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Insights into Bombesin receptors and ligands: highlighting recent advances

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Abstract

This following article is written for Prof. Abba Kastin's Festschrift, to add to the tribute to his important role in the advancement of the role of peptides in physiological, as well as pathophysiological processes. There have been many advances during the 35 years of his prominent role in the Peptide field, not only as editor of the journal Peptides, but also as a scientific investigator and editor of two volumes of the Handbook of Biological Active Peptides [146,147]. Similar to the advances with many different peptides, during this 35 year period, there have been much progress made in the understanding of the pharmacology, cell biology and the role of (Bombesin) Bn receptors and their ligands in various disease states, since the original isolation of bombesin from skin of the European frog Bombina bombina in 1970 [76]. This paper will briefly review some of these advances over the time period of Prof Kastin 35 years in the peptide field concentrating on the advances since 2007 when many of the results from earlier studies were summarized [128,129]. It is appropriate to do this because there have been 280 articles published in Peptides during this time on Bombesin-related peptides and it accounts for almost 5% of all publications. Furthermore, 22 Bn publications we have been involved in have been published in either Peptides [14,39,55,58,81,92,93,119,152,216,225,226,231,280,302,309,355,361,362] or in the Prof Kastin's Handbook of Biological Active Peptides [137,138,331].

I. Discovery of Bn peptides

In addition to Bn, A large number of other Bn related peptides subsequently were isolated (1970–1990), primarily from other amphibian skins, mainly by Profs Espamer/Nakajima and colleagues, and these fell into three general groups [75,77,129,138]. One group was comprised of the Bn related peptides with COOH termini ending in Gly-His-Leu-Met-NH_2;

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a second group comprised of the litorin-ranatensin related peptides ending in Gly-His-Phe-Met-NH_2 and third group the phyllolitorin related peptides ending in: Gly-Ser-Phe (Leu)-Met-NH_2 [75,77,129,138]. It was not until 1980 that the mammalian member of the Bn peptide subgroup was isolated from porcine stomach, the 27 amino acid peptide, Gastrin Releasing Peptide (GRP) by McDonald and colleagues [213]. It was found to have a very high homology to Bn sharing the same 7 COOH terminal amino acids, which is the biologically active end of the peptide [38,179,213]. In 1983 Minamino isolated the decapeptide, Neuromedin B (NMB) from porcine spinal cord [217] which he also later found to occur in larger forms of 30 and 32 amino acids [218]. Six of the 7 COOH terminal amino acids of NMB were identical to ranatensin. Subsequently in 1984 Minamino isolated the COOH terminal decapeptide of GRP from porcine spinal cord, and was called neuromedin C [GRP18-27][219]. No mammalian equivalent of phyllolitorin has been described.

Molecular studies demonstrate each that the various Bn peptides are derived from separate prohormones [331]. In the case of amphibians these studies show that many frog species in their skins contain multiple forms of Bn peptides with both Phe and Leu penultimate residues and that each is derived from separate genes [238,331]. For many years Bn was considered the mammalian equivalent of GRP, however, subsequently in the same frog was found different cDNA's encoding for both GRP and Bn with the frog GRP being much more analogous to mammalian GRP than frog Bn, leading to the conclusion that mammalian GRP is not the mammalian equivalent of frog Bn [239,331]. Therefore at present, no mammalian Bn peptide has been described that is equivalent to frog Bn [331].

II. Discovery of Bn peptide Receptors

Early functional studies and binding studies suggested more than one subtype of Bn receptor existed in mammalian tissues both in peripheral tissues and in the central nervous system (CNS)[38,129,164–166,321,365,366].

Subsequent molecular studies have identified and characterized three different mammalian Bn receptor (BnR) members including: the gastrin-releasing peptide receptor (GRPR)(BB_2); the neuromedin B receptor (NMBR)(BB_1) and an orphan receptor, named bombesin receptor subtype 3 (BRS-3)(BB_3), that is also included in this family [21,80,96,332,369]. BRS-3 is included in the BnR family of receptors even though at present the native ligand is unknown, because the human BRS-3 has 51% amino acid identities with a the human GRPR, and 47% with the human NMBR, demonstrating close similarity to these receptors [80,95,96,129,194,331]. Each of the three BnRs is a member of the G-protein coupled hepta-helical superfamily of membrane receptors.

In 1995, Nagalla et al [237] cloned a receptor from amphibian brain that had 61%, 56% and 70% identities to GRPR, NMBR and BRS-3, respectively. This receptor had a high affinity for [Phe^{13}] Bn, which was the most prevalent form in frog brain, and had a lower affinity for GRP and NMB [148,237]. This receptor was named BB4 for bombesin receptor subtype 4 [237]. At present no mammalian equivalent of the amphibian BB4 receptor has been described [129,331]. In 2003 Iwabuchi at al [124] described a BnR from chicken that had

high amino acid identities to frog BBR4 (70%), human BRS-3 (69%), but lower for human GRPR (58%) and hNMBR (52%). Pharmacologically this receptor had low affinity for GRP and NMB, but high affinity [DPhe^{6}, βAla^{11}, Phe^{13}] Bn (6–14) [124], a synthetic Bn analogue that has high affinity for human BRS-3 [201,275,299,301,355]. This receptor was called chBRS-3.5 because of its similarities to both frog BBR ad human BRS-3 [124]. No mammalian equivalent of this receptor has been described [129].

III. Distribution of BnR and ligands

The distribution of the native ligands, GRP and NMB as well as their receptors, GRPR and NMBR has been extensively examined by both immunohistochemical studies, binding studies for the receptors and molecular assessments of the mRNA distribution [129,164,228,245,310,332,364,369]. Both the native ligands and their receptors are found widely distributed in the CNS and peripheral tissues including the gastrointestinal tract; pulmonary, urogenital and reproductive system; numerous endocrine glands (adrenal, pituitary, thyroid, islets); and the hematopoietic system (phagocytic cells, macrophages) and immune cells [120,129,139,245,277]. In the monkey CNS both NMBR and GRPR mRNA were found in the amygdala, caudate nucleus, cerebellum, hippocampus, hypothalamus, thalamus and spinal cord [310]. In rat CNS binding studies a particularly high density of NMBR was found in the olfactory regions and central thalamic nuclei and a highest density of GRPRs in the hypothalamus, particularly the suprachiasmatic and paraventricular nuclei, which both agree with the mRNA distribution studies of these two receptors in rat brain [368].

The distribution of the BRS-3 receptor is less well studied and because the native ligand is unknown there is no information available on it. No binding studies on the distribution of the BRS-3 have been performed because until recently there were no high affinity ligands that bound specifically to the BRS-3 receptor [234]. The synthetic Bn peptide analog, [$_{D}$Tyr^{6}, βAla^{11}, Phe^{13}] Bn (6–14) can be radiolabeled and used for binding studies in human tissues, because it has high affinity for human BRS-3 [201,234,275,299,301,355], but is not useful in rodents, because it has a very low affinity for the mouse or rat BRS-3 [180]. Furthermore, its utility is limited because it has high affinity for GRPR and NMBR in all species examined [201,234,275,299,301,355]. In the monkey BRS-3 mRNA was found throughout the CNS with the highest amounts in the hypothamus and in low amounts in most peripheral tissues with the highest amount in the testis and lower amounts in the pancreas, thyroid, ovary and pituitary gland [310]. BRS-3 mRNA is found in the islets of mice, human, rhesus monkey and dog, but not in rat islets [82]. Immunohistochemical studies in the rat CNS [127] and gastrointestinal tract [273] demonstrated BRS-3 is strongly present in cerebral cortex, hippocampal formation, hypothalamus and thalamus in the CNS [127]. In the GI tract BRS-3 was found in all gut regions in nerves and non-neuronal tissues, including enteric and submucosal ganglia, myenteric ganglia and in cell bodies of c-KIT interstitial cells of Cajal, which are important in regulating GI motility [273]. Two recent studies have provided additional information. In one study using in situ hybridization the distribution of BRS-3 mRNA and its co-localization with various neurotransmitters was examined in rat and mouse brain [393]. BRS-3 was found in a variety of brain regions with the highest concentrations in the amygdala and hypothalamus [393]. Many of the BRS-3

