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Review

Bradykinin receptors and their antagonists

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Abstract

Bradykinin and related kinins act on two receptor types, named B_1 and B_2. Initially identified in classical bioassays, these receptors have been cloned and characterized in binding assays performed on plasma membranes of cells expressing the native or the transfected human kinin B_1 or B_2 receptor types. The two classification criteria recommended by Schild, namely the order of potency of agonists and the actual affinity of antagonists have been found to be applicable for receptor classification based not on data only from bioassays but also from other approaches (binding assays, molecular biology techniques). The order of potency for agonists was found with naturally occurring peptides (the kinins, their desArg^9-metabolites) and with selective agonists (e.g., [Hyp^3]bradykinin, [Aib^7]bradykinin): the findings obtained with agonists could be validated with various antagonists. Critical evaluation of the initial compounds, typified by D-Arg-[Hyp^3, D-Phe^7]bradykinin, has indicated that they are short-acting, partial agonists, non-selective for the bradykinin B_2 receptor because they can be metabolized to desArg^9-fragments that act on the kinin B_1 receptor. Use of such compounds has given rise to misunderstandings, especially with regard to new receptor types (e.g., type B_3), the existence of which was not confirmed by molecular cloning. A second generation of antagonists, represented by D-Arg[Hyp^3,Thi^5,D-Tic^7,Oic^8]bradykinin (HOE 140) has been found resistant to degradation, long-acting in vivo, selective and specific for the B_2 receptor and potent in all species tested. HOE 140 has been used successfully in basic pharmacology, in animal physiopathologies involving kinins and their receptors and even in clinical studies. A third generation of non-peptide B_2 receptor antagonists, whose prototype is FR 173657 ((*E*)-3-(6-acetamido-3-pyridyl)-*N*-[*N*-2-4-dichloro-3-[(2-methyl-8-quinolinyl)oxymethyl]phenyl]-*N*-methylamino carbonyl-methyl]acrylamide) is now emerging and may represent substantial progress since FR 173657 is a potent orally active, selective and specific antagonist of the human and other species B_2 receptors. There is also progress regarding antagonists for the B_1 receptor. The initial compounds, especially Lys-[Leu^8]desArg^9-bradykinin remain among of the most potent, specific and selective B_1 antagonists which, however, show partial agonistic effects in some B_1 receptor subtypes (e.g., the mouse). Progress has been made with AcLys-[D-βNal^7, Ile^8]desArg^9-bradykinin (R 715) and Lys-Lys-[Hyp^3, Cpg^5, D-Tic^7,Cpg^8]desArg^9-bradykinin (B 9958) which are pure B_1 antagonists in humans and rabbits; both peptides have shown resistance to degradation by peptidases and have little if any, residual agonistic activity on mouse and rat B_1 receptors. No non-peptide antagonists are yet available for the B_1 receptor. © 1998 Elsevier Science B.V.

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1. Introduction

The kallikrein-kinin system consists of plasma and tissue (or glandular) kallikreins; the first are expressed only in the liver (Clemens, 1994) and differ from the tissue kallikreins, which are encoded in various genes and expressed in a variety of cells (Clemens, 1994, 1997). Plasmatic high molecular weight kininogens (HMWK) and tissue low molecular weight kininogens (LMWK) derive from a single hepatic gene which by alternative splicing yields two mRNAs that differ in size (3.5 vs. 1.7 kb) and function (Schmaier, 1997). The system in plasma is considered to be a constitutive anticoagulant which protects the endothelium (Linz et al., 1995), while the second is an essential factor in the tissue reaction to noxious or artificial stimuli and in tissue repair. HMWK is the precursor of bradykinin while LMWK generates kallidin (Lys-bradykinin) both of which are further transformed (by carboxypeptidases M and N) into fragments (desArg^9-bradykinin and Lys-desArg^9-bradykinin) which display specific biological activities (Regoli and Barabé, 1980).

Bradykinin, kallidin and their fragments exert a variety of biological effects on (a) the endothelium (e.g., by promoting the release of nitric oxide, prostacyclin, endothelium-derived hyperpolarizing factor (Regoli and

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Barabé, 1980; Toda et al., 1987; Schini et al., 1990; Mombouli and Vanhoutte, 1995)) and (b) on the peripheral circulation, where they induce vasodilatation and increase blood flow (by reducing the tonus of arterial smooth muscle). They may also provoke plasma extravasation (Regoli and Barabé, 1980) (by contracting the capillary endothelium) and venoconstriction through stimulation of venous smooth muscle fibers (Gaudreau et al., 1981). In inflammatory states (Dray and Perkins, 1993), in asthma (Barnes, 1992), allergy (Polosa, 1993), after trauma and various lesions (Rodell, 1996), kinins promote the migration of cells from blood to tissues and activate various tissue components such as mast cells, fibroblasts, macrophages, the cells of the immune system (Bhoola et al., 1992), smooth muscle in almost every organ and the autonomic nervous system (sympathetic (Tousignant et al., 1987), and the parasympathetic (Lopes and Couture, 1992)) as well as sensory nerves (Steranka et al., 1988; Geppetti, 1993). These numerous effects result from the activation (by the kinins) of two receptor types (Regoli and Barabé, 1980; Regoli et al., 1998), the bradykinin B_2 receptor, which is constitutive (Regoli and Barabé, 1980) and is expressed by many cell types, and the kinin B_1 receptor, which is inducible and is formed de novo in various cells by stimuli which activate the cytokinin system, particularly interleukin 1β (Regoli et al., 1981; Deblois et al., 1989; Marceau, 1995).

