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Bombesin-Related Peptides and their receptors:

recent advances in their role in physiology and disease states

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Abstract

Purpose of review—Mammalian bombesin-related peptides, gastrin-releasing peptide(GRP) and neuromedin B(NMB) actions are mediated by two receptors (BB_1-,BB_2-receptor), which are closely related to the orphan receptor BRS-3(BB_3-receptor).The purpose of this review is to highlight advances in the understanding of these peptides in physiology/disease states.

Recent Findings—Pharmacologic/receptor-knockout studies showinvolvement of these receptors in a number of new processes/diseases. NMB/BB_1-receptor is an important physiological regulator of pituitary-thyroid function; in mediating behavior, especially fear/anxiety; in mediating satiety through different cascades than GRP/BB_2 receptors and for its autocrine tumor-growth effects. GRP/BB_2-receptor plays important roles in: mediating signals for pruritus; lung development/injury; small intestinal mucosal defense and CNS processes such as learning/memory. The signaling mechanisms of its potent growth effects are being elucidate and possible therapeutic targets identified. BB_3-receptor knockout mice provided insights for their obesity/glucose intolerance and demonstrate this receptor may be important in the lung response to injury, tumor growth and GI motility. Each receptor is frequently over-expressed in human tumors and have potent growth effects. This effect is being explored to develop new anti-tumor treatments, such as Bn-receptor ligands conjugated to cytotoxic agents.

Summary—This receptor family are involved in an increasing number of CNS/peripheral processes physiologically and in disease states, and increased understanding of their role may lead to novel treatments, especially for pruritus, CNS disorders, lung diseases and tumor localization/treatment.

Keywords

Bombesin; gastrin-releasing peptide; neuromedin B; BRS-3; tumor growth; satiety; TSH release; tumor imaging; obesity; peptide receptor mediated cytotoxicity

I. Introduction

The bombesin family of peptides received their unusual name because bombesin (Bn) and most of the subsequent other invertebrate members of this family were originally isolated from frog skins and they were named after the genus of the frog [1,2,3••] they were isolated from (i.e.

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Bn the European frog Bombina bombina). Bn is a tetradecapeptide with a COOH terminus ending in Gly-His-Leu-Met-NH_2 and subsequently was shown to closely resemble two mammalian Bn-related peptides, gastrin-releasing peptide (GRP) and neuromedin B (NMB). GRP is a 27 amino acid peptide originally isolated from porcine stomach, which shares the same seven COOH terminal amino acids with Bn, accounting for their similar biological activities. NMB is a decapeptide isolated from porcine spinal cord, which is similar to the frog peptide ranatensin, having a COOH terminus ending in Gly-His-Phe-Met-NH_2 [1,2,3••]. The human GRP-encoding gene is on chromosome 18q21, the NMB gene on chromosome 15q11 and they encode for 148 and 117 amino acid precursors, respectively. Studies of GRP and NMB immunoreactivity as well as their mRNA demonstrate these peptides are widely distributed in mammals in both the central nervous system and peripheral tissues, especially in the gastrointestinal (GI) tract. In the GI tract GRP is found primarily in neurons as well as submucosal and myenteric plexi with the highest amounts in the colon and small intestine. NMB is found throughout the GI tract, but is generally lower than GRP. In the CNS GRP is widely distributed in neurons with high levels in the forebrain, hypothalamic nuclei as well as sensory nuclei, whereas NMB is most abundant in the olfactory bulb, dentate gyrus and dorsal root ganglia [3••].

II. Mammalian Bn receptors

Three classes of closely related receptors comprise the mammalian Bn family of receptors: a 384 amino acid GRP-preferring receptor (called GRPR or BB_2-receptor), a 390 amino acid NMB-preferring receptor (NMBR or BB_1-receptor) and a 399 amino acid orphan receptor termed bombesin-receptor-subtype-3(called BRS-3 receptor or BB_3-receptor), which has 47-52% homology with the GRPR and NMBR [3••]. The natural ligand of the BRS-3 receptor is unknown and does not appear to be closely related to any known Bn-related peptide because this receptor in all species characterized (human, guinea pig, rat, sheep, mouse) has low affinity for all natural Bn-related peptides [3••,4]. Each of these receptors is a G protein-coupled receptor, which signal primarily through phospholipase C-mediated cascades, but also stimulate tyrosine phosphorylation of a number of signaling proteins, but in most tissues do not activate adenylate cyclase [3••]. The human BB_1-receptor gene is at chromosome 6p21-pter, the BB_2-receptor gene is at Xp22 and the human BB_3-receptor gene is at Xq25 [3••].

