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Review

Kinin receptors in pain and inflammation

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Abstract

Kinins are among the most potent autacoids involved in inflammatory, vascular and pain processes. These short-lived peptides, including bradykinin, kallidin and T-kinin, are generated during tissue injury and noxious stimulation. However, emerging evidence also suggests that kinins are stored in neuronal elements of the central nervous system (CNS) where they are thought to play a role as neuromediators in various cerebral functions, particularly in the control of nociceptive information. Kinins exert their biological effects through the activation of two transmembrane G-protein-coupled receptors, denoted bradykinin B_1 and B_2. Whereas the B_2 receptor is constitutive and activated by the parent molecules, the B_1 receptor is generally underexpressed in normal tissues and is activated by kinins deprived of the C-terminal Arg (des-Arg^9-kinins). The induction and increased expression of B_1 receptor occur following tissue injury or after treatment with bacterial endotoxins or cytokines such as interleukin-1β and tumor necrosis factor-α. This review summarizes the most recent data from various animal models which convey support for a role of B_2 receptors in the acute phase of the inflammatory and pain response, and for a role of B_1 receptors in the chronic phase of the response. The B_1 receptor may exert a strategic role in inflammatory diseases with an immune component (diabetes, asthma, rheumatoid arthritis and multiple sclerosis). New information is provided regarding the role of sensory mechanisms subserving spinal hyperalgesia and intrapleural neutrophil migration that occur upon B_1 receptor activation in streptozotocin-treated rats, a model of insulin-dependent diabetes mellitus in which the B_1 receptor seems to be rapidly overexpressed. Although it is widely accepted that the blockade of kinin receptors with specific antagonists could be of benefit in the treatment of somatic and visceral inflammation and pain, recent molecular and functional evidence suggests that the activation of B_1 receptors with an agonist may afford a novel therapeutic approach in the CNS inflammatory demyelinating disorder encountered in multiple sclerosis by reducing immune cell infiltration (T-lymphocytes) into the brain. Hence, the B_1 receptor may exert either a protective or detrimental effect depending on the inflammatory disease. This dual function of the B_1 receptor deserves to be investigated further.

Keywords: Bradykinin; Bradykinin B_1 receptor; Bradykinin B_2 receptor; Hyperalgesia; Neurogenic inflammation; Substance P; Leukocyte; T-lymphocyte

1. Introduction

Kinins belong to a group of 9–11 amino acid peptides including bradykinin, kallidin, T-kinin and their active metabolites, des-Arg^9-kinins. 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 (for review see Bhoola et al., 1992). T-kinin was identified exclusively in the rat (Okamoto and Greenbaum, 1983a,b). 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), which removes Arg^9 from kinins to produce the active metabolites des-Arg^9-kinins, neutral endopeptidase 24.11 (enkephalinase), which cleaves the C-terminal dipeptide Phe^8–Arg^9 from bradykinin, and kininase II (also named angiotensin-I-converting enzyme), which acts as dipeptidyl carboxypeptidase to remove the COOH-terminal dipeptide, Phe^8–Arg^9. Furthermore, angiotensin-1-converting enzyme cleaves 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 T-kinin are also subject to transformation into bradykinin by aminopeptidase activity (Kuoppala et al., 2000; Murphey et al., 2000; Campbell, 2000; Couture and Lindsey, 2000).

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2. Bradykinin receptors and signalling pathways

Kinins exert their biological effects through the activation of two receptors, denoted as bradykinin B_1 and bradykinin B_2 receptors on the basis of their distinct pharmacology (Regoli and Barabé, 1980; Marceau et al., 1998). Kinins are the endogenous agonists of the prevailing B_2 receptor, while des-Arg^9-bradykinin and des-Arg^{10}-kallidin are the preferential agonists for the B_1 receptor. Present evidence suggests that kallikreins and some other proteases activate human B_2 receptor directly, independent of bradykinin release. Thus, the B_2 receptor may belong to a new group of serine protease-activated receptors (Hecquet et al., 2000). Both bradykinin receptor genes have been cloned in human and various species and the hydrophobicity prediction for the residues indicates that both bradykinin B_1 and B_2 receptors have seven helix transmembrane domains, a structure common to other members of the rhodopsin superfamily of G-protein-coupled receptors ($G\alpha q/11$ and $G\alpha i$). The amino acid sequence of the human B_1 receptor (353 amino acid protein) is only 36% identical to the amino acid sequence (364 amino acid protein) of the human B_2 receptor (Menke et al., 1994), while the homology is only 30% between mouse bradykinin B_2 (366 amino acid) and B_1 (334 amino acid) receptors (Menke et al., 1994; Pesquero et al., 1996; see Couture and Lindsey, 2000 for review). The existence of interspecies bradykinin B_1 and B_2 receptor subtypes was confirmed on the basis of discriminating agonists and antagonists. For instance, the rabbit B_2 receptor subtype is pharmacologically similar to that found in human but different from that of the rat and guinea-pig B_2 receptor subtype (Regoli et al., 1994, 2001). Pharmacological evidence also suggests that the B_1 receptor found in dog, rat, mouse and hamster is a subtype that differs from the human, rabbit and pig B_1 receptor, which shows a preference for the presence of the N-terminal Lys residue of Lys-des-Arg^9-bradykinin (agonist) and Lys-[Leu^8]des-Arg^9-bradykinin (antagonist) (Regoli et al., 2001; Hess et al., 2001). Highly potent and selective peptide and non-peptide agonists and antagonists are available for the bradykinin B_2 receptor, while at the present time only peptide agonists and antagonists are readily available for the bradykinin B_1 receptor (Altamura et al., 1999; Regoli et al., 1998, 2001; Stewart et al., 2001).

Whereas the B_2 receptor is constitutive, the B_1 receptor is generally absent in normal tissues and healthy animals but expressed in animals diagnosed with an established infection (Siebeck et al., 1998). The B_1 receptor is induced and overexpressed during tissue injury, following treatment with bacterial endotoxins and cytokines such as interleukin-1β and tumor necrosis factor alpha (Marceau et al., 1998). The induction of B_1 receptor by cytokines is controlled by mitogen-activated protein kinase (MAP kinase) and by the transcriptional nuclear factor κB (NF-κB) (Larrivée et al., 1998; Ni et al., 1998a; Schanstra et al., 1998; Zhou et al., 1998; Campos et al., 1999; Sardi et al., 1999). Sequence analysis of human and rat B_1 receptor gene has revealed the presence of a transcriptional regulatory site for NK-κB in the promotor region (Bachvarov et al., 1996; Ni et al., 1998a,b).

Various signal transduction mechanisms have been described for kinins depending on the cellular type. This includes the activation of phospholipases A2, C and D with the subsequent release of prostaglandins, nitric oxide, inositol phosphates and diacylglycerol from membrane inositol phospholipids, leading to the mobilization of intracellular calcium and activation of several isoforms of protein kinase C . Besides these classical pathways, the B_2 receptor is also linked to the activation of protein tyrosine kinases and phosphatases as well as MAP kinase. Conversely, the B_1 receptor is primarily linked to the activation of phospholipase C and the phosphoinositide pathway (for reviews see Marceau et al., 1998; Couture and Lindsey, 2000).