The kinin B_1 and B_2 receptors are seven transmembrane (7TM) proteins coupled to G-proteins (Hess et al., 1994; Menke et al., 1994) and, when activated, promote phosphoinositol hydrolysis by phospholipase C (Bascands et al., 1993; Smith et al., 1995) or arachidonic acid release by phospholipase A_2 (Table 1) (see review by Bascands and Girolami, 1996). They show high affinities for bradykinin (the B_2 receptor) or for Lys-desArg^9-bradykinin (the B_1 receptor) and provoke smooth muscle contraction, neurotransmitter or autacoid release and the production of prostanoids (Regoli and Barabé, 1980). When activated by agonists, bradykinin B_2 receptors undergo desensitization and internalization (Austin et al., 1997) which account for the rapid reversibility of the biological effects in vitro. Conversely, the kinin B_1 receptors are not internalized and not desensitized (Levesque et al., 1995; Austin et al., 1997). This difference may be explained by the presence in the bradykinin B_2 receptor of a large C-terminal loop that contains Ser or Tyr residues, typical sites for phosphorylation (Hausdorff et al., 1989; Lohse, 1993; Ferguson et al., 1996).

2. Kinin receptor classification

The existence of two distinct receptors for the kinins, deduced from data obtained with biological assays (Regoli and Barabé, 1980) was confirmed with binding assays (see reviews by Hall, 1992 and Hall and Morton, 1997) and by the identification of two separate genes for the kinin B_2 and B_1 receptors in man (Hess et al., 1992; Menke et al., 1994). The pharmacological profiles were obtained with three different methodologies: (1) binding of [^{3}H]bradykinin in chinese hamster ovary cells (CHO-K1) (Eggerickx et al., 1992) as well as in kidney SV40 transformed African green monkey cells (COS-7) (Hess et al., 1992) transfected with the human bradykinin B_2 receptor gene; (2) binding of [^{3}H]bradykinin to plasma membranes of smooth muscle from the human umbilical vein (Gessi et al., 1997) and, (3) the contraction induced in strips of the human umbilical vein suspended in vitro (bioassay) (Gobeil et al., 1996a); these data are presented in Table 2, and compared with data from other species (rabbit and guinea pig).

Table 1
Molecular biology of kinin B_1 and B_2 receptors

	B_1	B_2
Receptor class	7TM[a]	7TM[b]
Amino acids	353	364
Homology B_1/B_2	36%	36%
B_1/AT_1	30%	
Transduction system	$G_{q/11}$ PLC PLA_2	$G_{q/11}$ PLC PLA_2
Binding parameters		
Transfected into COS-7	[^{3}H]Lys-des Arg^9-BK; K_d = 0.4 nM; B_{max} = 100 fmol/mg[a]	–
Transfected into CHO	–	[^{3}H]BK; K_d = 0.2 nM; B_{max} > 3000 fmol/mg[b]
Pattern of expression	Inducible	Constitutive
Desensitization	No	Yes
Internalization	No	Yes

Abbreviations: BK, bradykinin; PLC, phospholipase C; PLA_2, phospholipase A_2; TM, transmembrane.
[a]Menke et al. (1994); [b]Hess et al. (1992).

Table 2
Binding affinities (pIC_{50}, pK_i) and biological activities (pEC_{50}, pA_2) of various compounds on the human, rabbit and guinea pig bradykinin B_2 receptors

Peptides	Human				Rabbit	Guinea pig
	COS-7[a]	CHO-K1[b]	Umbilical vein binding[c]	Umbilical vein bioassay[d]	Jugular vein[e]	Ileum[e]
Agonists						
BK	9.9	9.1	8.9	8.6	8.5	7.9
Lys-BK	9.6	8.8	8.8	8.8	8.6	7.9
[Hyp^3]BK	n.d.	10.2	8.9	8.9	8.9	7.1
desArg^{9}BK	< 5.0	< 4.0	< 5.0	< 6.0	< 5.0	< 5.0
Lys-desArg^{9}BK	n.d.	n.d.	< 5.0	< 6.0	< 5.0	< 5.0
Antagonists						
[Thi^{5,8}, D-Phe^7]BK	6.7	6.6	n.d.	n.d.	6.7	5.9
HOE 140	10.2	9.4	9.8	8.4	9.2[f]	8.9[f]
WIN 64338	n.d.	n.d.	5.8	< 5.0	5.7[g]	7.8[g]
[Leu^8]desArg^{9}BK	< 5.0	n.d.	< 5.0	< 5.0	< 5.0	< 5.0

n.d.: not determined. BK: bradykinin, HOE 140: D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]BK (Icatibant) (Hock et al., 1991); WIN 64338: [[4-[[2-[[bis(cyclohexylamino)methylene]amino]-3-(2-naphthyl)-1-oxopropyl]amino] phenyl] methyl] tributylphosphonium chloride monohydrochloride (Salvino et al., 1993; Sawutz et al., 1994).