expressing neurons were glutamatergic, a few cholingergic or GABAergic, and also a few partially co-localize with corticotropin-releasing factor (CRF) and growth hormone-releasing factor (GHRH) suggesting interactions of BRS-3 with stress- and growth hormone endocrine systems [393]. In a second study using a specific BRS-3 radiolabeled agonist ([^{3}H]Bag-2) [102] in mice brain, moderate to abundant BRS-3 binding was seen in various hypothalamic nuclei (PVN, DMH, ARC, VMH, PH, Pe, MPA, NHA), forebrain areas, caudal brain (PBN, NTS), the amygdala and the thalamus [102]. The strong binding in hypothalamic nuclei support the importance of BRS-3 in feed behavior and energy metabolism which was first reported in BRS-3 knockout mice which developed obesity, hypertension and impairment of glucose metabolism [249].

IV. Pharmacology of Bn receptors/ligands

IV.A. Pharmacology of Bn receptor agonists

Numerous studies primarily using cells containing rat/mouse BnRs demonstrate that the m, rGRPR has 24–148 fold higher affinity for GRP than NMB and that the rNMBR has 60–250 fold greater affinity for NMB than GRP [25,28,29,129,201,301,365,369,371]. Recently a detailed study on the human GRPR/NMBR in native and transfected cells has been reported [355] and this demonstrates that human GRPR has a 647-fold higher affinity for GRP than NMB and that the hNMBR has a 640-fold higher affinity for NMB than GRP (Table 1). In this study of the 12 natural occurring Bn related peptides tested, three had an equal high affinity to GRP for the hGRPR (IC_{50}-0.12-0.5 nM)(Bn, alytesin, NMC) and none had and equal high affinity to NMB for hNMBR (IC_{50}-0.053 nM), however, GRP and NMB were the most selective for the hGRPR and hNMBR, respectively (Table 1) [355]. BRS-3 has low affinity (IC_{50}>1 uM) for GRP, NMB and all naturally occurring Bn analogues studied [80,201,300,301,355].

Recently there has been increased interest in developing high affinity BnR agonist ligands that are metabolically stable and can be coupled via various linkers to radiolabels that can be used to image tumors overexpressing BnR's (see later section) or coupled to cytotoxic compounds (radiolabeled [Peptide radioreceptor therapy (PRRT)] or chemotherapeutic or other tumoricidal agent) for antitumor treatment [128,235,241,286,308,391]. A large number of truncated Bn fragments or other synthetic Bn analogue are being used for this [241,308,391]. For this reason it is important to remember studies, which show that for the NMBR the minimal COOH terminal, peptide length required for full potency equal to NMB is the COOH terminal decapeptide [179]. For the GRPR the minimal GRPR or Bn COOH terminal fragment demonstrating agonist activity is the COOH-terminal heptapeptide and the minimal COOH fragment required for full affinity equal to Bn or GRP is the COOH-terminal nonapeptide [109,129,179,210].

Many synthetic agonist analogs of the biologically active COOH terminus of Bn/GRP related peptides have been synthesized either to develop a more metabolically stable analogue; more selective analogue for GRPR or NMBR; an analogue with even higher affinity than the native Bn peptide; to allow easier synthesis or to allow easier coupling to various compounds [38,129,202,290,309]. One of these synthetic Bn analogues that is receiving increased attention is [$_{D}$Phe^{6}, βAla^{11}, Phe^{13}] Bn (6–14) or its $_{D}$Tyr^{6} analogue,

because these two analogues have the unique property of having high affinity for all three human BnR's (Table 1), as well as the GRPR and NMBR of all species described and frog BB4 [148,201,234,275,299,301,355]. Therefore, except for rat or mouse BRS-3 [180] this analogue has universal high affinity for all BnRs (IC_{50}, 0.3–2 nM) (Table 1) and thus is a potentially useful compound for targeting various tumors overexpressing different BnRs for imaging or PRRT [308]. Extensive structure-function studies of Bn/GRP analogues have been performed and summarized [129] therefore only a few additional general comments will be made that are important in designing synthetic agonist analogues for use for imaging or PRRT. Numerous studies show the presence of Trp^8 and His^{12} in the biologically active CCOH terminus of Bn are essential for biologic activity [38,110,129,132,290,302]; analogues with the COOH terminal Met^{14} deleted (desMET^{14}-Bn/GRP analogues) have no agonist activity, but can function as potent antagonists (Table 1) [129,132,372,373]; the 1^{st} 5 amino terminal amino acids of Bn can be removed [56,129,355] and analogues such as [$_D$Phe^6]Bn(6–14) have an affinity equal to GRP for hGRPR, but have less selectivity(Table 1) [355]; analogues of various amphibian peptides such ranatensin, litorin or Bn can be used as high affinity hGRPR ligands, but they all have less selectivity than NMC or GRP analogues for the hGRPR(Table 1) [355]. Unfortunately in many cases the pharmacological evaluation of potentially useful BnR agonists can be misleading. The assays used are frequently cell signaling assays ($[Ca^{2+}]_i$, IP, etc) and the cells used are rarely native human BnR-containing cells, especially in the case of NMBR. Usually either transfected hBnR containing cells are used or cells containing rat or mouse BnRs[355]. Numerous studies show that the pharmacophore of rodent BnRs for Bn agonists can differ markedly from human BnR containing cells [129,355]. Furthermore, the stimulus-coupling in transfected cells can differ markedly from native BnR containing cells because the receptors are often overexpressed and may couple aberrantly [129,353]. Furthermore, studies demonstrate, particularly with potential peptide agonists, their agonist/antagonist efficacy can vary markedly in human and rodent cells containing BnRs [57,132,355,373,381]. Some of these points are well demonstrated in a recent study that compared the affinities and potencies for cell activation of 24 putative BnR agonists in cells containing native and transfected hBnRs and compared the results obtained to those seen on rat GRPR or NMBR containing cells [355]. In this study [355] no correlation was found between the affinities of the different BnR agonists for rat and human GRPRs (r=0.313,p=0.54).

The in vivo synthesis of GRP and NMB involves their cleavage from a pre-proform (PreproGRP-148 amino acids, preproNMB-76 amino acids) which consist of a signal peptide, the hormone sequence and a carboxyl terminal extended peptide [20,245,331]. The COOH terminal extended forms of GRP/Bn have low affinity for the GRPR (IC_{50}>1 uM), however, recently a number of papers have reported biologically active effects of COOH terminal extended Bn/GRP analogues [20,122,257]. These studies primarily report the COOH terminal extended peptides stimulation of various neoplastic cells, as well as reporting that different tumors, as well as some normal tissues, can secrete large amount of COOH terminal GRP peptides [20,122,257]. At present the receptor(s) mediating the actions of these COOH GRP terminally extended peptides is not clear with some studies reporting it is mediated by the GRPR whereas other report it is mediated by an unknown novel receptor [20,74,122,256,257].

