tissues and organs throughout the body. One such example of this disordered autoregulation in sepsis is the coronary microcirculation [128,129]. This phenomenon is thought to be due partly to the release of NO from iNOS expressed in vascular smooth muscle [128], an important mediator of sepsis-induced hypotension [130], however NO-independent mechanisms exist but remain to be elucidated [131,132]. Several studies support a role for the B1 receptor which has been implicated in the regulation of the coronary circulation in rat and rabbit models of endotoxemia [18,16,133]. Infusion of BK or DABK results in cardiovascular changes, particularly hypotension, similar to those occurring in endotoxic shock [18,134]. In animal models, endotoxin causes rapid activation of the kallikrein–kinin system increasing kinin levels [135,136]. This effect appears to be specific to LPS as the monophosphoryl lipid A derivative of bacterial LPS fails to induce B1 receptor-dependent responses to DABK in the rabbit in vivo [137]. Similarly, the pathological response to intravenous endotoxin in healthy human volunteers [138] is associated with activation of the kallikrein–kinin systems. In addition, consumption of pre-kallikrein and HMWK is also increased in patients with endotoxemia, and this is particularly true for patients with septic shock (or hypotensive sepsis) compared to those with uncomplicated sepsis [139–142].

6.1.1. Kinin receptors and sepsis

Support for a role of kinin receptors in the hypotensive response in sepsis is provided by several studies demonstrating a partial restoration of blood pressure following treatment with kinin receptor antagonists. Endotoxin treatment produces a profound biphasic hypotensive response, a brief early phase followed by a prolonged late phase. The first phase is sensitive to B2 receptor blockade [136,143], but not affected by B1 receptor antagonists (McLean, Perretti and Ahluwalia, unpublished observation). The prolonged phase, which is the stage at which patients present in the clinic, has been extensively studied and is known to be partially dependent on enhanced NO production from the induction of iNOS [130]. In a recent study [18] we showed that B1 receptor antagonists produced a partial reversal of the prolonged phase of endotoxin-induced hypotension. The inhibition of ACE/kininase II with captopril did not appear to markedly affect the role of B1 receptors in hypotension in this model [18]. Mice lacking the gene for the B2 receptor have been developed [115] and a full characterization of the responses to bacterial infection and endotoxic shock in these animals is needed. It was suggested that the immediate hypotensive response to endotoxin is markedly blunted in these animals [115]. This finding contrasts the observation made in the rat, and requires confirmation in a full study, but certainly suggests that the B1 receptor is involved in the hypotensive response to endotoxin.

6.1.2. Kinin receptor antagonists in the treatment of sepsis

A role for kinin receptors in endotoxic shock, while an attractive target, is not yet certain because specific metabolically stable kinin receptor antagonists have only recently been made available. The following sections describe some of the findings arising from studies of kinin receptor antagonists in animal models of endotoxic shock and human sepsis.

6.1.2.1. B2 receptor antagonists

Given the evidence implicating kinins in the pathogenesis of sepsis it is not surprising that pre-formed B2 receptors have been suggested to play a role in certain aspects of the septic syndrome. However, reports investigating the effects of B2 receptor antagonism in models of endotoxemia are conflicting showing both beneficial effects and negative efficacy. One of the first studies to investigate the effect of kinin receptor blockade in endotoxic shock was that of Wilson et al. [136] who tested the B2 receptor antagonist d-Arg-Hyp3-d-Phe2-bradykinin (NPC 567). In this study administration of LPS to rats resulted in an increase in circulating bradykinin and prostaglandin levels and a profound hypotensive response. NPC 567 infusion dramatically reduced mortality from 100 to 50% at 24 h which was accompanied by a significant reduction in 6-keto-PGF1α levels and partial reversal of the hypotensive effects. Other studies confirm beneficial effects of B2 receptor blockade in sepsis [144,145]. However, there are also contrary reports indicating no benefit of B2 receptor antagonism. In particular, the study by Feletou et al. [146] demonstrated that LPS-induced hypotension, metabolic acidosis and leukopenia in rabbits was unaffected by the B2 receptor antagonist S 16118. Furthermore, in mice, LPS administration induced over 90% mortality at 96 h which was not reduced by S 16118 [146]. Other studies in rodents...
report a negative efficacy for B₂ receptor blockade alone in experimental endotoxic shock [147,148] although a beneficial effect was observed when used in combination with leukocyte recruitment inhibitors (NPC 15669) [148].