[a]Hess et al. (1992) and [b]Eggerickx et al. (1992), Cloned human bradykinin B_2 receptors expressed in COS-7 and CHO-K1 cells, respectively. Binding to cell membrane preparations using [^{3}H]bradykinin as the labelled ligand. [c]Gessi et al. (1997). Binding to plasma membranes of smooth muscle from the human umbilical vein: labelled ligand; [^{3}H]bradykinin. [d]Gobeil et al. (1996a); [e]Regoli et al. (1990b); [f]Rhaleb et al. (1992); [g]Gobeil and Regoli (1994): results of bioassays. Abbreviations for aminoacids follow the recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (1983), other abbreviations are described as follows: Hyp, *trans*-4-hydroxy-L-proline; Thi, β-(2-thienyl)-L-alanine; Tic, L-(1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid); Oic, L-(3aS,7aS)-octahydro-indol-2-carboxylic acid.

Application of the first classification criterion, recommended by Schild (1973), the rank order for the potency of agonists on B_2 receptors, indicates that [Hyp^3]bradykinin, the natural kinin occurring in man (Maier et al., 1988; Kato et al., 1988) is slightly more potent than bradykinin and Lys-bradykinin, while desArg^9-bradykinin and Lys-desArg^9-bradykinin (the kinin B_1 receptor agonists) are inactive. Actual (measured in binding assays) and apparent affinities (evaluated in bioassays) differ in that higher values are obtained with the binding assays, possibly because the receptors are better accessible to peptidic ligands. Another reason for this discrepancy may be related to the ionic composition of the medium and the buffer used in the functional and binding assays (Hall, 1992). When data obtained with bioassays for rabbit jugular vein (Regoli et al., 1990b; Rhaleb et al., 1991; Gobeil and Regoli, 1994) and guinea pig ileum (Regoli et al., 1990b; Rhaleb et al., 1991; Gobeil and Regoli, 1994) are used for comparison, the human receptor shows the same order of potency as the rabbit receptor but is different from the guinea pig receptor, especially because of the low affinity of [Hyp^3]-bradykinin in the latter tissue. The differences found between human and rabbit receptors and the guinea pig receptor, are also seen for the antagonists, particularly with WIN 64338 ([[4-[[2-[[bis(cyclohexylamino)methylene] amino] -3- (2-naphthyl) -1-oxopropyl]amino]phenyl]methyl] tributyl phosphonium chloride monohydrochloride) (Salvino et al., 1993; Sawutz et al., 1994), a non-peptide compound that interacts with guinea pig but not with human or rabbit bradykinin B_2 receptors (Regoli et al., 1994a; Gobeil et al., 1996a). Data obtained with antagonists (Table 2) show the low potency of the first generation of peptidic compounds, exemplified by [Thi^{5,8}, D-Phe^7]bradykinin and the absence of antagonistic activity by the B_1 antagonist, [Leu^8]desArg^9-bradykinin. The only compound which consistently shows high affinity for the human bradykinin B_2 receptor site as well as for the rabbit and guinea pig sites is HOE 140, a compound which is known to be resistant to metabolic degradation (Hock et al., 1991) and may have a prolonged interaction with the bradykinin B_2 receptor. Again, the actual affinity as measured from the binding, is greater than that found in the bioassay: HOE 140 acts as a competitive antagonist for the human bradykinin B_2 receptor (Marceau et al., 1994; Félétou et al., 1995; Gobeil et al., 1996a), while it is non-competitive (non-equilibrium) for the rabbit bradykinin B_2 receptor (Rhaleb et al., 1992) which may explain the higher pA_2 values observed in this species. The above makes it evident that the biological functions attributed to the bradykinin B_2 receptor are sustained by proteins which differ from one species to another (bradykinin B_2 receptor subtypes) and show different pharmacological profiles, as illustrated in Table 2.

Cloned human kinin B_1 receptors expressed in COS-7 cells (Menke et al., 1994), and native human kinin B_1 receptors found in human embryonic lung fibroblast cells (IMR-90) (Menke et al., 1994) have been characterized, as have recently those in transformed human primary embryonal kidney cells (293 cells) (Bastian et al., 1997) using either an agonist ([^{3}H]Lys-desArg^9-bradykinin (Menke et al., 1994)) or an antagonist ([^{3}H]Lys-[Leu^8]desArg^9-bradykinin (Bastian et al., 1997)) radioligand. Data obtained in binding assays are compared with data from biological assays of the human kinin B_1 receptors from the

Table 3
Comparison between molecular biology, binding affinities (pIC_{50}, pK_i) and biological activities (pEC_{50}, pA_2 values) on various kinin B_1 receptor bioassay systems

