

Bombesin Receptors

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Overview

Bombesin is a 14 amino acid peptide isolated from frog skin. The mammalian counterparts of the frog peptide are neuromedin B (NMB) and gastrin-releasing peptide (GRP), as well as the biologically active GRP fragment neuromedin C (NMC). The first two receptors for these ligands to be cloned were designated BB₁ and BB₂, and were originally referred to as the NMB- and GRP-preferring bombesin receptors, after their respective endogenous ligands. More recently, a third mammalian bombesin receptor subtype, BB₃ (also known as BRS3), was cloned, although no endogenous ligand has been identified to date. A fourth bombesin receptor, BB₄, has been cloned from the frog, but as of yet there is no mammalian equivalent described. All the receptor subtypes identified to date couple via G_{q/11} to the phospholipase C signaling pathway. Each also activates phospholipase D and stimulates tyrosine phosphorylation of numerous proteins (p125^{FAK}, paxillin, others).

Bombesin receptor pharmacology was originally defined in terms of the rank order of potency of the endogenous ligands NMB, GRP and bombesin, with the rank order of potency being NMB > bombesin > GRP at the BB₁ receptor and GRP > bombesin > NMB at the BB₂ receptor. Further characterization became possible with the development of a range of peptide GRP antagonists. Two non-peptide BB₁ selective antagonists, PD 165929 and PD 168368, have been reported that possess affinities of 7.6 nM and 30 nM at the BB₁ receptor, respectively. PD 165929 is inactive at the BB₂ receptor, while PD 168368 has an affinity at this receptor of 1.2 μM. However, both compounds require solubilization in cyclodextrin, thus limiting their use *in vivo*. BB₃ has low affinity for all naturally

occurring bombesin-related peptides and its native ligand is unknown.

Bombesin receptors play a role in a variety of physiological and pathological processes in mammals, although the precise subtype(s) involved are not always established in each case. Both BB₁ and BB₂ receptors are widely distributed in the CNS as well as in the gastrointestinal tract and reproductive organs. In the CNS, bombesin-like peptides induce satiety, possibly via an interaction with corticotrophin-releasing factor. They also play a role in thermoregulation and induce histamine-independent pruritus. In addition, these peptides act via the BB₂ receptor in the suprachiasmatic and dorsal raphe nuclei to regulate circadian rhythms and the activity of the serotonergic system, resulting in an association with sleep disorders and depression. Recent studies show these peptides acting via BB₂ receptors are important in the regulation of emotionally motivated learning and memory. NMB functions as an autocrine regulator of TSH release by the pituitary and its release can be altered in hyper- or hypothyroid states. In the gastrointestinal tract, these peptides regulate smooth muscle contractility, pancreatic secretion, and the release of many other gastrointestinal peptides/hormones. Bombesin-like peptides also have a developmental role in the lung and the uterus. They function as potent growth factors for both normal and neoplastic tissues including lung, prostate, gastric and colonic cancers. Recent evidence suggests that the carcinogenic properties of these peptides are predominantly mediated by the BB₂ receptor. These peptides stimulate natural killer cell activity and chemotaxis. Recent studies also suggest a possible role of bombesin peptides acting via the BB₂ receptors in gut/

lung inflammatory reactions and reaction to oxidative stress as well as CNS disorders (autism, anxiety disorders). Recently, using knockout strategies it has been shown that mice lacking either the BB₁ or BB₂ receptor do not display any gross phenotypic changes from the wild type, while the BB₃ receptor knockouts exhibited an obese phenotype. Using knockout mice, both BB₂ and BB₃ receptors are shown to be important for insulin release by islets: BB₂ in satiety, BB₁ in regulating 5-HT neuronal activity in the dorsal raphe nucleus, and bombesin receptors may be involved in modulating emotion in some forms of anxiety.