3. Regulation of bradykinin receptors

In pathological conditions, the inducible B_1 receptor that mediates the inflammatory actions of kinins might be activated by the endogenous biologically active kininase I metabolite (des-Arg^9-bradykinin), which is increased at sites of inflammation (Raymond et al., 1995; Décarie et al., 1996b). Indeed, evidence from human lung fibroblasts (IMR-90) suggests upregulation of B_1 receptors by its own agonist, involving activation of protein kinase C and NF-κB through pertussis and cholera toxin-insensitive pathways (Schanstra et al., 1998). A synergistic interaction appears to exist between bradykinin B_1 receptor ligands and interleukin-1β to enhance the production of B_1 receptors (Phagoo et al., 1999). Studies in vivo with the model of inflammatory hyperalgesia point to the possibility that B_1 receptors may also be cross upregulated by B_2 receptor activation (via autocrine production of cytokines) and/or B_2 receptor desensitization (Campos et al., 1995). Activation of B_2 receptors is known to activate NF-κB, which can prime the expression of B_1 receptors (Pan et al., 1996; Phagoo et al., 1999; Schanstra et al., 1999). The possibility of a compensatory or reciprocal regulation of B_1 receptors relative to B_2 receptors was made less likely by results of a recent study which measured contractile responses mediated by kinin agonists in ex vivo rabbit blood vessels and mRNA for both kinin receptors in peripheral organs isolated from rabbit receiving several treatments including angiotensin-1-converting enzyme inhibitors (Marceau et al., 1999). Thus, the original observation of Nwartor and Whalley (1989), that angiotensin-1-converting enzyme inhibition can lead to upregulation of B_1 receptors, is not supported by results of a molecular study in the rabbit (Marceau et al., 1999). Nevertheless, a balance was proposed to exist between kininase I and kininase II pathways

in the metabolic degradation of kinins, and the inhibition of kininase II (angiotensin-1-converting enzyme) was found to shift the balance in favour of increased des-Arg^9-bradykinin production (Décarie et al., 1994, 1996a; Raymond et al., 1995). Thus, the significance of this latter observation with respect to kinin receptor regulation is still uncertain and requires further investigation.

It is now accepted that angiotensin-1-converting enzyme inhibitors can augment the response to bradykinin via the B_2 receptor independently of blocking its enzymatic degradation. Compelling evidence from tissue preparation and transfected cells reveals that angiotensin-1-converting enzyme inhibitors potentiate the effect of bradykinin and resensitize B_2 receptors which had been desensitized by the agonist. This effect of angiotensin-1-converting enzyme inhibitors is due to cross-talk between angiotensin-1-converting enzyme and B_2 receptors and occurs by induction of an allosteric modification of the B_2 receptor conformation that affects its signal transduction pathway (Erdös and Marcic, 2001). Recent evidence from our laboratory suggests that chronic treatment with angiotensin-1-converting enzyme inhibitors can also upregulate B_2 receptor binding sites (but not B_1 receptors) in the spinal dorsal horn of spontaneously hypertensive rats (Ongali et al., 2001). This finding may provide another mechanism by which angiotensin-1-converting enzyme inhibitors potentiate the effect of bradykinin. Whereas the mechanism of this phenomenon is still unknown, it may occur following inhibition of the sequestration of the B_2 receptor within the cellular membrane by angiotensin-1-converting enzyme inhibitors (Benzing et al., 1999). This provides evidence that kinin receptor expression can be regulated differently in peripheral and central tissues under normal and pathological conditions.

4. Bradykinin receptors in pain and inflammation

Results obtained with animal models suggest that B_2 receptors are involved in the acute phase of the inflammatory and pain response, whereas B_1 receptors participate in the chronic phase of the response (Dray and Perkins, 1993; Dray, 1997). This is likely to occur because B_2 receptor function is controlled by short-term mechanisms involving fast ligand dissociation, receptor desensitization and internalization, and on long-term stimulation, downregulation (Munoz and Leeb-Lundberg, 1992; Munoz et al., 1993; Mathis et al., 1996; Phagoo et al., 1999; Faussner et al., 1999; Marceau et al., 2001). In contrast, B_1 receptors elicit persistent responses and signalling that are subjected to very limited desensitization, and receptor internalization with very slow ligand dissociation. In addition, upon long-term agonist exposure, the B_1 receptor is upregulated (Mathis et al., 1996; Austin et al., 1997; Faussner et al., 1999). Chronic activation of B_1 receptors is likely to be amplified by the accumulation of des-Arg^9-bradykinin at the site of inflammation because the half-life of des-Arg^9-bradykinin is 4- to 12-fold longer than that of bradykinin (Décarie et al., 1996a; Marceau et al., 1998). For instance, in the carrageenan-induced inflammation model, the levels of des-Arg^9-bradykinin were 1.3- to 5-fold greater than those of bradykinin in the inflamed paw (Burch and DeHass, 1990; Décarie et al., 1996b). Upregulation of carboxypeptidase M (kininase I) may also account for the increasing endogenous level of des-Arg^9-kinin metabolites and bradykinin B_1 receptor agonists in inflammation (Schremmer-Danninger et al., 1998).

4.1. Specific role for the bradykinin B_2 receptor in inflammatory pain

Generated during inflammation and tissue injury, bradykinin is known as one of the most potent algogenic inflammatory mediators and regulators of the noxious heat sensitivity of nociceptors (Juan and Lembeck, 1974; Regoli and Barabé, 1980; Dray, 1997). The activation of B_2 receptors, constitutively expressed in primary sensory neurons (Steranka et al., 1988; Lopes et al., 1993; 1995), promotes polymodal nociceptor activation and hyperalgesia through the production of diacylglycerol and activation of protein kinase C (Burgess et al., 1989; Dray et al., 1992; Levine et al., 1993). Moreover, bradykinin can sensitize nociceptors following the release of prostaglandins, cytokines and nitric oxide either from sensory neurones, endothelial and immune cells or fibroblasts in addition to its interaction with mast cell mediators (Dray and Perkins, 1997). Bradykinin is known to facilitate the release of substance P and calcitonin gene-related peptide from rat sensory neurones in culture (MacLean et al., 1990; Vasko et al., 1994) as well as from peripheral terminals of capsaicin-sensitive primary afferents in several tissues and organs of different species (Geppetti, 1993). The increase of bradykinin-induced release of sensory neuropeptides is generally augmented by prostaglandins and reduced by cyclooxygenase inhibitors (Andreeva and Rang, 1993). These observations provide a solid rationale to explain the analgesia provided by pharmacological blockade of B_2 receptors with selective antagonists in acute inflammatory hyperalgesia models (Heapy et al., 1991; Beresford and Birch, 1992; Ferreira et al., 1993; Perkins et al., 1993; Sufka and Roach, 1996; Rupniak et al., 1997; Griesbacher et al., 1998; Calixto et al., 2000). This is also substantiated by the alterations of the nociceptive responses in B_2 receptor knockout mice (Borkowski et al., 1995; Boyce et al., 1996; Rupniak et al., 1997).

