

Bradykinin Receptors

Key References

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Overview

The nonapeptide bradykinin (BK) and Lys-BK (kallidin) are naturally occurring substances produced in most species by the proteolytic digestion of high or low molecular weight kininogen by plasma and tissue kallikrein, respectively, following a suitable stimulus. T-kinin (Ile-Ser-BK) is formed from T-kininogen in the rat. Removal of the C-terminal arginine of BK and Lys-BK by carboxypeptidases generates the peptides BK(1-8), also referred to as [des-Arg⁹]-BK, and Lys-BK(1-8), also known as [Lys-des-Arg⁹]-BK or [des-Arg¹⁰]-kallidin, respectively. Bradykinin and the related kinins possess a wide range of pharmacological actions and are believed to be important mediators of pain and inflammation in addition to being involved in the control of local blood flow.

Kinins induce their effects via two main types of receptor, designated B₁ and B₂, both of which belong to the superfamily of G protein-coupled receptors. Recently an orphan GPCR (GPR100) has been suggested to be a candidate BK receptor; however, further detailed characterization is required. BK(1-8) is a more potent agonist at the rodent/murine B₁ receptor as compared with its activity at the human B₁ receptor for which the B₁ agonist of choice is Lys-BK(1-8). The B₂ receptor is generally present in a wide variety of tissues. In contrast the B₁ receptor, which is expressed at low levels under normal conditions, appears to be up-regulated both *in vitro* and *in vivo* following exposure to noxious stimuli such as LPS and other inflammatory mediators such as IL-1 β , IL-2, IL-8, growth factors such as EGF and neurotrophic factors such as NGF.

The molecular cloning of cDNAs encoding the kinin receptors has provided direct evidence for the existence of B₁ and B₂ receptors as the products of distinct genes.

The human, dog, mouse and rat B₂ and B₁ receptors have been cloned, expressed, sequenced and characterized pharmacologically. Human and rabbit B₁ receptors, respectively, exhibit approximately 2,000- and 150-fold higher affinities for Lys-BK(1-8) relative to BK(1-8) whereas the mouse B₁ receptor exhibits a 2-3 fold higher affinity for BK(1-8) compared to Lys-BK(1-8). The homology between the human B₂ and B₁ receptor sequence is only 36% at the amino acid level. In comparison, the human B₁ receptor is 30% identical to the AT₁ angiotensin II receptor. Many cells co-express both B₁ and B₂ receptors. Both receptors interact with G α_q and G α_i through which they mediate intracellular signaling, including phosphoinositide hydrolysis and elevation of intracellular calcium.

Activation of both the B₁ and the B₂ receptor has been implicated in many pathophysiological disorders and efforts have been made to develop selective agonist and antagonist ligands for both receptors for use as pharmacological/biochemical tools and potential therapeutic agents. Blocking both receptors may be beneficial in certain circumstances, such as hyperalgesia, and peptide-based compounds have been developed that display high affinity for both receptors (e.g. B9430). Mice lacking the B₁ or B₂ receptor are available and are helping to elucidate the role of these receptors in development, and in normal and altered physiology. A wide selection of peptide (first generation), stabilized, more enzyme resistant (second generation) and non-peptide (third generation) agonists and antagonists are now available allowing a more detailed characterization of bradykinin B₁ and B₂ receptor function both in *in vitro* and *in vivo* systems. Antagonists and agonists at either the B₁ or B₂ receptor

have potential therapeutic utility in various disease indications. In this respect, B₂ receptor antagonists, such as the peptide, Icatibant (HOE 140) and the non-peptide, LF 16-0687Ms (Anatibant), are currently in clinical trials for the treatment of hereditary angioedema and traumatic brain injury, respectively. At the present time, no B₁ receptor antagonists are being investigated clinically.