Peptides	Human				Rabbit	Mouse
	COS-7[a]	IMR-90[a]	293[b]	Umbilical vein[c]	Aorta[d]	Stomach[e]
Agonists						
BK	5.7	5.1	< 5.0	< 6.0	< 5.0[f]	< 6.0
Lys-BK	7.4	7.2	8.9	< 6.0	< 5.5[f]	< 6.0
desArg^{9}BK	6.1	6.2	5.9	6.7	7.3	7.7
Lys-desArg^{9}BK	9.7	9.3	9.9	8.6	8.6	7.7
Antagonists						
HOE 140	< 5.0	< 5.0	5.9	5.5	< 5.0	< 5.0
desArg^{10}-HOE140	7.2	7.7	7.6	7.3	6.8	7.2
[Leu^8]desArg^{9}BK	6.4	6.9	6.4	6.4	7.3	6.9
Lys-[Leu^8]desArg^{9}BK	8.9	8.9	9.0	8.0	8.4	7.0

[a]Menke et al. (1994), [^{3}H]Lys-desArg^{9}BK as the labelled ligand. [b]Bastian et al. (1997), [^{3}H]-Lys-[Leu^8]desArg^{9}BK as the labelled ligand. [c]Gobeil et al. (1996a), [d]Regoli et al. (1998), [e]Nsa Allogho et al. (1995): results from bioassays. [f]Tissues treated with mergetpa (1 μM), a carboxypeptidase M inhibitor.

umbilical vein (Gobeil et al., 1996a) as well as of the kinin B_1 receptor of other species, the rabbit (Rhaleb et al., 1991) and the mouse (Nsa Allogho et al., 1995). The results summarized in Table 3 indicate that the naturally occurring kinins, especially bradykinin, have low affinities; Lys-bradykinin, however, retains fairly good agonistic potency (higher than that of desArg^9-bradykinin) in the three systems transfected with human kinin B_1 receptors, as if type-M carboxypeptidases were present, especially in the 293 cell preparation. This interpretation is an attempt to explain the difference in Lys-bradykinin potency observed in the cell culture preparations and in isolated tissues. In fact, during the prolonged in vitro incubations required by the binding techniques, even only a weak carboxypeptidase activity in the system could produce (and allow to accumulate), small amounts of the extremely potent ligand, Lys-desArg^9-bradykinin which is 10- to 150-fold more potent than its precursor Lys-bradykinin. On the other hand, accumulation of desArg^9-bradykinin, should it occur, could not increase the potency of bradykinin, the affinity of desArg^9-bradykinin being 3 to 4 log units less than that of Lys-desArg^9-bradykinin. Assuming that agonistic potencies of Lys-bradykinin may be overestimated, the data reported in Table 3 show a good correlation between the results of binding and biological assays, except for desArg^9-bradykinin whose biological activity is greater than could have been expected from the binding assay. DesArg^9-bradykinin is indeed a compound which discriminates between kinin B_1 receptor subtypes. It is 100 times less potent than Lys-bradykinin at the human kinin B_1 receptor, but only three times less potent at the rabbit kinin B_1 receptor and is equally active at the mouse kinin B_1 receptor. Similar potency ratios are observed with the two antagonists, [Leu^8]desArg^9-bradykinin and Lys-[Leu^8]desArg^9-bradykinin (see Table 3). These results make it clear that the presence of a Lys residue at the N-terminal of desArg^9-fragments is extremely important for the human kinin B_1-receptor, is fairly useful for the rabbit kinin B_1 receptor and plays no role for the mouse kinin B_1 receptor. The presence of a D-Arg instead of Lys, as in desArg^{10}-HOE 140 is associated with a strong decrease in affinity in the human and rabbit but not in the mouse kinin B_1 receptor, thus validating the suggested interpretation.

3. Kinin B_1 receptor antagonists

Antagonists for the kinin B_1 receptor were discovered almost 10 years before the antagonists for the bradykinin B_2 receptor. The first antagonist discovered, [Leu^8]desArg^9-bradykinin, was obtained by replacing the C-terminal Phe residue by Leu (Regoli et al., 1977) using the same approach that we had successfully applied a few years before the study of angiotensin II (Regoli et al., 1974). Elimination of the aromatic group at the C-terminal leaves affinity almost unchanged (compare pD_2 values of desArg^9-agonists with pA_2 values of antagonists in Table 3), while it eliminates biological activity completely in the human and rabbit kinin B_1 receptors. Phe^8 (and its aromaticity) is therefore instrumental for receptor activation, while the other 7 residues of desArg^{9}BK are needed for receptor occupation (binding) (Regoli and Barabé, 1980). The aromatic nucleus interacts with the receptor protein in such a way that the connections (binding) of the negatively charged G protein to the Lys or Arg residues of the receptor (3rd intracellular loop?) are suddenly broken and the G protein ($G_{q/11}$ in this specific case) is released from the receptor in the active state, ready to activate phospholipase C. Both [Leu^8]desArg^9-bradykinin and Lys-[Leu^8]desArg^9-bradykinin (which are 100 and 10 times more active, respectively in the human and the rabbit kinin B_1 receptors), do not interact with the bradykinin B_2 receptor (Table 3) and are therefore selective for the kinin B_1