4.2. Specific role for the bradykinin B_1 receptor in inflammatory pain

Recent immunohistochemical studies have shown basal expression of B_1 receptors in sensory ganglia as well as in central and peripheral nerve terminals of sensory neurons

(likely Aδ- and C-fibres) in the rat (Wotherspoon and Winter, 2000; Ma et al., 2000). This is in contrast, however, to results of binding studies which failed to detect any significant B_1 receptor binding sites in primary cultures of rat dorsal root ganglion neurones, in either the absence or presence of interleukin-1β pretreatment (Davis et al., 1996) and in the rat spinal dorsal horn, with the highly specific B_1 receptor radioligand, ^{125}I-HPP-des-Arg^{10}-Hoe 140 (^{125}I-3-4-hydroxyphenyl-propionyl-D-Arg^0-[Hyp^3,Thi^5,D-Tic^7,Oic^8]-des-Arg^9-bradykinin) (Ongali et al., 2001). Discrepant results of binding and of immunohistochemical studies may be due to the greater sensitivity achieved with receptor antibodies. Nevertheless, the significance of this low level of constitutive B_1 receptors in healthy animals is questionable as bradykinin B_1 receptor agonists did not affect nociception in normal rats or in acute models of inflammation (Dray and Perkins, 1997; Calixto et al., 2000; Fig. 1) and neither did they cause second messenger activation, neuropeptide release (e.g. calcitonin gene-related peptide) or electrophysiological events in sensory neurones under control or inflammatory conditions (Dray et al., 1992; Andreeva and Rang, 1993; Davis et al., 1996). Pharmacological antagonists of B_1 receptors induced analgesia only in animal models of persistent inflammatory mechanical and thermal hyperalgesia (Perkins et al., 1993, 1995; Perkins and Kelly, 1993, 1994; Davis and Perkins, 1994; Khasar et al., 1995; Rupniak et al., 1997; Poole et al., 1999; Bélichard et al., 2000) or of persistent visceral pain (Jaggar et al., 1998). These results were explained by the induction of B_1 receptors on cells other than sensory neurons (macrophages, fibroblasts or endothelial cells) where they may be responsible for releasing mediators (prostaglandins, cytokines and nitric oxide) that sensitize or activate the nociceptors (Davis et al., 1996; Dray and Perkins, 1997).

Nevertheless, in a rat model of neuropathic hypersensitivity following peripheral nerve injury, increased mRNA expression of the B_1 receptor occurred at 14 days post-injury in the lumbar dorsal root ganglia ipsilateral to the site of nerve injury while increased expression of B_2 receptor mRNA was already present at 48 h and was expressed bilaterally at 14 days. Analgesia was produced at both times by bradykinin B_2 receptor antagonists while bradykinin B_1 receptor antagonists had an analgesic effect only at 14 days after injury (Levy and Zochodne, 2000). Using gold-labelled bradykinin, upregulation of B_2 receptors and induction of B_1 receptors occurred both ipsi- and contralaterally in rat dorsal root ganglion neurons as early as 2 days after unilateral sciatic nerve injury induced by tight ligation (Petersen et al., 1998; Eckert et al., 1999). Hence, the induction or upregulation of bradykinin B_1 and B_2 receptors in sensory neurones could also contribute to the hyperalgesia following inflammatory pain (see below). The direct effect of kinins on sensory neurones can be sensitized by the action of prostaglandins or other mediators released from other cells by the activation of either bradykinin receptor.

The possibility that the B_1 receptor is involved in the physiological control of pain processes in the absence of inflammation cannot be excluded in species with constitutive B_1 receptors. For instance, the level of expression of the B_1 receptor appears to be more important in several peripheral organs of mice (ileum, stomach, kidney) in which functional responses were evoked with bradykinin

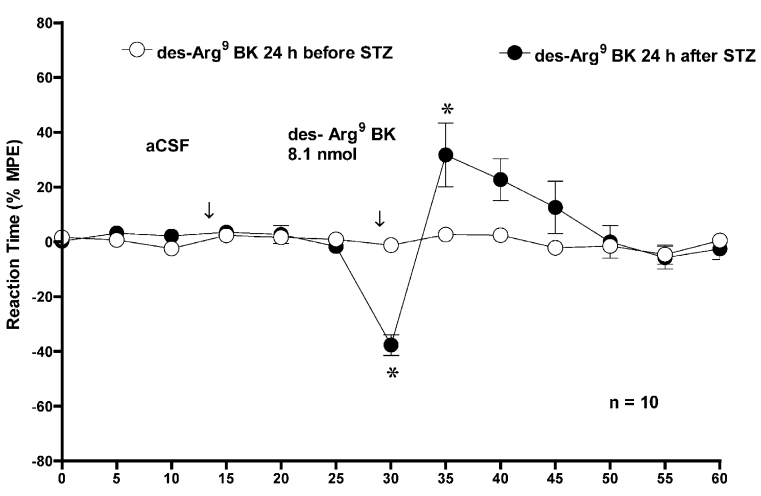

Fig. 1. Tail-flick latency changes produced by the intrathecal (L2–L3) injection of des-Arg^9-bradykinin (BK) (8.1 nmol) in male Sprague–Dawley rats (250–275 g) 24 h before and 24 h after the induction of diabetes (blood glucose $>$ 20 mM) with a single injection of streptozotocin (65 mg/kg, i.p.). The B_1 agonist was injected at 29 min (at the arrow) in rats which received 15 min earlier an intrathecal injection of artificial cerebrospinal fluid (aCSF). Each point represents the mean ± S.E.M. for 10 rats. Statistical comparison between values before and after the induction of diabetes was done with a two-way ANOVA and the Bonferroni test and significance is indicated by $^*P < 0.001$. Further information regarding the measurement of nociceptive threshold and methods is given elsewhere (Couture et al., 2000).

B_1 receptor agonists (Nsa Allogho et al., 1997; Pesquero et al., 2000). However, although bradykinin B_1 receptor mRNA was detected by reverse transcriptase polymerase chain reaction (RT-PCR) in sensory dorsal root ganglia neurones from wild-type and bradykinin B_2 receptor knockout mice, no depolarizing effects were induced with a bradykinin B_1 receptor agonist (Seabrook et al., 1997). In contrast, deletion of the B_1 receptor in mice compromises normal pain behaviour in models of both thermal and chemical nociception and leads to reduction of the activity-dependent facilitation (wind-up) of a nociceptive spinal reflex (Pesquero et al., 2000). Although results of the latter study support a physiological function for B_1 receptors in the spinal control of nociception in healthy mice, such a role for this receptor was demonstrated only during chronic inflammation or after its upregulation by cytokines in other animal species. Hence, a functional role for the B_1 receptor in the control of acute pain and nociceptive reflex in humans remains to be proven. The above-mentioned evidence from various animal models (mice being an exception to the rule) pleads for the general concept that B_1 receptors are primarily involved in persistent inflammatory pain.