Until recently the only known agonist of the BRS-3 receptor was peptide agonist, [$_D$Phe^6, bAla^{11}, Phe^{13}] Bn (6–14) or its $_D$Tyr^6 analogue, however these synthetic Bn analogues have the disadvantage of lack of specificity, because they also bind to, and activate, GRPRs and NMBR, with high affinity and potency (Table 1) [148,201,234,275,299–301,355]. Because mBRS-3 animals develop obesity, diabetes and metabolic disturbance [249], there has been increased interest in developing BRS-3 agonists for possible treatment of obesity [102,103,193,207,285]. Two groups have recently reported nonpeptide agonists that activate BRS-3 with high potency [103,206,207,285,320]. MK-5046 [(2S)-1,1,1-trifluoro-2-[4-(1H-pyrazol-1-yl)phenyl]-3-(4-[[1-(trifluoromethyl)cyclopropyl]methyl]-1H–imidazol-2-yl)propan-2-ol] is an orally active, selective potent BRS-3 agonist with activity in rat, mouse, dog, and human [103,285,320]. MK-5046 has high affinity for hBRS-3 (IC_{50}-18 nM) and very low affinity for hGRPR, hNMBR (IC_{50}>10,000 nM) (Table 1) [234]. MK-5046's interaction/activation of hBRS-3 differed from the peptide agonist, [$_D$Phe^6, βAla^{11}, Phe^{13}] Bn (6–14) in having greater receptor coupling spareness, a different pattern of activation of MAPK, p125FAK, Akt and paxillin and showing slower kinetics and a longer duration of action, demonstrating the peptide and MK-5046's activation of hBRS were not always concordant raising the possibility they could lead to different cellular responses [234]. A second group [206,207] reports a series of chiral diazepine analogues with low brain penetration, which also function as high affinity BRS-3 agonists. Results assessing affinity of two of these chiral diazepine analogues (9G, 9D) are shown in Table demonstrating that they function as selective BRS-3 ligands [281]. It is proposed that because of their low brain penetrance, they may lack side-effects seen in trials with MK-5046, and be potentially useful anti-obesity agents [207].

IV.A. Pharmacology of Bn receptor antagonists

There are a number of different chemical classes of GRPR antagonists, however the number of NMBR antagonists or BRS-3 antagonists is very limited [93,102,128,129,132,234,309]. In general six classes of GRPR antagonists exist with 5 classes being peptides or peptoid antagonists and one class being comprised of nonpeptide antagonists [93,102,129,132,234,309]: The five classes of GRPR peptide/peptoid antagonists include: $_D$-amino acid substituted substance P analogs [129,134,135]; amino acid substituted COOH terminal analogs of GRP/Bn including $_D$-amino acid substituted analogues such as [$_D$-Phe^{12}]Bn); statine substituted analogues such as JMV-594 [$_D$Phe^6]Bn,[$_D$Phe^6,Stat^{13}]Bn(6–14)][Bn(6–14) [110,129,185,302,308,349]; pseudopeptide analogues of the COOH terminus of BN/GRP particularly including analogues with CH_2NH replacing the peptide bond (i.e. CONH) especially in the penultimate position of Bn (13–14) or GRP [18,42,54,56,129,308]; [desMET^{14} Bn] or [desMet^{27}]GRPs analogues including desMET amides, alkylamides, esters, hydrazides or with other groups attached: and peptoid antagonists including PD176252 and related analogues [55,93,129,308,308,372,373]. Of these different classes of hGRP antagonists, the most widely used are various ψ13,4–pseudopeptide Bn analogues, [desMet^{14}/GRP^{28}] analogues and the [statine^{12}]Bn analogues which all have affinity for hGRP in the nanomolar range (Table 1) [93,129,195,308]. As with the case of BnR agonists discussed above, in most cases the pharmacology of these GRPR antagonists is limited because it was not performed on cells containing native human BnRs, and either cells transfected with human BnR were used in a few cases or more frequently cells were used

containing either native or transfected m,rBnR's. This is particularly important in evaluating whether a given peptide analogue behaves as a GRPR agonist or antagonist, because studies show not only can the pharmacophore of rodent receptors differ markedly from human but the coupling can be markedly different in different species as well as with overexpressing transfected receptors [129,132,353,373,381]. For example, many desMET^{14} Bn analogues are antagonists in guinea pig or mouse GRPR-containing cells but partial or full agonists in rGRPR- containing cell [129,373]. Furthermore, in cells transfected with different densities of GRPR, the ability to activate PLC and induce changes in cytosolic Ca^{2+} may be seen with some putative antagonists, only at high expressed receptor densities and not at the receptor densities occurring naturally [381].

For NMBR-containing cells there are no peptide antagonists with high affinity and selectivity [129]. In a recent study using both native and transfected BnR-containing cells [93] the peptoid antagonists, PD176252 and PD168368, had high affinity for the hNMBR (IC50-0.2-053) and both had selectivity for the hNMBR over the hGRPR, with PD16368 being the most selective (>2500-fold) (Table 1)[93].

Recently Bantag-1 (Boc-Phe-His-4-amino-5-cyclohexyl-2,4,5-trideoxypentonyl-Leu-(3-dimethylamino) benzylamide N-methylammonium trifluoroacetate) was reported to be a selective peptide antagonist for hBRS-3 [82,102]. In a recent detailed pharmacologic study [234] assessing both native hBRS-3 and transfected hBRS-3 cells, Bantag-1 had a high affinity for hBRS-3 (1–1.6 nM) and had >3000-fold selectivity for hBRS-3 over hGRPR or hNMBR-containing cells(Table 1). Furthermore, Bantag-1 [234] functioned as a competitive hBRS-3 receptor antagonist showing no agonist activity at this receptor and causing a parallel rightward shift in the cell activating dose-responses curves by either MK-5046 or the peptide agonist, [DPhe^{6}, βAla^{11}, Phe^{13}] Bn (6–14).

V. Cell signaling of Bn receptors

The principal signaling cascade by all BnR's is the activation of the phospholipase C (PLC) cascade with stimulation of changes in cytosolic Ca^{2+}, generation of diacylglycerol, and activation of protein kinases C's (PKCs) [95,128,129,297,307,376]. This is primarily accomplished through coupling to the Gq/11 and G12/13 families of heterotrimeric G-proteins [129,255,298]. BnR's activation stimulate a number of other signaling cascades including activation of Phospholipase D and A2, small GTP binding proteins such as Rho, protein kinase D and various ion channels [111,129,326,354,397]. After activation BnR's undergo a number of receptor modulatory processes including receptor phosphorylation [13,129,154,155,380], internalization and recycling [24–26,129,317,327,352,353,379], down-regulation [25–27,129,353] and desensitization [23,25–27,129]. Agonists, but not antagonists, characteristically stimulate internalization [43,129,197] and this was a key issue in originally using labeled agonists for Bn receptor imaging and cytotoxic studies [43,308], which are reviewed, below.

Two signaling cascades receiving increased attention is the recognition that, similar to many growth factor receptors, BnR activation stimulates numerous tyrosine kinase cascades and the recognition that many of the growth related effects of BnR's, especially in neoplastic

tissues, are mediated by transactivation of the epidermal growth factor receptor (EGFR) [31,95,128,129,138,183,223,229,231,297,340,347]. Studies on normal and neoplastic tissues demonstrate that stimulation of all three BnRs can result in potent stimulation of focal adhesion kinases (p125FAK, PYK-2); MAPK kinases especially ERK; EGFR; Src kinases; and paxillin [31,95,128,129,138,183,223,229,231,297,347]. In addition studies demonstrate that various BnRs can stimulate tyrosine phosphorylation of $p130^{cas}$; or stimulate phosphorylation resulting in alteration of PI3K-Akt signaling; activation of p90RSK1 and p70s6K [32,129,234,280]. Transactivation of the EGFR by BnRs has been shown to be an important signaling cascade mediating growth effects of these receptors on a number of different neoplasms including cancers of the lung (especially nonsmall cell tumors), head and next squamous cells, neuroendocrine cells and the prostate [70,129,138,223,229,231,297,347,394]. In a number of studies the transactivation of EGFR by BnRs has been shown to involve activation of phospholipase C, Src kinases, stimulation of matrix metalloproteinases and shedding of EGF-related ligands, as well as the stimulation of reactive oxygen species [70,223,229,231].