receptor: they do not interact with either the angiotensin AT_1 receptor or the neurokinin NK-1 receptors (as well as with a variety of other receptors (Regoli and Barabé, 1980)), and are therefore specific for the kinin B_1 receptor. The claim by Pruneau et al. (1995) that [Leu[8]]desArg[9]-bradykinin inhibits AT_{II}-induced contractions in the rabbit aorta could not be confirmed in our laboratory (Regoli et al., 1990b; Gobeil, F. Jr., personal observation). The [Leu[8]]desArg[9]-bradykinin and Lys-[Leu[8]]desArg[9]-bradykinin exert a competitive antagonism on the rabbit (Regoli et al., 1977; Regoli and Barabé, 1980) and the human kinin B_1 receptors (Gobeil et al., 1996a): they show a rapid onset of action and rapid reversibility (however both less for Lys-[Leu[8]]desArg[9]-bradykinin than for [Leu[8]]desArg[9]-bradykinin (Drouin et al., 1979)) in the rabbit kinin B_1 receptor, like their corresponding agonists, and so far have proved to be the most useful tool for (a) kinin B_1 receptor characterization, (b) kinin B_1 receptor classification (see above), (c) for the identification of different kinin B_1 receptor subtypes (in various species, see above) and (d) for studying the role of kinin B_1 receptors in physiology and in pathologies (e.g., Dray and Perkins (1993) as in inflammation and pain).

The active site of the kinin B_1 receptor, which discriminates between the side-chains of Phe and Leu may be small enough to accept and bind small non-peptide compounds (antagonists and perhaps even agonists) in the same way as the angiotensin AT_1 receptor accepts Losartan and the tachykinin NK-1 receptor binds its selective non-peptide antagonists (see review by Regoli et al., 1994b). There are therefore reasons to believe that non-peptide kinin B_1 receptor antagonists will soon be available. For the moment, we continue to develop peptide analogues of the early prototypes and several compounds have recently been described (Gobeil et al., 1996b,c; Stewart et al., 1996) or will soon be published (Gobeil et al., submitted). Among the new compounds worthy of mention is the AcLys-[D-βNal[7], Ile[8]]desArg[9]-bradykinin (R 715) which is partially resistant to metabolic degradation and shows high affinities for the human, the rabbit and mouse kinin B_1 receptors (see Table 4). The availability of R 715 has permitted the characterization and classification of kinin B_1 receptors in the mouse (Nsa Allogho et al., 1995) and in other species (e.g., the rat (Gobeil et al., 1996c)) because of its high affinity and absence of residual agonistic activity. In a recent study (Nsa Allogho et al., 1995), we were able to show that the initial prototypes, both [Leu[8]]desArg[9]-bradykinin and Lys-[Leu[8]]desArg[9]-bradykinin, act as partial agonists ($\alpha^E > 0.5$) at the mouse kinin B_1 receptor and cannot be used for receptor classification. Using R 715, we were able to show that the mouse kinin B_1 receptor has a significantly (by 1.5 log units) lower affinity for the kinin B_1 receptor antagonists than the human and rabbit kinin B_1 receptors. Moreover, the Lys at the N-terminal does not contribute to the increase in the antagonists' affinity for the mouse kinin B_1 receptor contrary to what was found for the human and rabbit kinin B_1 receptors. Therefore, the N-terminal amino group could be acetylated (to prevent degradation by aminopeptidases) without loss of potency. R 715 exerts a competitive type of antagonism at the human (Gobeil et al., 1996c), the rabbit (Gobeil et al., 1996c) and the mouse (Nsa Allogho, unpublished results) kinin B_1 receptors and was therefore used to demonstrate that, according to the criteria of Schild (1973), the mouse kinin B_1 is a subtype that differs from the human and the rabbit kinin B_1 receptors (see Table 4).

Two other compounds listed in Table 4, the D-Arg-[Hyp[3],Igl[5],D-Igl[7],Oic[8]]-bradykinin (B 9430) (Stewart et al., 1996) and the Lys-Lys-[Hyp[3],Cpg[5],D-Tic[7],Cpg[8]]-desArg[9]bradykinin (B 9958) (Stewart et al., 1996), prepared at Corteck (Denver, USA), confirm the existence of a kinin B_1 receptor subtype in the mouse. B 9958 is a decapeptide containing two Lys residues of the N-terminal, the human naturally occurring residue (Hyp) in position 3 and three other substitutions intended to prevent proteolytic degradation. B 9958 shows a higher affinity for the human than for the rabbit (Gobeil et al., 1997) and especially the mouse kinin B_1 receptors (present study). B 9958 is a kinin B_1-selective receptor antagonist which does not interact with the human, the rabbit or the mouse bradykinin B_2 receptor (Stewart et al., 1996; Gobeil et al., 1997; present study) and is to be considered the most potent antagonist for the human kinin B_1 receptor. Mention has to be made also of other compounds listed in Table 4, the desArg[9]-derivatives of HOE 140, D-Arg-[Hyp[3],Thi[5],D-Tic[7],Oic[8]]-desArg[9]-bradykinin (S 0765), and the D-Arg-[Hyp[3], D-Phe[7]]desArg[9]-bradykinin, two bradykinin B_2 receptor antagonists. Despite the presence of residues such as Thi[5], D-Tic[7] and Oic[8] that should protect from enzymatic degradation, the antagonistic potencies of D-Arg-[Hyp[3],Thi[5],D-Tic[7],Oic[8]]desArg[9]-bradykinin in the three kinin B_1 functional sites are the same as those of D-Arg-[Hyp[3], D-