Expression levels of these receptors have been studies in numerous species [3••] and in one detailed study in monkeys [5] the highest levels of the BB_1-receptor were in the testis and stomach as well as in the CNS including the amydala, caudate nucleus, hippocampus, hypothalamus, thalamus, brain stem and spinal cord. In monkeys [5] the highest levels of the BB_2-receptor are in the pancreas, with lesser amounts in the prostate, stomach and skeletal muscle. In the monkey CNS the BB_2-receptor is widely distributed with the highest amounts in the hypothalamus, basal ganglia and lateral olfactory tract nucleus. In the monkey [5] the BB_3-receptor is found in the greatest amount in the testis and CNS with the distribution more restricted than the BB_2-receptor, but with high amounts of the BB_3-receptor in the hypothalamus, followed by the pituitary gland, amydala, hippocampus and caudate nucleus. In the rat GI tract using specific BB_3-receptor antibodies [6], the BB_3-receptor was detected in myenteric and submucosal ganglia and in the interstitial cells of Cajal, which led the authors to propose it may play an important role in GI motility.

The BB_1-receptor has greater than a 100-food higher affinity for NMB than GRP, whereas the BB_2-receptor has a greater than 50-fold higher affinity for GRP than NMB [3••]. Bn has relatively high affinity for both the BB_1-receptor and the BB_2-receptor, therefore many of the older pharmacological studies, both in vitro and in vivo, which usually used Bn as the agonist, provide limited information about the subtype of Bn receptor involved [3••]. Whereas BB_3-receptor has low affinity for all natural occurring Bn-related peptides, a synthetic Bn ligand,

[D-Tyr^6, β-Ala^{11}, Phe^{13}, Nle^{14}] bombesin $_{6-14}$, has been described [7] which has high affinity for the human and monkey BB_3-receptor and this peptide or its analogues are being widely used to study the presence of the BB_3-receptor, as well as other Bn receptors in human tissues by autoradiographic methods [8,9,10•]. This synthetic peptide has the unique property of having high affinity also for the BB_1-receptor and BB_2-receptor from all species. However, recently, using detailed structure-function studies of this ligand, a few selective BB_3-receptor agonist have been described which may prove useful to study its role in physiology and disease processes [11-13]. A number of classes of high affinity receptor antagonists are described for the BB_1-receptor, but only a few with lower affinity exist for the BB_1-receptor and none for the BB_3-receptor, which could be useful to explore their roles in normal and pathologic conditions [3••]. Because of the lack of good antagonists for all classes of these receptors, mice with targeted deletion of one of these receptors are being increasingly used to assess their roles in physiological and pathologic states.

Both GRP and NMB contain a COOH terminal amide that is essential for high affinity interaction [3••]. However, recently a number of studies have provided evidence that non-amidated precursor forms of GRP stimulate proliferation and migration of human colorectal cancer cells [14-16] through a novel receptor, which is at present uncategorized.

III. Bn peptides and their receptors. Recent advances

III.A. General

In the following sections specific advances with GRP/ BB_2-receptor, NMB/ BB_1-receptor and BB_3-receptor will be covered separately, except in the areas of satiety, antitumor treatment and imaging which will be considered together.

III.B. GRP/ BB_2-receptors -Recent advances

GRP and stimulation of BB_2-receptors are known to cause a broad spectrum of pharmacological and biological responses [3••]. These include stimulation of smooth muscle contraction in the GI/urogenital tract with profound effects on motility and GI peristalsis [3••,17], potent effects on immune cells, stimulation of secretion and hormone release including insulin (gastric, pancreatic, colon, endocrine organs), potent growth effects on normal and neoplastic tissues [18••,19••], and potent CNS effects including regulating circadian rhythm [20,21], thermoregulation, anxiety [22•], satiety [3••] and various behavioral features [22•]. Recent advances in the effect of GRP in cancer and satiety will be discussed in a latter section.

Recent studies suggest an important role for GRP/ BB_2-receptor in a number of new areas including mediation of pruritus [23••], lung development and lung diseases [3••,24,25,26••, 27], small intestinal mucosal defense/prevention of injury [28] and various CNS processes including memory. In a recent study [23••] evidence was presented that activation of the BB_2-receptor in the dorsal spinal cord is important for mediating pruritus. GRPR knockout mice showed significantly decreased scratching behavior in response to pruritogenic stimuli, while other responses were normal. Furthermore, administration of a BB_2-receptor antagonist into the spinal fluid inhibited scratching behavior in three different models of itching [23••]. The authors [23••] point out the BB_2-receptor may represent the first molecule identified that is dedicated to mediating the itch response in the spinal cord and may provide an important therapeutic target for the treatment of chronic pruritic conditions. GRP/BB_2-receptor activation is proposed to be important in normal lung development and in mediating the lung injury in premature infants with bronchopulomonary dysplasia (BPD) [3••,24,25,26••,27]. In one recent study [27] GRP given to newborn mice induced features of human BPD including interstitial pulmonary fibrosis and alveolarization. In a hyperoxic baboon model of BPD [26••] the early overproduction of Bn-like peptides correlated with the development of BPD-like histologic