5. Central kinins in pain process

Compelling evidence suggests that kinins may act as modulatory transmitters via the activation of B_2 receptors in the physiological control of spinal and supraspinal nociceptive neurotransmission. All components of the kallikrein–kinin system have been identified in the brain and spinal cord, including kinin precursors (kininogens), kinin-releasing enzymes (kallikreins), kinins, bradykinin B_2 receptor and kinin-degrading enzymes (for a review see Couture and Lindsey, 2000). When administered into the cerebral ventricles, bradykinin caused an antinociceptive effect through a noradrenergic mechanism in rabbits (Ribeiro et al., 1971; Ribeiro and Rocha E Silva, 1973) or nitric oxide in mice (Germany et al., 1996) and by stimulating B_2 receptors in rat brain (Pelá et al., 1996). The locus coeruleus and the principal sensory trigeminal nucleus were identified as the most likely brain sites involved in the antinociceptive effect of bradykinin in rats (Couto et al., 1998). Nociceptive behavioural activity was increased following the intrathecal administration of bradykinin in the awake rat (Laneuville and Couture, 1987; Lopes and Couture, 1992). This nociceptive behavioural excitation lasted less than 1 min and was followed by a longer period of quietness (10–15 min), which was associated with an increase of the thermonociceptive threshold in the rat tail-flick test (Laneuville and Couture, 1987; Laneuville et al., 1989). The initial nociceptive response was described as a direct action of bradykinin on B_2 receptors located on sensory terminals projecting to the superficial laminae of the spinal cord. On the other hand, the antinociceptive response (also mediated by B_2 receptors) was shown to be due to the release of noradrenaline from descending inhibitory neurons projecting to the dorsal horn, with the subsequent activation of α-adrenoceptors (Laneuville et al., 1989). These results were corroborated by in vitro autoradiography demonstrating the presence of specific bradykinin B_2 receptor binding sites in the spinal dorsal horn and their enriched presynaptic localization on both primary sensory Aδ and C-fibres and spinal noradrenergic terminals (Lopes et al., 1993, 1995). Although bradykinin does not affect the basal release of calcitonin gene-related peptide from the dorsal horn of the rat spinal cord in vitro, the release of calcitonin gene-related peptide was enhanced in response to dorsal root stimulation via the activation of B_2 receptors and a prostaglandin-mediated mechanism (Andreeva and Rang, 1993). Studies using an in vitro neonatal rat spinal cord-tail preparation have shown that bradykinin, by acting on B_2 receptors, can depolarize either the peripheral or central terminals of capsaicin-sensitive primary afferent nerve fibres, which in turn causes depolarization of ventral root motoneurons (Dray et al., 1988, 1992; Dunn and Rang, 1990). A postsynaptic site of action for bradykinin on dorsal horn second-order nociresponsive neurons is also possible, as a significant density of specific B_2 receptor binding sites persisted in superficial laminae of rat dorsal horn after destruction of primary sensory C-fibres with capsaicin, or after removal of all projecting sensory fibres following dorsal rhizotomy (Lopes et al., 1995). As in these studies, iontophoretic bradykinin caused a slow excitation of cat spinal dorsal horn neurons that were excited by noxious thermal stimulation of the skin (Henry, 1976). Finally, a role for kinins and B_2 receptors has been proposed in the second phase of the response of dorsal horn nociceptive neurons in the rat formalin test (Chapman and Dickenson, 1992). The presence of bradykinin-like immunoreactivity in rat spinal dorsal horn interneurons and/or projection neurons reinforces a putative role of this peptide in spinal sensory function (Lopes and Couture, 1997).

6. Bradykinin receptors in inflammation and leukocyte trafficking

Whereas the B_2 receptor is involved in most of the cardinal signs of acute inflammation, including increased vascular permeability, venoconstriction, arterial dilatation and pain through the activation of sensory nerve terminals, this receptor has a limited role in the cellular component of the inflammatory response involving leukocyte recruitment within the microcirculation (McLean et al., 2000a). The pro-inflammatory effects of B_1 receptors include promotion of blood-borne leukocyte trafficking, edema and pain.

In addition to B_1 receptors, kallikreins and kininogens are found on the surface of circulating and synovial neutrophils, which represents an effective way to deliver

kinins at the site of inflammation (Böckmann and Paegelow, 2000; Bhoola et al., 2001). Neutrophil migration into inflamed tissue in response to chemotactic attraction by cytokines released during the primary immune response and the activation of complement, was impaired in B_1 receptor-deficient mice (Pesquero et al., 2000; Araújo et al., 2001). B_1 receptor activation induces all three phases of the leukocyte (corresponding to more than 90% neutrophils) recruitment process; cell rolling, adhesion and emigration (McLean et al., 2000a,b). Furthermore, the B_1 receptor may play a role in the life span of neutrophils at sites of inflammation as its presence is required for the maintenance of the apoptotic process in neutrophils (Araújo et al., 2001).

In a model of guinea pig lung inflammation induced by the intravenous injection of Sephadex beads, B_1 receptor activation induced pulmonary leukocyte infiltration which was blocked by a B_1 receptor antagonist (Perron et al., 1999). A constitutive B_1 receptor was found to mediate the inflammatory response induced by intrapleural injection of B_1 agonists in a murine model of pleurisy. This inflammatory response that included increased vascular permeability and cell influx, mainly neutrophils, and, to a lesser extent, mononuclear cells, was mediated by the release of primary sensory neuropeptides such as substance P and calcitonin gene-related peptide and also by nitric oxide (Vianna and Calixto, 1998). Therefore, the murine B_1 receptor responses appear to result from the direct or indirect activation of sensory neurons. This is reminiscent of the effect of bradykinin in airway neurogenic inflammation that also supports a potential role for kinins in the pathophysiology of airway diseases (Geppetti, 1993; Bertrand and Geppetti, 1996; Proud, 1998).

Although B_1 receptors appear to be constitutively expressed on murine neutrophils (Araújo et al., 2001), B_1 agonists have no direct effect on neutrophil activation in vitro (Ahluwalia and Perretti, 1996). However, results of recent immunocytochemical studies suggest the presence of B_1 receptors on primary sensory A-δ and C-fibres in the rat (Ma et al., 2000; Wotherspoon and Winter, 2000). The expression of B_1 receptors on murine sensory neurons may have a physiological role (Pesquero et al., 2000). Thus, it is feasible that B_1 agonists act directly on sensory neurones to release substance P and calcitonin gene-related peptide, which in turn influence neutrophil chemoattraction through endothelium expressing peptide receptors (Vianna and Calisto, 1998; Ahluwalia and Perretti, 1999). Substance P and calcitonin gene-related peptide induce rapid expression of vascular endothelial cell adhesion molecules (E-selectin, P-selectin and intercellular adhesion molecule-1), which play a primary role in the rolling and adhesion of circulating neutrophils (Matis et al., 1990; Sung et al., 1992; Smith et al., 1993; Nakagawa et al., 1995). P-selectin knockout mice (Johnson et al., 1995) and double knockout mice for P- and E-selectin (Frenette et al., 1996) show a decrease in neutrophil mobilization.

Alternatively, B_1 receptors may activate indirectly sensory C afferent fibres through the release of prostaglandins (Dray and Perkins, 1993), mast cell mediators (McLean et al., 2000a) and cytokines, especially interleukin-1 (Perretti et al., 1993; Ahluwalia and Perretti, 1994). The existence of a cytokine component in the pro-inflammatory effect of B_1 receptors is supported by the finding that B_1 receptors are involved in the release of various interleukins in addition to chemotactic peptides and leukotrienes from macrophages (Tiffany and Burch 1989; Sato et al., 1996) and lung fibroblasts (Koyama et al., 2000). However, the presence of B_1 receptors (constitutive or induced) coexisting with B_2 receptors (constitutive) on macrophages is dependent on species, tissues and the stage of cellular maturation (Böckmann and Paegelow, 2000). Released interleukin-1β is a pro-inflammatory cytokine having multiple acute and chronic effects. First, interleukin-1β can upregulate the expression of B_1 receptors (Marceau et al., 1998). Second, interleukin-1β is able to cause neutrophil migration (Pettipher et al., 1986; Rampart and Williams, 1988; Perretti and Flower, 1993; McIntyre et al., 1991) through the release of substance P and calcitonin gene-related peptide from sensory C afferent fibres (Perretti et al., 1993; Ahluwalia and Perretti, 1994, 1996). This effect of interleukin-1β on neutrophil accumulation is impaired in tachykinin NK_1 receptor knockout mice in a murine air pouch model (Ahluwalia et al., 1998) and is consistent with the role of substance P in neutrophil adhesion and migration (Kähler et al., 2001). Released substance P from sensory fibres can, in turn, amplify these events and perpetuate a positive feedback mechanism of inflammation by increasing the release of inflammatory cytokines from macrophages (interleukin-1β and tumor necrosis factor-α) via tachykinin NK_1 receptor (Ho et al., 1997). The interplay between interleukin-1 and B_1 receptors was clearly established in murine models of inflammation where neutrophil accumulation induced by interleukin-1β was due to upregulation of B_1 receptors whose activation causes the release of substance P and calcitonin gene-related peptide from sensory C afferent fibres (Ahluwalia and Perretti, 1996; McLean et al., 2000a,b). This occurs independently of B_2 receptor expression except that at very high doses, bradykinin can cause B_2 receptor-mediated leukocyte recruitment through the release of platelet-activating factor possibly from the endothelium and macrophages (Shigematsu et al., 1999). Thus, cytokines, in concert with kinins (B_1 receptor) and sensory neuropeptides (substance P and calcitonin gene-related peptide), may regulate neutrophil interstitial accumulation and trafficking to the inflammatory site.