Bombesin Receptors

CURRENTLY ACCEPTED NAME ^a	BB ₁	BB ₂	BB ₃
ALTERNATE NAME	Neuromedin B-preferring (NMB-R)	GRP-preferring (GRP-R)	BRS ₃
STRUCTURAL INFORMATION	390 aa (human)	384 aa (human)	399 aa (human)
SUBTYPE SELECTIVE AGONISTS	NMB (N3762) > Bombesin (B4272) > GRP (G8022)	GRP (G8022) > Bombesin (B4272) > NMB (N3762)	Ac-Phe-Trp-Ala-His(τβZ1)-Nip-Gly-Arg-NH ₂
SUBTYPE SELECTIVE ANTAGONISTS	PD 168368, PD 165929, BW 1023U90	[D-Phe ⁶ ,Cpa ¹⁴ -ψ13-14]-Bombesin(6-14), [D-Phe ⁶]-Bombesin(6-13) ethyl ester	Not known
RECEPTOR SELECTIVE ANTAGONISTS	[Leu ¹³ -(ψ-CH ₂ NH)-Leu ¹⁴]-Bombesin (B127), [Tyr ⁴ -D-Phe ¹²]-Bombesin (B129), ICI 216,140 (I123)	[Leu ¹³ -(ψ-CH ₂ NH)-Leu ¹⁴]-Bombesin (B127), [Tyr ⁴ -D-Phe ¹²]-Bombesin (B129), ICI 216,140 (I123)	Not known
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-BH-NMB, [¹²⁵ I]-[D-Tyr ⁰]NMB [¹²⁵ I]-[Tyr ⁴]-Bombesin [¹²⁵ I]-[D-Tyr ⁶ ,β-Ala ¹¹ ,Phe ¹³ ,Nle ¹⁴]-Bombesin(6-14)	[¹²⁵ I]-[D-Tyr ⁶]-Bombesin(6-13) methyl ester, [¹²⁵ I]-[Tyr ⁴]-Bombesin, [¹²⁵ I]-[D-Tyr ⁶ ,β-Ala ¹¹ ,Phe ¹³ ,Nle ¹⁴]-Bombesin(6-14)	[¹²⁵ I]-[D-Tyr ⁶ ,β-Ala ¹¹ ,Phe ¹³ ,Nle ¹⁴]-Bombesin(6-14)
TISSUE EXPRESSION	CNS (olfactory bulb, central thalamic regions, amygdala), GI tract (esp. esophagus), bronchial epithelial cells, testis, uterus	CNS (spinal sensory ganglia, hypothalamus, basal ganglia, amygdala), GI tract, reproductive system, lung (bronchial epithelial cells)	CNS (habenula, thalamic nuclei), hypothalamus, cortex, testis (rat), lung (bronchial epithelial cells)
PHYSIOLOGICAL FUNCTION	Release of thyroid stimulating hormone, regulation of stress response	CNS actions, circadian rhythm control, satiety, regulate sympathetic nervous system and emotionally-motivated learning, maintenance normoglycemia, GI (gallbladder contraction, motility and peristaltic wave regulation, pancreatic secretion, acid secretion regulation, islet function, potent stimulant release of numerous GI hormones)	Regulation energy and glucose homeostasis
DISEASE RELEVANCE	Autocrine function (altered in hypo/hyper-thyroidism), growth factor, some tumors, regulation of stress response, CNS disorders (autism, anxiety), gut/lung inflammatory disorders	Growth factor, numerous tumors (prostate, lung, gastric, colon), broncho-pulmonary dysplasia, tobacco-related injury	Knockout mice are obese and develop glucose intolerance

Abbreviations

BW 1023U90: N-[3-(4-Hydroxyphenyl)-1-oxopropyl]-L-histidyl-L-tryptophyl-L-alanyl-L-valyl-N-[(1S)-2-[(2R)-2-[[[(1S)-2-amino-2-oxo-1-(phenylmethyl)ethyl]amino]methyl]-1-pyrrolidinyl]-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl]-D-alaninamide

GRP: Gastrin releasing peptide

ICI 216,140: (CH₃)₂CHCO-His-Trp-Ala-Val-D-Ala-His-Leu-NHCH₃

Nip: Piperidine 3-carboxylic acid

NMB: Neuromedin B

PD 165929: 2-[3-(2,6-Diisopropyl-phenyl)-ureido]3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionate

PD 168368: 3-(1H-Indol-3-yl)-2-methyl-2-[3(4-nitrophenyl)-ureido]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

PD 176252: 3-(1H-Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide

PhPr: Phenylpropanoyl

FOOTNOTES

^a A novel bombesin receptor comprising 377 aa has been cloned in frog. Referred to as a BB₄ receptor, it displays relative agonist potencies of [Phe¹³]-bombesin > GRP > NMB, is blocked by [D-Phe⁶]-bombesin (6-13) propylamide and can be radiolabeled using [¹²⁵I]-[Tyr⁴]bombesin.