Table 4
Apparent affinities of kinin B_1 receptor antagonists on human, rabbit and mouse tissues

Antagonists	Human	Rabbit	Mouse	References
	Umbilical vein	Aorta	Stomach	
Lys-[Leu[8]]desArg[9]BK	8.0	8.4	7.0	3,4
D-Arg-[Hyp[3],D-Phe[7]] desArg[9]BK	n.d.	6.8	7.0	1,2
R 715	8.5	8.4	7.0	3,3,4
B 9430	7.7	7.2	6.1	5,5,6
B 9958	9.2	8.5	7.2	5,5,6

R 715: AcLys-[D-βNal[7],Ile[8]]desArg[9]BK (Gobeil et al., 1996c); B 9430: D-Arg-[Hyp[3],Igl[5],D-Igl[7],Oic[8]]BK (Stewart et al., 1996); B 9958: Lys-Lys-[Hyp[3], Cpg[5], D-Tic[7], Cpg[8]]desArg[9]BK (Stewart et al., 1996); n.d. not determined. Abbreviations for the aminoacids: βNal, β-3-(2-naphthyl)-alanine; Igl, 2-indanylglycine; Cpg, cyclopentylglycine.

References: 1, Rhaleb et al. (1991); 2, Nsa Allogho et al. (1998); 3, Gobeil et al. (1996b); 4, Nsa Allogho et al. (1995); 5, Gobeil et al. (1997); 6, present study.

Phe[7]]desArg[9]-bradykinin, which is less protected against proteolysis. Both compounds show average antagonistic potencies, little or no residual agonistic activities but offer no advantage with respect to AcLys-[D-β Nal[7], Ile[8]]desArg[9]-bradykinin or Lys-Lys-[Hyp[3],Cpg[5],D-Tic[7],Cpg[8]]desArg[9]-bradykinin. In some species (e.g., the rabbit), D-Arg-[Hyp[3],Thi[5],D-Tic[7],Oic[8]]desArg[9]-bradykinin is not selective because it also blocks the bradykinin B_2 receptor when applied in the same range of concentrations as those used to block the kinin B_1 receptor (Regoli et al., 1994a; Gobeil et al., 1996b).

4. Bradykinin B_2 receptor antagonists

Antagonists for the bradykinin B_2 receptor were discovered by Vavrek and Stewart (1985), who changed the steric position of the C-terminal dipeptide Phe[8]-Arg[9] of bradykinin, with the replacement of Pro[7] by a D-Phe residue. The [D-Phe[7]]bradykinin analog is a partial agonist with weak antagonistic potency both at the guinea pig (Vavrek and Stewart, 1985) and the rabbit (Rhaleb et al., 1991) bradykinin B_2 receptor. The potency was, however, rapidly improved by the addition of a D-Arg at the N-terminal and the replacement of Pro[3] by Hyp (Vavrek and Stewart, 1985). D-Arg-[Hyp[3],D-Phe[7]]bradykinin (NPC 567), its homologue D-Arg-[Hyp[3],Thi[5,8],D-Phe[7]]bradykinin in which the two Phe (in positions 5 and 8) were replaced with an unnatural aminoacid (possibly to confer resistance to degradation) and D-Arg-[Hyp[3],D-Phe[7],Leu[8]]bradykinin (Rhaleb et al., 1991) in which Phe[8] is replaced by a Leu to remove aromaticity from the C-terminal, represent the first generation of bradykinin B_2 receptor antagonists. They were used extensively for several years in animal studies of kinin receptor pharmacology (Stewart and Vavrek, 1991; Regoli et al., 1990a,b) before the discovery of HOE 140. As shown in Table 5, these compounds are more potent on the rabbit than on the guinea pig and the mouse bradykinin B_2 receptor and are almost inactive on the human bradykinin B_2 receptor. Moreover, they are not selective for the bradykinin B_2 receptor, because they can be rapidly converted into desArg[9]-metabolites by carboxypeptidases (types M and N) and then act as antagonists of the kinin B_1 receptor (Rhaleb et al., 1991) (see Table 4). They are also substrates of other proteases in plasma and in tissues and consequently their half-life is very short (Wirth et al., 1991). They are partial agonists (D-Arg-[Hyp[3], D-Phe[7], Leu[8]]bradykinin however much less so) (see Rhaleb et al., 1991) with consistent residual agonistic effects (50%) in various tissues and could not be used for receptor classification. It is using these compounds that Rifo et al. (1987) could postulate the existence of two different receptors in the rat vas deferens and that Farmer et al. (1989) could hypothesise the existence of a bradykinin B_3 receptor in the guinea pig trachea; two concepts which have not been validated by others (Regoli et al., 1993; Pruneau et al., 1995; see also the various analysis presented in a recent book edited by S.G. Farmer, 1997) (Table 5). With the discovery of HOE 140 (Icatibant), a second generation of bradykinin B_2 receptor antagonist was introduced. The new peptidic compound is potent and selective for the bradykinin B_2 receptor and shows high affinities in all species in which it has been tested (see Table 5). It has a long duration of action (> 60 min) owing to its protection from enzymatic degradation and its prolonged interaction with the bradykinin B_2 receptor (Hock et al., 1991; Wirth et al., 1991; Lembeck et al., 1991; Gobeil et al., 1996d). Its action is slowly reversible even on wash-out from in vitro preparations (Hock et al., 1991; Rhaleb et al., 1992). When injected intraarterially to rats, HOE 140 blocks the effect of exogenous BK for more than 60 min (Wirth et al., 1991; Gobeil et al., 1996d), which makes the compound very useful for in vivo studies. HOE 140 is quite potent on the human bradykinin B_2 receptor, but less so on other bradykinin B_2 receptors (see Table 5). Also, it exerts a competitive type of antagonism on the human (Marceau et al., 1994; Félétou et al., 1995; Gobeil et al., 1996a), as mentioned earlier, but not on other bradykinin B_2 receptor systems (e.g., rabbit and guinea pig) (Regoli et al., 1993). In these latter preparations, HOE 140 is considered to be a