It is worth nothing that the pro-inflammatory effect of bradykinin mediated by the activation of B_2 receptors in the murine model of pleurisy concerns almost exclusively the migration of macrophages, involving the release of several mediators (histamine, nitric oxide, tachykinins from sensory C fibres and prostaglandins) while neutrophils and

plasma extravasation were little affected, contrary to the effects of B_1 receptor activation (Saleh et al., 1997). Other authors have also reported that bradykinin either increases the number of eosinophils in the rat pleural cavity through the lipoxygenase pathway (Pasquale et al., 1991) or inhibits lipopolysaccharide-induced eosinophil accumulation in the mouse pleural cavity via a B_2 receptor-mediated prostaglandin mechanism (Silva et al., 1999). B_2 receptors may also play a critical role in mediating allergic mast cell-dependent inflammation in rat pleurisy, including early protein exudation and neutrophilia and late pleural eosinophil influx (Bandeira-Melo et al., 1999). Plasma exudation in rat carrageenin-induced pleurisy was mediated by B_2 receptors (Majima et al., 1997).

7. Bradykinin B_1 receptor on T-lymphocytes

Bradykinin B_1 receptor immunoreactivity was observed on vascular endothelial and perivascular inflammatory cells in brain samples taken at autopsy from multiple sclerosis patients (Prat et al., 2000). In addition, the expression of this receptor was upregulated on T lymphocytes ($CD3^+$ cells) derived from peripheral blood of multiple sclerosis patients; it was correlated with the clinical activity of the disease and was virtually absent in healthy control subjects and patients with other neurologic or inflammatory disorders such as epilepsy, chronic inflammatory demyelinating polyneuritis, and systemic lupus erythematosus (Prat et al., 1999). The authors also found that pro-inflammatory cytokines (tumor necrosis factor-α and interferon-γ) are potent inducers of B_1 receptor gene expression in freshly isolated human T lymphocytes and that signalling through this receptor with a bradykinin B_1 receptor agonist can negatively regulate T-cell migration in vitro. In keeping with this finding, interferon-γ also increased the expression of B_1 receptors on human brain endothelial cells in vitro. Activation of this receptor after its induction with interferon-γ increased blood–brain barrier permeability to large molecules (bovine serum albumin) and reduced interleukin-8 release from these cells (Prat et al., 2000). Therefore, the latter studies revealed a dissociation between permeability of fluids and leukocyte trafficking. It was proposed that bradykinin B_1 receptor agonists can reduce immune cell infiltration into the brain as a consequence of both a reduction in chemokine secretion in endothelial cells and a direct anti-migratory effect on peripheral T-lymphocytes. Since migration of systemic T cells into the CNS is believed to initiate the inflammatory demyelinating disorder encountered in multiple sclerosis (Owens and Sriram, 1995) and since high levels of des-Arg^9-bradykinin, but not of bradykinin, have been found in blood of rabbits with experimental allergic encephalomyelitis, a classical animal model of multiple sclerosis (Germain et al., 1988), Bradykinin B_1 receptor agonists might be of potential therapeutic value in this CNS inflammatory disease.

8. Bradykinin receptors in edema and vascular permeability

The production of edema and vascular permeability is mainly mediated through the constitutive B_2 receptor in several models of acute visceral and cutaneous inflammation such as pancreatitis and cystitis or whether it occurs in response to treatment with carrageenan or collagenase (Burch and DeHass, 1990; Damas and Remacle-Volon, 1992; Wirth et al., 1992; Décarie et al., 1996b; Griesbacher and Legat, 1997, 2000). However, both B_1 and B_2 receptors appear to be involved in the development of local inflammatory responses (paw edema/protein extravasation leading to joint swelling) in rat models of acute and chronic arthritis (Cruwys et al., 1994; Blais et al., 1997; Bhoola et al., 2001) and in the rabbit inflamed joint where synovial blood flow is increased (Cambridge and Brain, 1998). The latter results are clinically relevant since all components of the kallikrein–kinin system have been measured in the synovial fluid of patients with rheumatoid arthritis and gout (Melmon et al., 1967; Jasani et al., 1969; Eisen, 1970; Hargreaves et al., 1988). In rat models, there was a pronounced upregulation of B_1 receptor-mediated edema formation either after complete B_2 receptor desensitization over a period of 7 days, acute (24 h) systemic treatment with lipopolysaccharide *E. coli*, long-term systemic treatment with *Mycobacterium bovis* bacillus Calmette-Guérin, intradermal injection of interleukin-1β and tumor necrosis factor-α, or 8 and 10 weeks after the induction of diabetes with streptozotocin (Campos and Calixto, 1995; Campos et al., 1995, 1996, 1997, 1998, 2001). The B_1 receptor-mediated rat paw edema was ascribed to the release of substance P and calcitonin gene-related peptide from sensory C afferent fibres, serotonin from mast cells and prostaglandin synthesis. This neurogenic response induced by the B_1 receptor was blocked by dexamethasone and cycloheximide, indicating the involvement of de novo protein synthesis in the upregulation of B_1 receptors (Campos et al., 1998; Ferreira et al., 2000). Further pharmacological evidence suggests that upregulation of B_1 receptor-mediated rat paw edema following intradermal injection of interleukin-1β and tumor necrosis factor-α involves the activation of protein kinase C, tyrosine kinase or MAP-kinases and the transcriptional factor NF-κB (Campos et al., 1999). A recent study has also demonstrated that endotoxin upregulates B_1 receptor-mediated edema formation in a non-human primate model (deBlois and Horlick, 2001).

9. Putative role of kinins in diabetes-induced pain and inflammation

Experimental evidence suggests that diabetes is another stimulus that can upregulate B_1 receptors. Current evidence indicates that insulin-dependent diabetes mellitus is

due to an autoimmune response associated with overproduction of cytokines, including interleukin-1β and tumor necrosis factor-α, that leads to the destruction of pancreatic islet β-cells (Hussain et al., 1996; Rabinovitch and Suarez-Pinzon, 1998; Rabinovitch, 1998). Hyperglycemia and the resulting oxidative stress can also activate NF-κB (Yerneni et al., 1999), which is known to induce the B_1 receptor (Marceau et al., 1998). Therefore, both the overproduction of cytokines and hyperglycemia could trigger the expression of B_1 receptor through NF-κB in diabetes.