6.1.2.2. B₁ receptor antagonists  B₁ receptor-mediated hypotensive responses have been demonstrated and characterised in rabbit [16], rat [18] and pig [104] models of endotoxemia indicating a potential role for this receptor in the hypotensive response to endotoxin. Administration of B₁ receptor antagonists blocks the hypotensive effect of exogenously administered B₁ receptor agonists [16,18]. The only report investigating the effect of B₁ receptor blockade on the endotoxic shock-associated hypotension was performed recently in our laboratory [18]. We showed that B₁ receptor blockade with DALBK or des-arg¹⁰HOE140 produced a modest reversal (5–9%) of endotoxin-induced hypotension. Therefore activation of B₁ receptors may have a modest role to play in the vascular changes associated with endotoxemia, however the possibility of synergism with other therapies has not been tested. The effect of selective B₁ receptor antagonists on mortality associated with endotoxemia is unclear. Siebeck et al. [145] showed that B₁ receptor blockade attenuates endotoxin-induced mortality in pigs, whereas additional B₁ receptor blockade seemed to reverse these beneficial effects [145]. However, the effect of B₁ receptor blockers alone was not tested. The reasons for this apparent contradiction regarding the role of B₁ receptors is unclear but may be related to species differences. The pattern of B₁ receptor expression in endotoxic pigs is reportedly confined to the smooth muscle with no endothelial expression [63]. In contrast, endotoxin-induced, B₁ receptor-mediated vasodilation in rat vessels is endothelium-dependent [18] similar to human coronary arteries [85]. However, it is possible that B₁ receptor activation is protective, at least in the porcine model of endotoxic shock, which may or may not be relevant in other species. Alternatively, the level of B₁ receptor blockade may be important; partial inhibition may be beneficial whereas complete blockade is detrimental. Further studies with selective metabolically stable kinin receptor antagonists are required to address this controversy.

6.1.2.3. Mixed kinin receptor antagonists  It is possible that the apparent contradictory findings with kinin receptor antagonists lie in their receptor selectivity. Certain peptidic B₂ receptor antagonists are non-selective and have some efficacy at B₁ receptors in vivo. CP-0127 is a peptide dimer of two single chain BK antagonists linked together creating a compound with high potency in vitro [149] and long duration of action in vivo [143]. The pharmacology of this compound is unique in that it appears to be a specific B₂ receptor antagonist in vitro [150]. However, in vivo it behaves as a B₂ receptor antagonist with moderate B₁ receptor antagonist activity (Cheronis, J.C. 1999. Personal communication). CP-0127 itself does not have B₁ receptor antagonist activity but its two metabolites, the mono and bis-des-Arg derivatives do. Their potency is relatively low but they are more stable and consequently accumulate (Cheronis, J.C. 1999. Personal communication). Administration of such compounds (e.g. CP-0127, NPC-567) inhibit hypotension and improve survival in rats and rabbits challenged with endotoxin [136,143]. This improvement over B₂ receptor blockade alone would imply that compounds possessing affinity at both kinin receptors may prove advantageous in the therapy of sepsis [151]. Indeed, CP-0127 marginally improves survival in patients with gram-negative sepsis [152], and it is possible that this beneficial effect is correlated with the efficacy of this compound at B₁ receptors.

6.2. I/R injury

I/R injury is an inflammatory state also associated with B₁ receptor induction. In both in vitro and in vivo models of myocardial I/R functional B₁ receptor expression is induced [153]. In rat isolated hearts ischemia-induces B₁ receptors that upon activation modulate noradrenaline release or preserve endothelium-dependent vasodilation [101,103,154]. Further support for a role of kinins in I/R injury is provided by the demonstration that the kallikrein–kinin system in the heart is activated as demonstrated by an increase in the levels of kinins in the effluent of isolated perfused hearts [41,155]. Similarly kinin levels are elevated in in vivo myocardial I/R injury; an effect further increased by kininase II inhibition [156,157].

Recent studies indicate that BK, acting via B₂ receptors, has a protective effect in I/R injury of the rat mesenteric microcirculation [158] and rabbit myocardium [159]. Additionally treatment with angiotensin-converting enzyme inhibitors further attenuate the extent of I/R injury, an effect associated with elevated levels of endogenous kinins [159]. Indeed, intracoronary perfusion of exogenous BK is protective against I/R-induced ventricular fibrillation [160,161]. B₁ receptors have also been suggested to play a protective role since B₁ receptor antagonism blocks DABK- or BK-induced decreases of I/R-induced noradrenaline outflow and arrhythmia [101].