Bradykinin Receptors

CURRENTLY ACCEPTED NAME	B ₁	B ₂
ALTERNATE NAME	BK ₁	BK ₂
STRUCTURAL INFORMATION	353 aa (human)	364 aa (human)
TYPE SELECTIVE AGONISTS (PEPTIDE)	BK(1-8) (B4397), Lys-BK(1-8), Sar[D-Phe ⁸]-BK(1-8)	BK (B3259), Lys-BK, Ile-Ser-BK (B1643), [Phe ⁸ -(ψ-CH ₂ NH)-Arg ⁹]-BK, [Hyp ³ , Tyr(Me) ⁸]-BK, [Hyp ³]-BK (B7775), RMP-7 (Cereport), LF 150943
TYPE SELECTIVE AGONIST (NON-PEPTIDE)	Not known	FR 190997
TYPE SELECTIVE ANTAGONISTS (PEPTIDE)	[Leu ⁸]-BK(1-8), Lys-[Leu ⁸]-BK(1-8), [des-Arg ¹⁰]-HOE 140 (H158), B9958	HOE 140 (H157), NPC 17731, D-Arg[Hyp ³ , Thi ⁵ , HypE(trans-propyl) ⁷ , Oic ⁸]-BK
TYPE NON-SELECTIVE ANTAGONISTS (PEPTIDE)	B9430	B9430
TYPE SELECTIVE ANTAGONISTS (NON-PEPTIDE)	SSR240612	Bradyzide (B1680), FR 173657, LF 160687
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-Lys-BK(1-8), [³ H]-[des-Arg ¹⁰ , Leu ⁹]-Kallidin, [³ H]-[des-Arg ¹⁰]-Kallidin	[¹²⁵ I]-[Tyr ⁸]-BK, [³ H]-BK, [³ H]-NPC 17731
TISSUE EXPRESSION	Inducible following tissue injury in most cells and tissues	Constitutive: Most cells and tissues
PHYSIOLOGICAL FUNCTION	Not known	Local blood flow
DISEASE RELEVANCE	Pain, inflammation, edema, infection/sepsis, asthma, renal/cardio protection, tumor/angiogenesis, diabetes	Pain, inflammation, edema, CNS trauma/edema/stroke, infection/sepsis, asthma/rhinitis, renal/cardio protection, tumor/angiogenesis, pancreatitis, hereditary angioneurotic, edema, cirrhosis

Abbreviations

BK: Bradykinin

Lys-BK: Kallidin

Ile-Ser-BK: T-Kinin

Bradyzide: (2S)-1-[4-(4-Benzhydrylthiosemicarbazido)-3-nitrobenzenesulfonyl]-pyrrolidine-2-carboxylic acid (2-(2-dimethylaminoethyl)methylamino)ethylamide

B9958: Lys-Lys-Arg-Pro-Hyp-Gly-CpG-Ser-DTic-Cpg

B9430: D-Arg-Arg-Pro-Hyp-Igl-Ser-D-Igl-Oic-Arg

LF 150943 (JMV1116): D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-(3S)[amino]-5-(carbonylmethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one-Arg

LF 160687: 1-[[2,4-dichloro-3-[[[(2,4-dimethylquinolin-8-yl)oxy] methyl]phenyl]sulfonyl]-N-[3-[[4-(aminoiminomethyl)phenyl] carbonylamino]propyl]-2(S)-pyrrolidinecarboxamide

FR 173657: ((E)-3(6-Acetamido-3-pyridyl)-N-[N-[2,4-dichloro-3-[(2-methyl-8-quinolyl)oxymethyl]phenyl]-N-methylamino carbonylmethyl]acrylamide)

FR 190997: (8-[2,6-Dichloro-3-[N-[(E)-4-(N-methylcarbamoyl)cinnamidoacetyl]-N-methylamino]benzyloxy]-2-methyl-4-(2-pyridylmethoxy)quinoline

HOE 140: D-Arg[Hyp³, Thi⁵, D-Tic⁷, Oic⁸]BK

NPC 17731: D-Arginyl-L-arginyl-L-prolyl-(4R)-4-hydroxy-L-prolylglycyl-L-phenylalanyl-L-seryl-(4S)-4-propoxy-D-prolyl-(2S,3aS,7aS)-octahydro-1H-indole-2-carbonyl-L-arginine

RMP-7 (Cereport): Arg-Pro-Hyp-Gly-Thi-Ser-Pro-4-Me-TyrΨ((CH₂NH)Arg

SSR240162: (2R)-2-(((3R)-3-(1,3-benzodioxol-5-yl)-3-[[[(6-methoxy-2-naphthyl)sulphonyl]amino]propanoyl]amino)-3-(4-[[2R,6S)-2,6-dimethylpiperidinyl]methyl]phenyl)-N-isopropyl-N-methylpropanamide hydrochloride

FOOTNOTES