The streptozotocin model is that most commonly used to study the cardiovascular and neuropathic complications of diabetes. Streptozotocin is an antibiotic extracted from *Streptomyces acromogenes*, which is selectively toxic for pancreatic islet β-cells where it causes inflammation associated to cytokines (Tomlinson et al., 1992; Lukić et al., 1998). Pharmacological evidence suggests that the B_1 receptor intervenes in the pathogenesis of streptozotocin-induced diabetes in mice as bradykinin B_1 receptor antagonists normalize glycemia and renal function (Zuccollo et al., 1996, 1999). Also, a functional B_1 receptor is overexpressed in the stomach of these animals (Pheng et al., 1997). More recently, the B_1 receptor was reported to be induced in both kidney and spinal cord of rats treated 3 weeks earlier with streptozotocin. In isolated glomeruli, the B_1 receptor participates in the reduction of MAP kinase activation by an angiotensin-1-converting enzyme inhibitor (Mage et al., 2001) while, in the spinal cord, the activation of the B_1 receptor causes a vasopressor response that is mediated by prostaglandins (Cloutier and Couture, 2000). With regard to the pain process, B_1 receptor activation in streptozotocin-pretreated rats causes changes in the thermonociceptive threshold in the rat tail-flick test (Fig. 1). The intrathecal (i.t.) injection of the B_1 agonist, des-Arg^9-bradykinin (8.1 nmol), did not affect the nociceptive threshold in control rats. However, the agonist induced a biphasic response in the same animals, 24 h after treatment with streptozotocin. The hyperalgesic response at 1 min

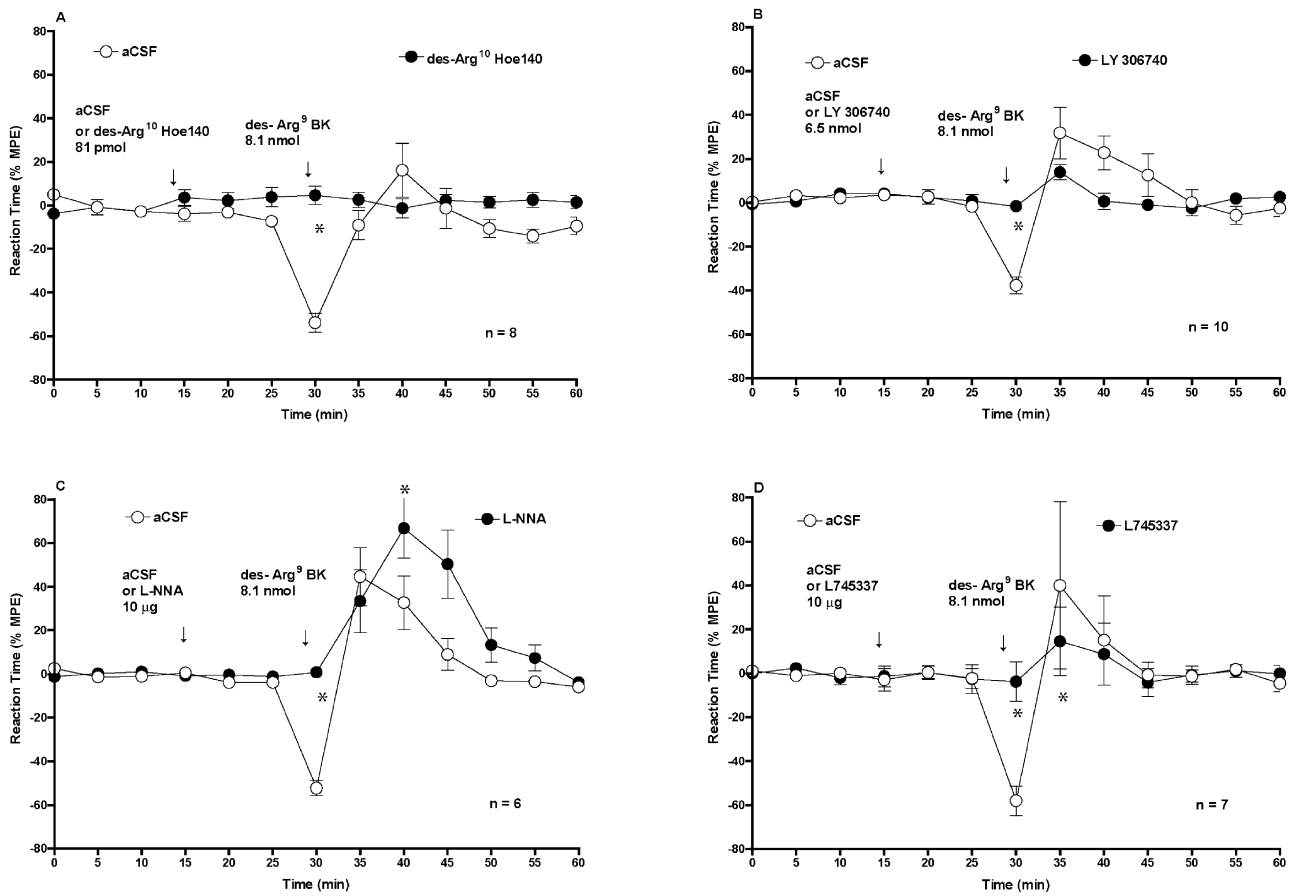

Fig. 2. Effects of several treatments on the biphasic response induced by the intrathecal injection of des-Arg^9-bradykinin (BK) (8.1 nmol, at 29 min) in rats which received streptozotocin, 24 h earlier. The following treatments were given at 14 min instead of aCSF: (A) 81 pmol des-Arg^{10}-Hoe 140, B_1 receptor antagonist; (B) 6.5 nmol LY 306740, NK_1 receptor antagonist; (C) 10 µg N^G-nitro-L-arginine (L-NNA), inhibitor of nitric oxide synthase or (D) 10 µg L745337, cyclooxygenase-2 inhibitor. The B_1 agonist was given alone (control) and in the presence of one inhibitor one day apart. Each rat received only one treatment. The response to des-Arg^9-bradykinin was blocked reversibly by each treatment as the response was back to control values (agonist alone) on the subsequent day. The baseline nociceptive threshold was not affected by any treatment. Each point represents the mean ± S.E.M. for (n) rats in each group. Statistical comparison to the response to des-Arg^9-bradykinin in the absence (aCSF) of treatment was made with a two-way ANOVA and the Bonferroni test and significance is indicated by $^* P < 0.001$.

post-injection was followed by a secondary antinociceptive effect at 6 min after the injection of the B_1 agonist. This biphasic response was completely blocked by the prior i.t. injection of 81 pmol des-Arg[10]-Hoe 140 (des-Arg[9]-D-Arg [Hyp[3],Thi[5],D-Tic[7],Oic[8]]-bradykinin) (B_1 receptor antagonist, Wirth et al., 1991) 15 min earlier (Fig. 2). The hyperalgesic response induced by des-Arg[9]-bradykinin was blocked by the prior i.t. injection of either 6.5 nmol LY 306740 (*R*-1-[*N*-(2-methoxybenzyl)acetylamino]-3-(1*H*-indol-3-yl)-2-[*N*-(2-(4-cyclohexylpiperazin-1-yl)acetyl)amino]-propane) (substance P antagonist selective for the tachykinin NK_1 receptor, Hipskind et al., 1996), 10 μg N^G-nitro-L-arginine (L-NNA, inhibitor of nitric oxide synthase, Lamontagne et al., 1996) or 10 μg L745337 (5-methanesulphonamido-6-(2,4-difluorothio-phenyl)-1-indanone) (inhibitor of cyclooxygenase-2, Warner et al., 1999) (Fig. 2). In contrast, the hypoalgesia induced by the B_1 agonist remained either unchanged or significantly enhanced (with L-NNA) by the latter treatments (Fig. 2). These data suggest that the hyperalgesic response elicited by i.t. des-Arg[9]-bradykinin results from the activation of B_1 receptors on central terminals of primary sensory C-fibres in the spinal dorsal horn, thereby causing the release of substance P and the subsequent activation of postsynaptic tachykinin NK_1 receptors linked to the production of nitric oxide and prostaglandins via the cyclooxygenase-2 pathway. This putative mechanism, shown schematically in Fig. 3, is thought to increase sensory neurotransmission