VI. BnR function in normal tissues (Table 2)

GRP and NMB primarily function as neurotransmitters or, neuromodulators, in addition to functioning in an autocrine and paracrine manner in both normal tissues and in neoplastic tissues often as growth factor [99,129,138,139,145,325]. The latter area will be dealt with in the next section.

In older studies numerous Bn related peptides in both animal and human studies were reported to have a wide range of activities involving almost every normal tissue of the body including endocrine, respiratory, gastrointestinal, immune, urogenital, hematopoietic, and skeletal, CNS, spinal cord, and peripheral/enteric nervous system. To a large degree these have been summarized in previous publications [68,128,129,129,192,245,376] and will not be reviewed in detail here. With the development of selective receptor tools such as selective antagonists, studies with selective agonists, and the ability to investigate the BnR involved in various responses using molecular approaches (receptor knockout animals, antisense, etc), it has became possible to identify which BnR is mediating different responses. This is an important issue because in early studies, frequently bombesin was used, or another amphibian peptide, such as ranatensin or litorin, and in most cases these were subsequently found to have high affinity for both GRPR and NMBR's [201,355], which occur together in many tissues. Therefore it was not really possible to establish exactly which subtype was mediating a given response. An additional problem in regard to assessing the actions of Bn peptides and their receptors in either physiological or pathophysiological processes is that their effect can either be due to direct action on the target tissue or due to an indirect action by releasing other GI hormones and neurotransmitters. Both NMB and especially GRP have been found to be potent stimulants of a large number of other gastrointestinal hormones/ neurotransmitters (Table 2) [66,90,129,212].

In the case of a number of physiological, as well as pharmacologic responses, it is now clear which BnR subtype mediates the responses and some are briefly summarized in Table 2 and briefly commented on below. These conclusions come from studies of receptor knockout

mice: the correlation of binding studies with biologic responses; the use of specific antagonists, especially for the GRPR or the use of selective agonists such as GRP or NMB [129,246,247,355]. The use of BRS-3 specific knockout mice has proved particularly valuable for giving insight into this receptor in physiological or pathophysiological conditions because until recently no selective agonist or antagonist existed for this receptor.

As can be seen in Table 2 both GRPR and NMBR have been established to mediate a large number of physiological/pharmacological responses in the nervous system (CNS, spinal cord, peripheral nervous system) as well as in almost every peripheral tissue. The information for BRS-3 is more limited because of the lack of pharmacological tools until recently and the lack of identify of its native ligand, but it is increasing recently. As many of these actions have been covered in recently reviews [95,128,129,139,192,245,376] only a few specific areas will be commented on here.

It has long been reported that bombesin has an effect on satiety and pharmacological studies using selective agonists and antagonists suggested that GRPR and likely also the NMBR mediated these effects [129,161,171]. Studies using targeted disruption of the GRPR, NMBR and BRS-3 demonstrate that all three BnR subtypes have a role in satiety and energy homeostasis [129,161–163,249,259]. Mice with GRPR disrupted demonstrated an increase in meal size consistent with a satiety signaling deficit [47,161,163]; those with NMBR knockouts initially had no effect on food intake or satiety found [247], however in a more recent study [259] they were found to have resistance to the development of diet induced obesity: and finally mice with BRS-3 disrupted developed obesity, hypertension, impaired glucose metabolism and insulin resistance [208,249]. This was accompanied by a reduced metabolic rate, hyperphagia and increased feeding efficacy, increased meal size, and alterations in glucose transport [129,161,162,193,208,243]. Studies show that mice, human rhesus and dog all have high expression of BRS-3 in the islets [82]. Using siRNA to BRS-3, and a selective agonist (Bag-1) or specific antagonist (Bantag-1)[82], activation of BRS-3 was found to have an important effect on insulin secretion in response to hyperglycemia and therefore to be important in regulating insulin secretion. Studies suggest that BRS-3 has important effects on both adipose tissue [243] and skeletal muscle (myocytes) [94,279,280]. In BRS-3 knockout mice markedly impaired stimulated glucose uptake in adipose tissue is found due to inactivity of the GLUT4 transporter [243]. BRS-3 was found to be down regulated in myocytes of obese patients, patients with diabetes mellitus or patients with both disorders [94,279,280] and myocytes from patients with the two altered metabolic states alone or together, had increased sensitivity to BRS-3 stimulated glucose uptake [94,279,280]. In addition to these peripheral effects of BRS-3 in glucose/energy metabolism, BRS-3 in the CNS is expressed in neurons containing orexin, a peptide particularly important in mediating satiety and feeding behavior [87], and was also expressed in cells surround the CNS orexin neurons [87]. In studies of cell function, BRS-3 agonists increase cytosolic calcium in many of these cells and in the orexin neurons [87], as well as causing depolarization and increased firing of the orexins neurons. The authors concluded that with CNS BRS-3 receptor activation, indirect inhibition of orexin neurons occurs though a GABAergic input as well as direct activation of orexin neurons [87]. This led the authors [87] to suggest that that pharmacological alteration of the activity of the BRS-3 pathway could be a novel approach to treatment of obesity [87].

One of the earliest assays of biological activity of Bn-related peptides was the ability to cause contraction of smooth muscle from all tissues examined [38,75,77,129]. It is now clear that GRPR and NMBR mediate smooth muscle contractile effects in both the gastrointestinal, urogenital and respiratory tracts (Table 2). In general, GRPR activation is primarily responsible for muscle contraction of gastric antrum and fundic; small intestinal; gallbladder, pulmonary tract, some functions the urogenital tract such as ejaculation and in meditating the descending phase of the peristaltic reflex (Table 2). In contrast in the esophagus and urogenital tract activation of the NMBR is particularly important for smooth muscle contraction, and in the colon, both GRPR and NMBR are important in mediating smooth muscle contraction (Table 2). These functional results are consistent with limited data from receptor localization studies which show a high density of NMBR in the esophagus [365,366] and urogenital tract, whereas high densities of GRPR receptors are found in the both circular and longitudinal muscle layers of the gastric antrum and fundus, ileum and on neural elements in the myenteric plexus of these regions [21,133,221,233,310,364]. There are no functional studies on BRS-3 related to motility, but in PCR studies BRS-3 mRNA has been detected in stomach, small intestine and colon in two studies [273,310] but not in others [248]. However, by immunocytochemical analysis in all regions of the GI tract examined (antrum, duodenum, ileum and colon), BRS-3 was localized in both nerves sand in non-neuronal cells [273]. In the enteric nervous system, BRS-3 was detected in both myenteric and submucosal ganglia and in fibers distributed in the longitudinal and circular muscle layers [273]. In this study [273] BRS-3 was detected in cell bodies and processes of the c-kit interstitial cells of Cajal, which throughout the gastrointestinal tract are considered as the pacemaker cells that initiate electrical rhythmicity and which lead the authors to propose that BRS-3 could be involved in regulating gastrointestinal motility [273]. With the recent availability of BRS-3 selective agonists and antagonists, this can now be studied. In addition to their ability to alter motility functioning as a peripheral neurotransmitter, studies also demonstrate activation of CNS BnR’s; primarily GRPR can have prominent motility effects as well as secretory effects in the gastrointestinal tract [175,274,330]. These include, with intraventricular distraction of Bn, increases in tonic and phasic gastric pressure [330], slowed gastric emptying and small intestinal transit, increased colonic transit [274], alteration of the migratory motor complex [107], inhibition of biliary secretion and gastric acid secretion [344]. Similar effects are reported with intraventricular distraction of GRP, suggesting GRPR mediation, for acid secretion [175,344,345] and inhibition of gastric empting [175].