That kinins exert a protective effect in I/R is surprising because of their well-known proinflammatory actions. Especially since B₂ receptors have been implicated in the pathogenesis of post ischemic pancreatitis [162] and the fact that B₁ receptors play a role in initiation of the leukocyte–endothelial interaction that occurs in global ischemia of the brain [163]. However, in a rat model of cerebral artery occlusion, opposing effects of B₂ and B₁ receptor antagonism have been described [164]. Antagonism of B₂ receptors reduced cerebral infarct whereas B₁ receptor blockade reversed the beneficial effect of the B₂ receptor antagonist [164]. In this model B₁ and B₂ receptors have differential effects on ischemic brain pathology.

Therefore, it appears that kinin receptor activation has
the potential to modulate I/R injury. Further studies are required to fully understand the mechanisms and functional relevance of these observed effects and to determine under which conditions these effects are protective or contributory to the pathology of I/R injury.

6.2.1. Ischaemic preconditioning

Activation of the kallikrein–kinin system is necessary for the cardioprotective effect of preconditioning and involves activation of both B₂ [165] and B₁ [101,154] receptors. The use of selective antagonists has shown that B₂ receptor activation mediates the benefits of ischaemic preconditioning on certain features of I/R injury; reduced arrhythmias [166], reduced infarct size [167] and improvement of post-ischaemic ventricular recovery [168]. B₁ receptor activation appears to be important in the protection provided by ischaemic preconditioning on endothelial function [154] as well as inhibiting noradrenaline overflow and preventing ventricular fibrillation at reperfusion [101]. In contrast to their role in I/R injury, which is less clear, B₁ receptors are clearly important in the protection afforded by ischaemic preconditioning.

6.3. Atheromatous disease

Immunoreactivity for the human B₁ receptor is markedly increased in atheromatous plaques of the coronary, vertebral, femoral and pericallosal arteries [65]. Intense labelling for B₁ receptors was shown to be most apparent on the ECs, foamy macrophages, infiltrating leukocytes and in proliferating SMCs. Immunoreactive B₂ receptors were also expressed in these lesions, but with a consistently lower intensity relative to the B₁ receptor. Pilot studies in the rabbit on the effects of high dietary cholesterol on B₁ receptor expression in cardiac tissue were negative [14] whilst in the same study, endotoxin treatment caused marked cardiac B₁ receptor expression. Taken together these studies suggest that up-regulation of B₁ receptors expression may occur as a result of the inflammatory nature of atherosclerosis, but not simply as a result of hypercholesterolemia. The precise role of B₁ receptors (contributory or protective) in the development of ischaemic heart disease is difficult to predict and requires further study.

6.4. Angioplasty

Evidence suggesting a role for B₁ receptors in the pathogenesis of angioplasty-induced vascular injury was provided in a recent study by Pruneau et al. [169]. In this study balloon catheter injury to the rabbit carotid artery led to the development of a contractile response to the B₁ receptor agonist DABK. This induction of reactivity to DABK was associated with the proliferation of SMCs but a causal relationship between the two findings was not demonstrated [169]. B₁ receptor stimulation has been shown to cause contraction and DNA synthesis in cytokine treated rabbit aortic SMCs, the latter effect being unique to cytokine-treated cells [20]. As such, B₁ receptor induction may play a role, in concert, in the altered reactivity and hypertrophic medial responses to injury in arteries following angioplasty although further studies are required to confirm this. In contrast, B₂ receptor activation also leads to suppression of DNA synthesis in PDGF-stimulated rat mesenteric artery SMCs [170], although the significance of this finding remains to be determined.

6.5. Other diseases

The role played by B₁ receptors in other diseases of the cardiovascular system such as hypertension, cardiac failure and their associated complications is unknown. It is interesting to note that increased production of inflammatory cytokines occurs in human cardiac failure [171] that would be expected to stimulate wide spread B₁ receptor induction. Polymorphisms in the human B₁ receptor gene have been identified and appear to be associated with the risk of end-stage renal disease [172,173]. An allele in which a single base substitution (G699→C) occurs in the putative promoter region with significantly lower frequency in a population of renal failure patients and determines an increased activity of promoter function [173]. B₁ receptor polymorphisms have been suggested to have a protective effect in the development of end-stage renal disease [172]. Whether B₁ receptor polymorphisms exist for other cardiovascular diseases remains to be determined.

7. Conclusions

B₁ receptors are involved in certain cardiovascular inflammatory pathologies such as endotoxic shock, atheromatous disease, and myocardial ischaemia. Furthermore, the inducibility of the receptor makes it an attractive target for therapeutic interventions. Drug development efforts, however, will need to be acutely aware of the possibility that activation of B₁ receptors may be pathogenic or protective depending on the disease and tissue affected.

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