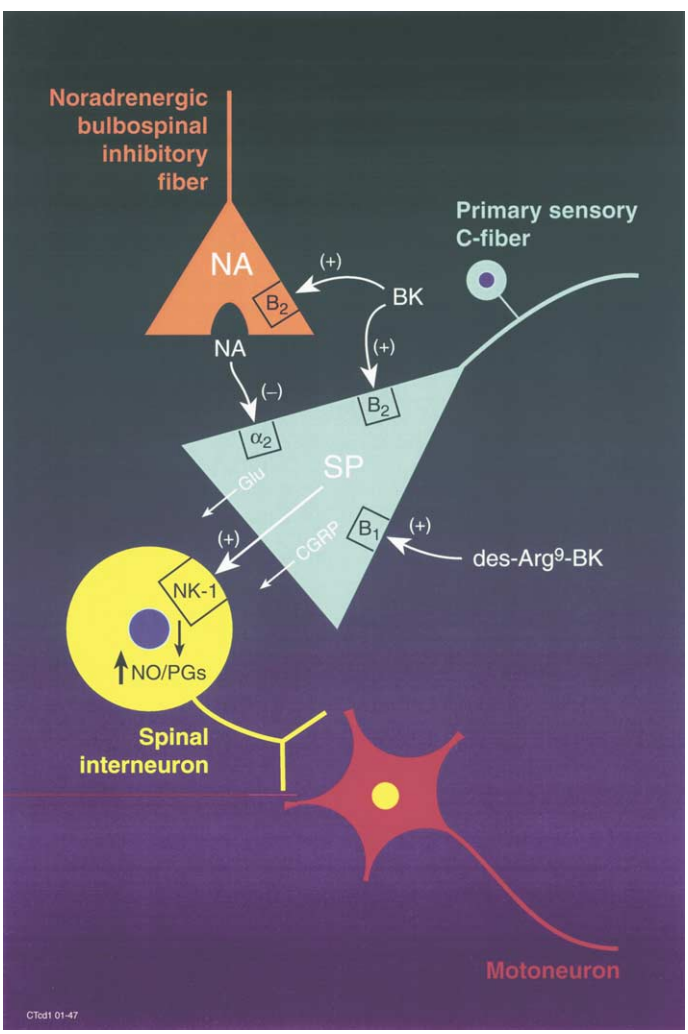

Fig. 3. Schematic representation of our current understanding of the spinal sites and mechanisms of action of bradykinin (BK) and des-Arg[9]-BK on thermal nociception in streptozotocin-diabetic rats. The antinociception induced by intrathecal (i.t.) BK would result from the activation (+) of B_2 receptor on terminals of bulbospinal inhibitory fibres promoting the release of noradrenaline (NA) which, in turn, inhibits (−) the spinal nociceptive reflex through the activation of α_2-adrenoceptors located on primary sensory terminals. The initial behavioural excitation induced by i.t. BK is likely due to the direct activation of B_2 receptors located on sensory terminals, thereby enhancing the release of sensory neuromediators such as substance P (SP), calcitonin gene-related peptide (CGRP), glutamate (Glu), neurokinin A and galanin. The hyperalgesic response elicited by i.t. des-Arg[9]-BK would result from the activation of the inducible B_1 receptor on primary sensory terminals to augment the release of substance P that leads to the subsequent activation of postsynaptic NK_1 receptors linked to the production of nitric oxide (NO) and prostaglandins (PGs) via the cyclooxygenase-2 pathway. Endogenous kinins are believed to originate from cerebrospinal fluid and dorsal horn projecting fibres (Couture and Lindsey, 2000).

in the spinal cord of streptozotocin-diabetic rats. In a parallel study, we showed that i.t. substance P induced the same biphasic effect as des-Arg^9-bradykinin in both control and streptozotocin-diabetic rats; the hyperalgesic response to substance P was also inhibited by treatment with LY306740, L-NNA and L745337, which further supports the participation of substance P in the spinal effect of the B_1 agonist (Harrisson and Couture, 2001). However, the mechanism underlying the hypoalgesic response induced by des-Arg^9-bradykinin is still unknown and does not appear to be associated to opioids, prostanoids or catecholamines because the response was resistant to naloxone, indomethacin or α_2-adrenoceptor blockade (Harrisson and Couture, 2001).

Recently, we also found in rats made diabetic with streptozotocin 4 days earlier that the injection of des-Arg^9-bradykinin (100 nmol/site) into the pleural cavity (i.pl.) caused leukocyte migration; 80% of the cells being mononuclear (mostly macrophages with 10–20% lymphocytes) and 20% corresponding to neutrophils at 4 h post-injection (Fig. 4). The maximal response was seen at 8 h post-injection for mononuclear cells and at 4 h for neutrophils. Whereas the mononuclear cells remained elevated for at least 24 h, the number of neutrophils returned to the control values by 12 h post-injection. Des-Arg^9-bradykinin also increased leukocyte infiltration at 4 h post-injection in control rats although the effect was significantly less than that in streptozotocin-diabetic rats (Vianna et al., 2001). The migration of both mononuclear and neutrophil cells induced by des-Arg^9-bradykinin was significantly reduced by the following pretreatments administered to three separate groups of animals: des-Arg^{10}-Hoe 140 (B_1 receptor antagonist, 100 nmol/site i.pl.; Wirth et al., 1991), pyrrolidine–dithiocarbamate (inhibitor of NF-κB, 100 mg/kg i.p.; Campos et al., 1999) or LY 303870 (*R*-1-[*N*-(2-methoxybenzyl)acetylamino]-3-(1*H*-indol-3-yl)-2-[*N*-(2-(4-(peperidin-1-yl)peperidin-1-yl)acetyl)amino]-propane) (NK_1 receptor antagonist, 10 nmol/site i.pl.; Iyengar et al., 1997). In contrast, pretreatment with Hoe 140 (D-Arg^0-[Hyp^3,Thi^5,D-Tic^7,Oic^8]-bradykinin) (B_2 receptor antagonist, 10 nmol/site i.pl.; Hock et al., 1991) potentiated the effect of the B_1 agonist on leukocyte migration, suggesting that the B_2 receptor exerts an effect opposite to that of the B_1 receptor on cell migration by a still unknown mechanism. Based on these results and on the literature reviewed above (Section 6), a putative mechanism is presented in Fig. 5. Bradykinin B_1 receptors are induced and upregulated simultaneously at both the central terminals (spinal cord, see Fig. 3) and peripheral terminals (lung) of primary sensory C-fibres present in the streptozotocin-diabetic rats. Their activation in the lung would lead to the release of substance P and the subsequent activation of endothelial NK_1 receptors to induce the rapid expression of vascular endothelial cell adhesion molecules, which promote neutrophil migration through the endothelium. It is also possible that a B_1 agonist influences neutrophil migration by