Each of the three BnR subtypes are widely distributed in the CNS and spinal cord, and a large number of studies now establish the each of these has important actions as a central neurotransmitter/neuromodulator in both normal functions (Table 2) and in pathological disorders (Table 3). The latter category is discussed briefly in the next section. Particularly revealing has been the result from the studies of mice with targeted disruption of one of the three Bn receptor subtypes.

Disruption of each of the three receptors results in prominent behavioral effects, which differ in the three different receptor knockout animals [387]. GRPR knockout mice demonstrate elevated spontaneous activity, and increased nonaggressive social responses [367,370,387]. In addition they have altered olfactory related behavior not due to a defect in

olfactory sensation, but probably due to altered GRPRs in the medial preoptic area [387,388]. In contrast to NMBR and BRS-3 knockout mice, GRPR mice showed no alterations in emotion anxiety testing [387,388]. NMBR knockout mice differ from BRS-3 mice in showing no changes in the taste preference test or in social interaction assessing nonaggressive or aggressive social response [247,387]. In an emotion/anxiety testing, NMBR knockout mice showed no defect in anxiety but showed the opposite change from BRS-3 animals with a significant decrease in risk assessment behavior [384]. In contrast, BRS-3 deficient mice show changes in the taste reference test including elevated preference for sweets, and increased aversion for bitterness, while they had a decreased nonaggressive social response [383,387]. They also showed decreased spontaneous activity in isolated conditions that usually lead to increased activity [387]. In contrast, to the GRPR and NMBR knockout animals, which showed no alteration in anxiety tests, BRS-3 knockout mice exhibited reduced levels of anxiety [384]. These results suggest that the three BnR subtypes are involved in different behavior processes.

Numerous recent studies report both GRP and NMB are important spinal neurotransmitters [7,120,306,337]. This is particularly true in pathological states where increasing evidence supports a prominent role for BnR's in mediating pruritic stimuli [128,150,336–338,377,396]. In the spinal cord GRP in the dorsal root ganglion neurons activates GRPR to play an essential role in mediating nonhistaminergic impulses due to itch, however in histaminergic itch responses it plays a minor or negligible role [6,150,337]. However, recent studies [335,336,396] provide support for the involvement of both GRPR and NMBR in mediating pruritic responses. Intracerebroventricular injection of GRP or NMB causes an itching scratch response [335] as does intrathecal injections of either GRP or NMB [336]. In both cases [335,336] the itch responses for GRP or NMB are inhibited by a specific GRPR antagonist or NMBR antagonist, respectively providing support for the involvement of both BnR subtypes in mediating pruritic behavior [335,336]. Studies of mice with the combination of GRPR KO and NMBR KO show significant defects in response to histaminergic itch providing support for both classes of receptors in mediating pruritic responses. Additional studies support the conclusion that glutamate acts as a neurotransmitter for GRPR-sensitive and insensitive pruritic synaptic transmission in the spinal cord [150], that the mu-opioid receptor (MOR) isoform, MOR1D can heterodiamerize with GRPR in the spinal cord to mediate pruritic responses [184], MrgprA3 expressing neurons co-expressing GRP and MRgprC11 are important in mediating chloroquine – induced itching [181] and that descending serotonin neural pathways facilitate the GRPR itch signal via 5-HT1 receptors to augment itch specific output and that disruption of this interaction markedly attenuate itch transmission [395]. Recent studies also provide strong support for the importance of GRPR functioning as a spinal neurotransmitter in functions of the urogenital tract. GRPR activation in the spinal cord is required for ejaculation and penile erections in male rats [153,306,346] and in female rats administration of GRPR or Bn results in the contraction of the female urethra [278].

VII. BnR function in disease and a therapeutic target (Table 3)

BnR's possible role in a number of diseases was briefly discussed in the previous section and has been dealt with in number of reviews [95,128,129,193,377] so only a few areas will

be briefly covered here. Also some aspects of BnR's as a possible therapeutic target in different areas (Table 3) will be briefly covered here.

As discussed in an earlier section many tumors overexpress BnR's (See Table 2), particularly GRPR [78,114,128,137,191,287,308,358,391]. This is not an uncommon event, for example, GRPR is overexpressed in >70% of cancers of the lung (small and nonsmall cell type), breast, prostate, exocrine pancreas, head and neck squamous cell, and glioblastomas [129,137,287]. NMBR and BRS-3 are less frequently overexpressed, but some tumors particularly overexpress these [137,287]. For example, 67% of nonsmall lung cancer cells and almost 50% of intestinal carcinoids have overexpressed NMBR, whereas 25–35% of bronchial carcinoids and small cell lung cancers have BRS-3 overexpressed [137]. Furthermore, GRP and NMB have been shown to have autocrine growth effects on many of these tumors; being synthesized and secreted from the tumor as well as the tumor possessing GRPR or NMBR so that the secreted product can feedback and stimulate growth [129,137,138,156,224]. Recent studies demonstrate that one of the principal signaling pathways used by NMBR and GRPR to stimulate tumor growth is by transactivating of the epidermal growth factor receptor (EGFR) in the tumor membrane, a cascade that requires activation of phospholipase C, mobilization of cellular calcium and stimulation of PKC as well as activation of SRC kinases, stimulation of matrix metalloproteinase, with membrane shedding and release of EGF related peptides and the generation of reactive oxygen species [70,138,223,229]. The elucidation of this signaling cascade has raised the possibility of blockade of this cell signaling mechanism at numerous points including receptor blockade could interrupt autocrine tumor growth (Table 3) [53,129,139,183,186,224,229,334]. Studies in a number of different tumors have shown that the combination of a GRPR or NMBR receptor antagonist with an EGFR tyrosine kinase inhibitor can have a potentiating effect on tumor death [138,223,229,348].

The overexpression of BnR's on so many common tumors, often which have a poor prognosis in patients with extensive disease, has led to considerable interest in the possibility of using the BnR overexpression not only to localize the tumor, but also to deliver cytotoxic agents (Table 3) [195,196,308,315,391]. Both aspects of this approach are now widely used for the localization and treatment of neuroendocrine tumors (NETs) overexpressing somatostatin receptors [30,159]. ^{111}In- or ^{68}Ga-labeled somatostatin analogues are now the method of choice to assess the localization of the primary NET and an extent of disease, with the use of ^{68}Ga labeled somatostatin analogues with positron emission tomographic imaging (PET imaging) now shown to be the most sensitive imaging method available [30,130,159]. Furthermore, numerous studies report that ^{177}Lu- or ^{90}Y-labeled somatostatin analogues are effective at treating patients with advanced NETs [30,130,159] and this has led to a prospective phase 3 study that is now being performed in patients with advanced, malignant small intestinal NETs. Unfortunately somatostatin receptors are not over-expressed by many of the more common malignant tumors, but as discussed above, BnRs are frequently overexpressed by these tumors. Therefore, this has generated considerable interest in the possibility that a similar approach to that used in NETs with somatostatin analogues, can be used with Bn analogues in these more common malignant tumors for both their localization as well as treatment of advanced disease [195,196,308,315,391].