Table 5
Apparent affinities of bradykinin B_2 receptor antagonists on human, rabbit, guinea pig and mouse tissues

Antagonists	Human	Rabbit	Guinea pig	Mouse	References
	Umbilical vein	Jugular vein	Ileum	Stomach	
D-Arg-[Hyp[3],D-Phe[7]]BK (NPC 567)	5.2	8.0	5.4	7.1	8,1,1,2
D-Arg-[Hyp[3],D-Phe[7],Leu[8]]BK (R 493)	5.5	8.6	6.4	8.1	3,1,1,4
HOE 140	8.4	9.2	8.9	8.3	3,5,5, 4
FR 173657	8.2	8.9	8.4	8.1	6,6,6,4
desArg[10]-HOE140 (S 0765)	< 5.0	7.4	< 5.0	5.2	7,7,7,8
B 9430	8.4	9.1	8.4	8.1	9,9,8,8

NPC 567 (Stewart and Vavrek, 1991); R 493 (Rhaleb et al., 1991); HOE 140: D-Arg-[Hyp[3],Thi[5],D-Tic[7],Oic[8]]BK (Icatibant) (Hock et al., 1991); FR 173657: (*E*)-3-(6-acetamido-3-pyridyl)-*N*-[*N*-2-4-dichloro-3-[(2-methyl-8-quinolinyl)oxymethyl]phenyl]-*N*-methylamino carbonyl-methyl]acrylamide, Asano et al., 1997); S 0765 (Wirth et al., 1991); B 9430: D-Arg-[Hyp[3],Igl[5],D-Igl[7],Oic[8]]BK (Stewart et al., 1996).

References: 1, Rhaleb et al. (1991); 2, Nsa Allogho et al. (1998); 3, Gobeil et al. (1996a); 4, Nsa Allogho et al. (1995); 5, Rhaleb et al. (1992); 6, Rizzi et al. (1997); 7, Gobeil et al. (1996b); 8, present study; 9, Gobeil et al. (1997); 10, Gobeil, unpublished data.