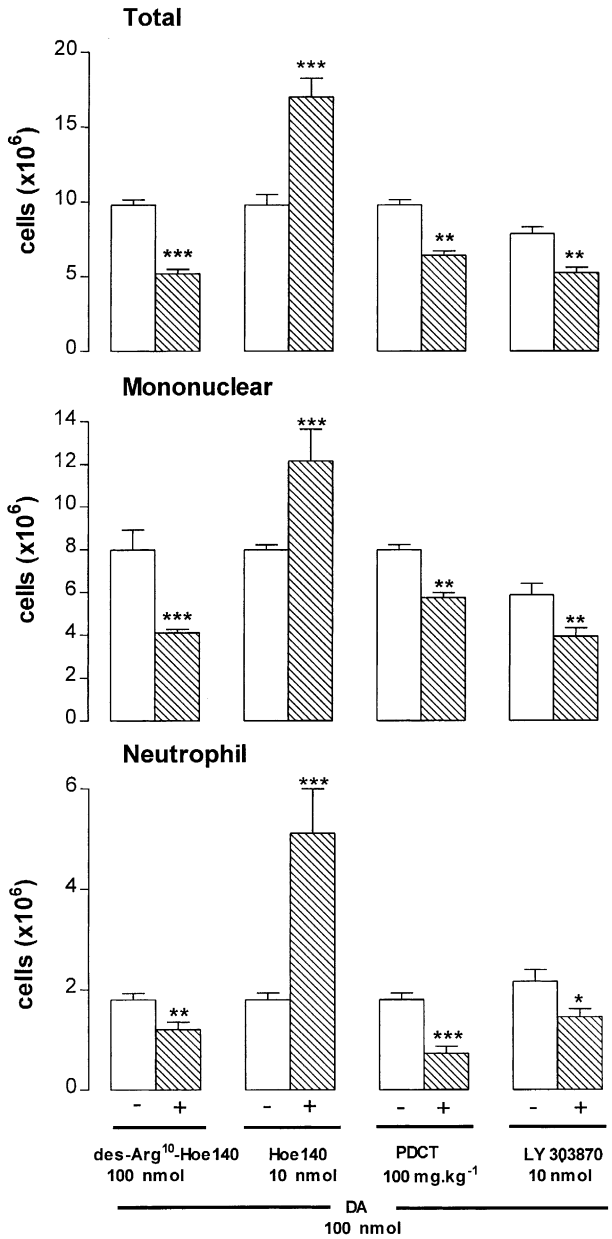

Fig. 4. Increase of leukocyte migration: total, mononuclear and neutrophils 4 h after the intrapleural (i.pl.) injection of 100 nmol/site des-Arg^9-bradykinin (DA) in rats made diabetic (blood glucose >14 mM) with a single dose of streptozotocin (65 mg/kg, i.p.) 4 days earlier. Shown are effects of the B_1 agonist in the absence (open columns) and presence (hatched columns) of several inhibitors at the dose indicated: des-Arg^{10}-Hoe 140 (B_1 antagonist), Hoe 140 (B_2 antagonist), pyrrolidine-dithiocarbamate or PDCT (inhibitor of NF-κB) and LY 303870 (NK_1 antagonist). Data represent the means ± S.E.M. for 6–10 rats in each group. Statistical comparison with the corresponding control value was done with Student's *t*-test for unpaired samples and significance is indicated by $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

stimulating B_1 receptors located on endothelial cells. Macrophages and lung fibroblasts have B_1 receptors and their activation leads to the release of cytokines such as interleukin-1α and tumor necrosis factor-α (Sato et al., 1996; Koyama et al., 2000). These cytokines are known to

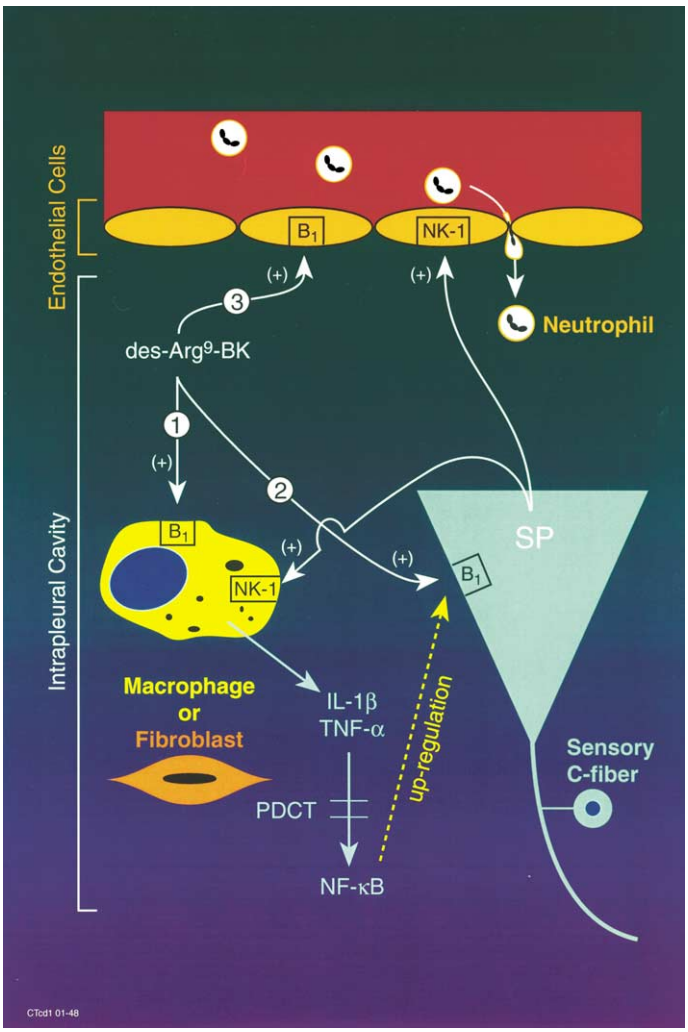

Fig. 5. Schematic representation of the putative mechanisms involved in the pro-inflammatory effect of the B_1 agonist, des-Arg^9-bradykinin, in the pleural cavity of streptozotocin-diabetic rats. It is proposed that the B_1 agonist promotes neutrophil infiltration either indirectly, following the stimulation of primary sensory C-fibres which leads to the release of substance P (SP) and the subsequent activation of NK_1 receptor on endothelial cells, or directly on activation of B_1 receptors on the endothelium. Moreover, cytokines could be released either from macrophages or from fibroblasts by SP, or by the B_1 agonist. Cytokines are thought to activate the transcriptional factor, NF-κB, involved in the upregulation of the B_1 receptor on sensory terminals.

upregulate the expression of B_1 receptor through NF-κB. This may be a reasonable explanation for the cell migration response measured at 4 h after the injection of the B_1 agonist in control rats and the inhibitory effect of pyrrolidine–dithiocarbamate in steptozotocin-diabetic rats. Finally, released substance P from sensory fibres may in turn activate NK_1 receptors on immune cells to facilitate the release of cytokines, which would amplify and perpetuate the inflammatory process.

10. Conclusion

Molecular and pharmacological evidence supports a role for B_2 receptors in the acute phase of the inflammatory and pain response, whereas B_1 receptors most likely intervene in the chronic phase of inflammatory and pain processes. Recent anatomical and functional studies suggest that the B_1 receptor is induced on sensory fibres through the cytokine network to cause neurogenic inflammation, hyperalgesia and leukocyte infiltration. Because of its multicellular location and mode of persistent signalling mechanism, the B_1 receptor is likely to exert a strategic role in inflammatory diseases, particularly those with an immune etiology (diabetes, asthma, rheumatoid arthritis and multiple sclerosis). In addition to the pro-inflammatory effects of bradykinin receptors, B_1 receptors may exert a protective effect in brain inflammatory diseases such as multiple sclerosis by reducing T-lymphocyte infiltration into the brain. This intriguing dual action of the B_1 receptor (deleterious versus beneficial) deserves to be investigated further and to be taken into account in the therapeutic management of inflammatory immune diseases when a central neurodegenerative component is present.

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