At present >200 studies have reported results investigating a wide range of Bn/GRP related analogues coupled to primarily radiolabeled compounds to image BnR overexpressing tumors either with or without PET imaging or for use for targeted peptide receptor mediated radiotherapy (PRRT) resulting in cytoxicity (Table 3) [15,129,178,195,196,308,315,391]. A number of these studies reported excellent imaging of the BnR overexpressing tumors as well as cytotoxicity in other cases [15,129,195,196,308,315,391]. Almost all of these studies were in animals or were in vitro studies and initially all were performed with BnR agonist analogues to allow internalization [195,196,276,308,315,391]. Recently it has been reported than radiolabeled BnR antagonists give higher uptake and better imaging, and thus have the potential to deliver more cytotoxic agent to the tumors, and thus in the future, may play a more prominent role than radiolabeled agonist for both imaging and PRRT [43,91,196]. A few studies have reported results of pilot studies using various radiolabeled BnR analogues in small numbers of patients with cancers of the breast, prostate, gastrointestinal stromal tumors and colonic cancer [16,64,71,143,205,308,318,319,359]. In general these studies show promising results but the number of patients studied was small, detailed comparisons to other imaging modalities were not frequently done, and possible changes in management by this method were not assessed, therefore at present the value of this methodology is unclear. In prostate cancer, there is particular interest in possible BnR imaging/cytotoxicity, because of its frequent overexpression of BnRs, and limited imaging modalities available [196,308,315]. Preliminary studies in patients with different extents of prostate cancer indicate that GRPR-binding radiopharmaceuticals are likely to be useful in early stage disease prior to androgen therapy and not in late disease stages [143,205]. In addition to radiopharmaceuticals, BnR ligands have been coupled to other compounds to enhance imaging as well as to other potentially cytotoxic compounds [308]. The former include coupling Bn analogues to iron oxide nanoparticles for enhancing sensitivity of magnetic resonance imaging [125,204], to various fluorescent molecules which can be used for in vivo imaging [41,173,187,222] or to nanorods containing a photoacoustic imaging moieties [108]. Potentially cytotoxic compounds include coupling Bn analogues to chemotherapeutic agents [camptothecin [88,227,232], doxorubicin [240,241,258], paclitaxel [303,304]]; marine toxins [230]; to diphtheria toxin [360]; to mitochondria-disruptive peptides [40]; to agents that activate polyclonal T lymphocytes [398]; coupled to other immunotherapeutic agents that lead to cell death [48,49]; to photosensitizers [73,73,236,282] and to siRNA or adenoviral delivery vectors[116,242,308,374,375,375]. In addition BnR agonists have been one of the main targeting agents coupled to various nanoparticle carriers to assess delivery [44,342] or for targeted delivery of various cytotoxic agents including chemotherapeutic agents [docataxel [157], doxorubicin [1,3]]; radiolabeled analogues [140]; or gold nanoparticles [45]. Similarly various BnR agonists have been coupled to liposomes or micelles for target delivery of various cytotoxic agents including chemotherapeutic agents [4], radiolabeled compounds [2] or various cytotoxic Au-coupled compounds [289].

Manipulation of BnRs could potentially have an important therapeutic role in obesity, food intake and energy/glucose metabolism (Table 3) [129,193,214,215,279,370,386,387]. This has occurred because of the demonstrated role of each of the three human BnRs, the GRPR, the NMBR and BRS-3, in regulating satiety, with evidence from both receptor knockout studies [163,249,259,370,387] and from pharmacological studies using Bn receptor agonists

and antagonists [50,161,169,170,311]. Recent studies with BRS-3 have particularly highlighted this area for potential therapeutics. BRS-3 knockout mice developed obesity, hypertension, and hyperphagia, reduced metabolic rate, and metabolic disturbances [82,243,249]. These changes are associated with the hyperinsulinemia and an impaired insulin response to hyperglycemia, [208], development of leptin resistance [189], hyperleptinemia [189], overexpression of melanocortin (MC) receptors in the hypothalamus as well as an enhanced MCH hyperphagia response [189]. Furthermore, BRS-3 animals have impaired glucose uptake in adipose tissue due to abnormality of GLUT4 [243]. These results are supported by studies using siRNA to BRS-3, or specific BRS-3 agonists or antagonists which demonstrate BRS-3 plays an important role in insulin release to hyperglycemia, rising the possibility that not only does it have a potential role in obesity, but also in diabetes mellitus [82]. This conclusion is further support by studies showing BRS-3 has important effects on both adipose tissue [243] and skeletal muscle (myocytes) [94,279,280] which are important in metabolic/glucose homeostasis. In BRS-3 knockout mice markedly impaired stimulated glucose uptake in adipose tissue is found due to inactivity of the GLUT4 transporter [243]. BRS-3 was found to be down regulated in myocytes of obese patients, patients with diabetes mellitus or patients with both disorders [94,279,280] and myocytes from patients with the two altered metabolic states alone or together, had increased sensitivity to BRS-3 stimulated glucose uptake [94,279,280]. The potential to treat obesity with BnR agonists is supported by recent studies using BRS-3 selective agonists/antagonists [102,103]. In mice BRS-3 selective agonists (Bag-, Bag-2) [102] increased metabolic rate and reduced food intake and body weight, whereas a BRS-3 antagonist (Bantag-1) increased food intake and body weight. In a second study [103] the selective nonpeptide BRS-3 agonist, MK-5046, inhibited food intake in mice and increased metabolic rate in wild type mice but not BRS-3 knockout mice. In rats and dogs MK-5046 also reduce body weight and caused a modest increase in body temperature, heart rate and blood pressure [103]. Recently [206,207] in order to attempt to decrease the side-effects possibly due to CNS penetration with MK-5046, potent BRS-3 agonists which are chiral diazepine analogues, have been developed which have low CNS penetration, (analogues 9f, 9g) and high affinity for the BRS-3 receptor(Table 1). It is proposed [206,207] to study their effect on body weight in animals but at present there is no data available to determine their effectiveness or possible side effects. A number of genetic studies using genotyping, direct sequencing, linkage studies and genomic wide scanning have been performed looking for associations of Bn peptides or BnR's with obesity or eating behaviors [35,36,51,117,270,329]. In these studies mutations in the BRS-3 were not found to be a major cause of obesity in Japanese [117] and a neuromedin beta polymorphism was associated with obesity, weight change and/or eating behavior changes [35,36,270,329].

Chronic pruritus is a very common ailment occurring in 25% of geriatric patients and 7% of a general population [357,390]. Itching is distinct from pain and is mediated both by C-fibers and thinly myelinated Aδ nerve fibers [182,350,377] As reviewed in an earlier section, numerous studies now provide strong support for the conclusion that an itch specific circuitry exists with Mas-related G protein coupled receptors (MrgprA3) expressing primary sensory neurons innervating the epidermis and their central zones connect in GRPR expressing neurons in the superficial spinal cord [128,182,346,377]. GRP is expressed in a

subset of dorsal root ganglion (DRG) neurons [337] and activation these neurons is important in mediating especially nonhistaminergic impulses due to itch, playing either a minor or negligible role in mediating histaminergic responses [6,150,337]. Recent studies [335,336,396] show both GRPR and NMBR spinal neurons are involved in mediating pruritic responses. Other recent studies showing glutamate acts as a neurotransmitter for GRPR-sensitive and insensitive pruritic synaptic transmission in the spinal cord [150]; that the mu-opioid receptor (MOR) isoform, MOR1D can heterodiamerize with GRPR in the spinal cord to mediate pruritic responses [184] ; MrgprA3 expressing neurons co-expressing GRP and MRgprC11 and are important for mediating itch [181] and that the GRPR itch signal acts via 5-HT1 receptors to augment itch specific output [395]. All of these studies show the central important of activation of GRPR, and to a lesser extent NMBR, in mediating pruritic responses in various pathological and disease states, raising the possibility that blockade of this pathway either alone or in combination with other recently recognized co-neurotransmitters mediating the itch response, can result in a new approach to treatment (Table 3).