non-equilibrium antagonist which interacts with the same receptor sites as bradykinin but dissociates slowly and prevents full occupation of receptors by the agonist. HOE 140 has been used extensively in animals to block exogenous bradykinin (Wirth et al., 1991; Lembeck et al., 1991). It has also been used in various pathological states to evaluate the role of kinins in pain and hyperalgesia (Dray and Perkins, 1993) and in inflammatory states (rhinitis, asthma, cystitis, pancreatitis, etc.) (Proud et al., 1988; Farmer, 1997; Maggi, 1997; Griesbacher and Lembeck, 1992). For a detailed analysis and discussion of the data obtained in various disease models, the reader is referred to the above papers. HOE 140 has been used for clinical trials to cure acute rhinitis (Austin et al., 1994) and asthma in severe asthmatic patients (Akbary et al., 1996). HOE 140 dose dependently antagonised house dust-mite-induced nasal blockade in patients with allergic rhinitis (Austin et al., 1994). It was however inactive on pollen-induced seasonal allergic rhinitis (Austin et al., 1994). HOE 140, given by inhalation for 4 weeks, showed some beneficial effects in asthmatic patients (Akbary et al., 1996). Some positive therapeutic effects appear to have been obtained with bradykinin B_2 receptor antagonists in the prevention of cerebral oedema (Whalley, E.T., personal communication). It must, however, be kept in mind that HOE 140 is a relatively large peptide and therefore does not possess all the favourable pharmacokinetic properties that are required for therapeutic application in humans. A better assessment of the role of kinins in human pathologies should be possible with the use of non-peptide, orally active antagonists (a third generation of bradykinin B_2 receptor antagonists) that include WIN 64338 and FR 173657. The first compound has already been described and shown to exert a moderate antagonism in the guinea pig (even in the airways (Farmer and DeSiato, 1994; Sherrer et al., 1995)), but is inactive on human tissues (Regoli et al., 1994a; Gobeil et al., 1996a; Gessi et al., 1997). FR 173657 was discovered recently by workers at Fujisawa (Osaka, Japan) (Asano et al., 1997; Inamura et al., 1997) and represents the first orally active bradykinin B_2 receptor antagonist which shows high potencies in many animal species. Its potency (in terms of pA_2) varies from 8.9 in the rabbit (Rizzi et al., 1997) to 8.1 in the mouse (Nsa Allogho et al., 1997) and it is the only bradykinin B_2 receptor antagonist that is completely inactive on the kinin B_1 receptor of humans, rabbits and mice (see Table 5). FR 173657 is quite potent on the human bradykinin B_2 receptor (pA_2 value of 8.2 obtained on the umbilical vein (Rizzi et al., 1997). This antagonistic potency is similar to that measured by Aramori et al. (1997) in a binding assay, using either the native human bradykinin B_2 receptors expressed by the IMR-90 cells (pIC_{50} 8.5) or the transfected bradykinin B_2 receptors in the CHO cells (pIC_{50} 8.1). FR 173657 is also potent in vivo; it inhibits the bradykinin-induced bronchoconstriction in guinea pigs (ED_{50} 0.075 mg/kg per os) and the induction of paw oedema by carrageenin (ED_{50} 6.8 mg/kg i.p.) (Asano et al., 1997). The last two compounds of Table 5, D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]desArg^9-bradykinin and D-Arg-[Hyp^3,Igl^5,D-Igl^7,Oic^8]-bradykinin have been already described as kinin B_1 receptor antagonists (see Tables 3 and 4). They also exert antagonistic activities on bradykinin B_2 receptors; D-Arg-[Hyp^3,Thi^5,D-Tic^7,Oic^8]desArg^9-bradykinin shows marked difference between species since it is practically inactive ($pA_2 < 5.5$) on the human, guinea pig and mouse bradykinin B_2 receptors but has a moderate potency (pA_2 7.4) on the rabbit bradykinin B_2 receptor (Table 5). Most important is the dual activity of D-Arg-[Hyp^3,Igl^5,D-Igl^7,Oic^8]-bradykinin, a peptidic compound that in spite of having and Arg at the C-terminal, shows not only high antagonistic potencies on the human (Gobeil et al., 1997), guinea pig (Stewart et al., 1996; present study) and especially rabbit bradykinin B_2 receptors (Gobeil et al., 1997) but also moderate potencies on the human and the rabbit kinin B_1 receptors (Gobeil et al., 1997) (compare data presented in Tables 4 and 5). These results confirm the findings of Stewart et al. (1996) who measured pIC_{50} values for D-Arg-[Hyp^3,Igl^5,D-Igl^7,Oic^8]-bradykinin on human ileal B_1 and B_2 receptors (Zuzack et al., 1996) of 7.3 and 8.6, respectively.

5. Conclusion

Kinins exert their multiple biological effects through the activation of two receptor types that have 7TM protein structures and are well differentiated from one another. Selective agonists and antagonists for each receptor type have been identified in the last 20 years, and their use has led to the demonstration of B_2 and B_1 receptor subtypes related to species. The development of the antagonists has followed the general pattern already seen with other peptide (e.g., angiotensin, neurokinin) receptors, whereby the initial compounds are fragile (rapidly metabolized) peptides (e.g., D-Arg[Hyp^3, D-Phe^7]bradykinin) which are succeeded by peptidic antagonists partially or completely protected (e.g., HOE 140) from metabolic degradation and ultimately orally active non-peptide antagonists (e.g., FR 173657). These latter molecules possess the basic characteristics required for clinical investigations. This development has already been achieved for antagonists of the bradykinin B_2 receptor, and other non-peptide antagonists can be expected which will have the pharmacokinetic properties required for optimal clinical application in health and disease. Progress has also been realized in the field of kinin B_1 receptor antagonists; the initial compounds (e.g., Lys-[Leu^8]desArg^9-bradykinin) which are still widely used especially for the human and rabbit B_1 kinin receptors, have been followed by a new generation of antagonists, partially resistant to peptidases (e.g., R 715) and useful not only on the human and rabbit but also on mouse and rat kinin B_1 receptors. This category of potent and selective

kinin B_1 receptor antagonists also includes B 9958 as well as ambivalent compounds (mixed B_1 and B_2 kinin receptor antagonists) such as B 9430, which have been used successfully to evaluate the role of kininergic receptors in experimental physiopathologies. Non-peptide kinin B_1 receptor antagonists are expected soon and will allow an appropriate assessment of the physiopathological roles of the kinin B_1 receptor.

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