As reviewed in the previous sections many studies including using receptor localization methods, receptor knockout mice, pharmacological studies using BnR selective agonists or antagonists, antisense constructs, and behavioral studies, all provide evidence that each of the three BnRs are widely present in the CNS and have wide ranging effects. Because of this, it has been proposed that BnRs especially the GRPR, could be a promising target in various CNS disorders, such as autism, cognitive disorders, schizophrenia, dementia and well as neurological disorders such those involving memory, neuroprotective effects during stroke, and in the treatment of CNS tumors, especially gliomas or neuroblastomas (Table 3) [129,291–294]. In some cases alterations in GRP or GRPR have been found in patients with neurodegenerative, psychiatric or neurodevelopment disorders or in brain tumors to support these proposals [291,294]. Gliomas and neuroblastomas are included in this list of proposed targets because studies demonstrate that they frequently overexpress GRPR (85–100%), GRPR activation has a growth stimulatory effect and inhibition of GRPR inhibits their proliferation [72,79,84,85,85,137,138,271,339]. At present there are no prospective clinical studies that have established the value of targeting BnRs in these diseases.

It has been proposed that BnRs (particularly the GRPR) would be a good molecular target for the treatment of inflammatory disorders [264,266,389]. This proposal was made because Bn- related peptides and/or activation of BnRs has been shown to play an important role in various inflammatory processes. Evidence supports a role for Bn related peptides and their receptors in a wide spectrum of inflammatory processes including gastritis [263,264,266,288], uveitis [260,264,266], arthritis [98,100,10,251,252,264,266], small intestinal or colonic inflammation [5,12,104,264,266], experimental sepsis [52,61,264,266,267], acute lung inflammation and injury [59,65,264,266,266,341] and gastrointestinal inflammation [10,151,264,266]. These studies suggest BnRs plays different roles in these processes because in some inflammatory processes Bn/GRP is protective and ameliorates the damage from various noxious agents in the stomach, small intestine and in the colon [5,9,12,104,264,266,284], whereas in other inflammatory conditions of the colon or lung, either Bn/GRP stimulate the inflammation or Bn/GRP antagonists ameliorate the inflammation [59,62,65,260,264,266,341,382]. In the latter case a number of studies support

the conclusion that activation of GRPR due to increased release of bombesin like peptides from pulmonary neuroendocrine cells is a common denominator for a number of lung diseases, particularly those associated with decreased alveolarization, including both bronchopulmonary dysplasia and emphysema [59,65,266,341]. One area that has received particularly attention is the ability of Bn/GRP to improve side effects of total parenteral nutrition (TPN). These including reversing TPN's impairment of upper respiratory tract immunity [126]; preventing the atrophy of Peyer's patches and dysfunction of M cells [86]; preventing the decrease in salivary gland adaptive immunity; [269]; preventing the decrease in intestinal lymphocyte population and reversing decreases in CD4+ and CD8+ T cells as well as small intestinal IgA levels [176]: reversing the decrease in both respiratory and intestinal IgA levels as well as maintaining lamina propria IL-4 levels and memory B cells [89,141,392] and preserving immunity to bacterial pneumonia [69]. At present there are no controlled studies, which have established the clinical value of altering BnR activity in any human inflammatory disease.

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Abbreviations

βAla	βAlanine
Bantag-1	selective BRS-3 peptide antagonist
Bn	bombesin
BnR	bombesin receptor
BRS-3(BB3)	bombesin receptor subtype 3
COOH terminus	carboxyl terminus
CCK	cholecystokinin
CNS	central nervous system
Cpa	chlorophenylalanine
DAG	diacylglycerol
EC1	extracellular domain 1
ERK	extracellular regulated kinase
EGFR	epidermal growth factor receptor
fBB4	frog bombesin receptor subtype 4
GRP	gastrin-releasing peptide
GRPR	gastrin-releasing peptide receptor (BB2)
GPCR	G protein-coupled receptor

5-HT	serotonin, 5-hydroxytryptamine
IC1	intracellular domain 1
IR	immunoreactivity
MK-5046	selective nonpeptide BRS-3 agonist
NMB	neuromedin B
NMBR	neuromedin B receptor (BB1)
NMC	neuromedin C
NSCLC	nonsmall cell lung cancer cell
PKC	protein kinase C
PKD	protein kinase D
PLC	phospholipase C
TM	transmembrane region
SP	substance P
ψ bonds	pseudopeptide bonds
$p125^{FAK}$	p125 focal adhesion kinase
Stat	statine
TPA	12-O-tetradecanoyl-phorbol-13-acetate

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Highlights

- During Prof Kastin's editorship 5% of articles related to bombesin (Bn) peptides
- In this Festschrift we review our studies and latest advances by others
- Advances in pharmacology, cell biology, patho- and normal physiology are reviewed
- With new ligands, molecular studies their role in many processes is being clarified
- Particularly important is possible roles in imaging/treating tumors, pruritus, obesity

Table 1

Affinity of human BnR subtypes for various agonist/antagonists.

Variable	Affinity (nM)		
	hNMBR (BB_1)	**hGRPR (BB_2)**	**hBRS-3 (BB_3)**
I. Natural occurring Agonist[a]			
GRP	148	0.19	>3,000
NMB	0.052	35	>3,000
NMC [GRP(18–27)]	37	0.14	>3,000
Bombesin (Bn)	2	0.07	>3,000
II. Synthetic Agonists[a]			
[D-Phe^6, β-Ala^{11}, Phe^{13}, Nle^{14}] Bn $_{6–14}$	0.21	0.048	1.3
[D-Phe^6] Bn $_{6–14}$	1.3	0.17	>3,000
[D-Tyr^6, (R)-Apa^{11}, Phe^{13}, Nle^{14}] Bn $_{6–14}$[b]	160	110	8.2
[D-Tyr^6, Apa-4Cl^{11}, Phe^{13}, Nle^{14}] Bn $_{6–14}$[b]	590	258	2.8
Ac-Phe,Trp, Ala, His,(tBzl),Nip,Gly,Arg-NH_2[b]	>10,000	>10,000	63
MK-5046 [c]	>10,000	>10,000	18
Compound 9G [d]	>10,000	>10,000	70
Compound 9D [d]	>10,000	>10,000	121
II. Antagonists[d]			
[D-Phe^6] Bn $_{6–13}$ methyl ester	>10,000	4	5300
[D-Tpi^6, Leu^{13}, Leu^{14}, ψ13–14]$Bn_{6–14}$ [RC3095]	870	1	>10,000
PD 168368	0.51	1700	>10,000
PD 176252	0.53	170	>3,000
D-Nal, Cys,Tyr,D-Trp,Lys,Val,Cys,Nal-NH_2	2500	605	340
[[Tyr^4, D-Phe^{12}] Bn $_{6–14}$	3100	912	>10,000
[Leu^{13}, ψ13–14, Leu^{14}]$Bn_{6–14}$	>10,000	8	>10,000
[D-Phe^6, Leu^{13},Cpa^{14}, ψ/13-14]$Bn_{6–14}$	>10,000	1	>10,000
(3Ph-Pr^6),His^7, D -Ala^{11}, D -Pro^{12}, ψ13–14, Phe^{14}]Bn(6–14)(BW2258U89)	5,000	0.23	7,000

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Variable	Affinity (nM)		
	hNMBR (BB_1)	**hGRPR (BB_2)**	**hBRS-3 (BB_3)**
[D-Arg[1], D-Trp[7,9], Leu[11]]substance P	>4,500	1,800	>10,000
Bantag-1 [b]	>10,000	>10,000	1

[a] Data are from [28,93,198–201,234,299,301,355]

[b] Data are from [199–201]

[c] Data are from [234]

[d] Data are from [281]

Abbreviations : Ac, acetyl; Apa, 3-amino,propionic acid; Apa-4Cl, 4-chloro,3-amino,propionic acid; Bantag-1, Boc-Phe-His-4-amino-5-cyclohexyl-2,4,5-trideoxypentonyl-Leu-(3-dimethylamino) benzylamide *N*-methylammonium trifluoroacetate; Cpa, chlorophenylalamine, GRP, gastrin-releasing peptide; His(tBzl), histidine(tBenzl); MK-5046, (2S)-1,1,1-trifluoro-2-[4-(1H–pyrazol-1-yl)phenyl]-3-(4-[[1-(trifluoromethyl)cyclopropyl] methyl]-1H–imidazol-2-yl)propan-2-ol; Nip, piperidine-3 carboxylic acid; Nal, β-napthylalanine; Orn, ornithine; ψ; pseudopeptide bond, (*i.e.*, CONH changed to CH_2NH); Ph-Pr, phenylpropanolamine ; PD176252, (3-(1H–Indol-3-yl)-N-[1-(5-methoxy-pyridin-2-yl)-cyclohexylmethyl]-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide); PD168368, (3-(1H–Indol-3-yl)-2-methyl-2-[3(4-nitro-phenyl)-ureido]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; SP, substance P; Tpi,2.3.4.9-tetrahydro-1H–pyrido[3,4-b]indol-3carboxylic acid); (9g), [(5R)-4-([3-(2-methylpropoxy)phenyl]acetyl)-8-(trifluoromethyl)-2,3,4,5-tetrahydro-1H–pyrido[2,3-e][1,4]diazepin-5-yl]acetic acid [207]: 9D [207].

Table 2

Bombesin rector subtype mediating various physiological/pharmacological responses to Bn analogue

CNS	**GI tract**
Satiety factor-GRPR[105,163,367], NMR [167,170,171,259], BRS-3 [162,249,384]	**Stomach** Acid secretion- GRPR[112,316]
	Gastric emptying-GRPR [66]
Thermoregulation-GRPR [19,163], NMBR[247], BRS-3 [172]	Gastric fundic contraction-GRPR[115,168,216,247,296], Gastric smooth muscle cells-GRPR, NMBR[321] Mucosal cells –GRPR [83]
Behavior effects(fear, memory, locomotor activity, social behavior, anxiety)-GRPR[324,367,388], NMBR[22,385], BRS-3 [102,383,384,387]	Somatostatin release from D-cells -GRPR[312,316]
	Esophagus
Regulation of Circadian rhythm-GRPR [144,211] Induce hyperglycemia-GRPR[123,272],BRS-3 KO mice develop glucose intolerance [249]	Longitud. Muscle contraction NMBR [131,216,366]
Spinal cord neurotransmitter-GRPR, NMBR[84,128,336,396]	**Pancreas**
	Enzyme secretion GRPR[113,136,365]
Peripheral Nervous system	Insulin secretion-(GRPR-[262], BRS-3 KO Inc insulin [208,249]
Peripheral neurotransmitter-NMBR, GRPR[99,220,378]	Growth- GRPR-[129,177]
	Pancreatic duct fluid /electrolyte secretion-[343]
Hormone release	
CCK-GRPR[66,113]	
GLP1-GRPR [261]	**Small intestine**
Gastrin-GRPR [97,115,129,212,313,361], NMBR[149]	motility GRPR [66,99,216],BRS-3 [273] ion transport-GRPR [46]
Glucagon-GRPR[149,268]	Muscle contractility-GRPR [152,216,356]
Somatostatin-GRPR[115,312,316], NMBR[188]	
Enteroglucagon [149]	**Colon**
Insulin-GRPR[113,149,261,361],NMBR [149]	Electrolyte transport-GRPR[351]
GIP -GRPR [97,361]	Colon mucosal membranes-GRPR[221,244]NMBR [209]
Pancreatic polypeptide GRPR[113,361]	Colonic motility, Peristalsis-GRPR[99], muscle contraction-GRPR,NMBR [34]
PYY GRPR [361]	**Gallbladder contraction**
Neurotensin-GRPR[295]	GRPR [66,113,265,283,296,314], NMBR [253,254]
Satiety factor-GRPR[105,163,367], NMR [167,170,171,259], BRS-3 [162,249,384]	
Endocrine	**Other systems**
Thyroid TSH gene regulation/function-NMBR[250]	**Pulmonary**
	Fetal lung development/growth-GRPR, NMBR [322]
Hypothalmic-Pituitary Release LH,GnRH-NMBR[37] Potentiate ACTH secretion by CRF in pituitary cells-GRPR[17] Prolactin/ growth hormone release from pituitary cells-GRPR[118]	Contraction peripheral airways –GRPR[160] Stimulation of ventilation-GRPR [142]
Adrenal	

CNS	**GI tract**
Intracerebroventricular Bn's increase plasma catecholamines by activation of sympatho- adrenomedullary axis –GRPR [323]	
Immune/Hematopoietic	
Chemoattractant effect on monocytes, macrophages, neutrophils lymphocytes-GRPR [60,67]. Stimulate phagocytic cells-GRPR[63]. Stimulate macrophage IL-1 release-GRPR[174]	**Nasal mucosal secretion** GRPR, NMBR [11]
Endocrine	**Bone**
Thyroid TSH gene regulation/function-NMBR[250]	Proliferation of osteoblasts-NMBR [305]
Hypothalmic-Pituitary Release LH,GnRH-NMBR[37] Potentiate ACTH secretion by CRF in pituitary cells-GRPR[17] Prolactin/ growth hormone release from pituitary cells-GRPR[118]	**Urogenital tract**
Adrenal Intracerebroventricular Bn's increase plasma catecholamines by activation of sympatho-adrenomedullary axis –GRPR [323]	Electrolyte transport across endometrium-GRPR [363] Ejaculation/male sexual function-GRPR [153,306]
Immune/Hematopoietic	Urinary bladder membranes/muscle-–NMBR [33,190,296], GRPR [190]
Chemoattractant effect on monocytes, macrophages, neutrophils lymphocytes-GRPR [60,67]. Stimulate phagocytic cells-GRPR[63]. Stimulate macrophage IL-1 release-GRPR[174]	Ejaculation/male sexual function-GRPR [153,306]

Table 3

BnR function in disease and/or as possible therapeutic target.

1.	**Tumor imaging [GRPR>NMBR, overexpressing tumors]** (prostate, lung, colon, breast, pancreatic, had neck squamous cell, neuroblastomas, glioblastomas) [78,114,128,137,191,287,308,358,391]
2.	**BnR Targeted treatment of tumors overexpressing BnRs with cytotoxic BnR agonists/antagonists(GRPR>NMBR)** [78,114,128,137,191,287,308,358,391][Radiolabeled or other agonists or antagonists coupled to other cytotoxic agent]
3.	**BnR antagonists as antitumor agents** [95,120–122,137,138,203]
4.	**Obesity, satiety disorders** (GRPR>NMBR, BRS-3)[50,161,192,193,215,249,386]
5.	**Treatment of pruritic disorders (GRPR>NMBR**)[8,95,106,158,328,333,346,377]
5.	**Target for psychiatric/neurological disorders** [129,291–294]
6.	**Target for inflammatory disorders** [264,266,389]