features and the blockage of GRP partially reversed these effects, leading the authors to suggest such an approach could have important implications for preventing BPD in premature infants. GRP has been shown to be protective to the small intestine in various injury models, enhance gut barrier function, prevent the atrophy of enteric ganglia caused by FK506 in small bowel [29-32] and in a recent study [28] to prevent the atrophy of Peyer's patches and dysfunction of M cell in rabbits receiving long-term parenteral nutrition. These studies suggest GRP agonists may have a potential therapeutic role in diseases causing this type of injury. Numerous studies in rodents provide evidence that GRP/ BB_2-receptor activation is important for memory as well as a number of social behaviors (learning, grooming, stereotypy) [22•,33]. These results were supported by a recent study [34] in which the administration of BB_2-receptor antagonists in neonatal rats resulted in marked impairment of memory, and social interaction. These changes have led one group [22•] to propose that the BB_2-receptor should be consider a therapeutic target in a subset of human CNS diseases, especially those involving memory, learning and fear.

III.C.NMB/ BB_1-receptors -Recent advances

NMB and activation of BB_1 receptors are known to stimulate the contraction of GI/urogenital smooth and alter GI motility [3••], to potently inhibit thyrotropin release from the pituitary acting as an autocrine and paracrine regulator [3••,35], have potent CNS effects including on satiety [3••,36•], thermoregulation [3••], mediating stress and fear responses and other behaviors such as spontaneous activity [3••,37,38]. The effects on satiety and tumor growth will be considered in a separate section below. In a recent study [39••] using BB_1-receptor knockout mice, the importance of NMB as a physiological regulator of pituitary thyroid axis function and gene expression was confirmed. In this study [39••] BB_1-receptor activation was found to be important for thyrotroph gene regulation and function with its activation leading to a state where TSH release is facilitated, especially in response to TRH. In two recent studies [40•,41] in rats using various Bn receptor antagonists, evidence was provide that BB_1-receptor activation affects both anxiety and fear responses, while the BB_2-receptor affected the fear response and it was proposed that antagonists to the BB_1-receptor as well as the BB_2-receptor might represent a novel class of anxiolytic agents.

III.D.BB_3 receptors-Recent advances

Because there are no specific antagonists to this receptor, the synthetic agonist, [D-Tyr^6, β-Ala^{11}, Phe^{13}, Nle^{14}] bombesin $_{6\text{-}14,}$ is a nonselective agonist for this receptor and the natural ligand is unknown, the clues to its possible role in physiological and pathological processes have come from studies of BB_3-receptor knockout mice or from proposals from localization studies of the receptor [3••]. The initial study of BB_3-receptor knockout mice [42] reported the mice had mild obesity, hypertension and impairment in glucose metabolism, which were associated with increased feeding behavior and increased leptin levels. A subsequent study showed these knockout mice have a 2.3 fold increase in insulin levels and the impaired glucose metabolism is mainly due to impaired GLUT4 translocation in adipocytes [43]. Another study demonstrated increased levels of the melanin-concentrating hormone(MCH) receptor and pre-pro-MCH in the hypothalamus of BB_3-receptor knockout mice and its was proposed this may trigger the hyperphagia. Other studies demonstrated these animals have altered behaviors including modulating anxiety [3••,44].

Recent studies demonstrate that BB_3-receptor containing cells are expressed in developing and fetal lungs, the expression is increased in response to injury, such as after inhalation of ozone, and this results in proliferation of bronchial epithelial cells [3••,45,46]. A recent study demonstrates [46] that ozone simulates AP-2 alpha and PPARalpha to increase the activity of the BB_3-receptor gene promoter leading to increased BB_3-receptor expression. An additional insight into a possible role for the BB_3-receptor in the GI tract came from a recent receptor

localization study [6] where the BB_3-receptor was found in highest densities in myenteric/submucosal ganglia and in the C-kit interstitial cells of Cajal. The authors to proposed it may be involved in regulating motility, because of the known pacemaker function of these cells.

III.E.BB receptors-Recent advances-Satiety

Numerous studies have demonstrated that the three Bn receptor subtypes are involved in satiety [3••,47]. Evidence from some studies suggest activation of these receptors can have direct and indirect effects on satiety cascades, because bombesin can block the orexigenic effect of ghrelin [47,48] A recent study [36•] demonstrates that BB_2-receptor's satiety effects are mediated through different peripheral neural pathways than the BB_1-receptor -mediated satiety. This conclusion was reached because only BB_1-receptor's satiety effects were inhibited by capsaicin suggesting an involvement of primary sensory afferent pathways only in the BB_1-receptor pathway [36•]. A recent study [49] demonstrates that NMB is expressed in both human and rodent adipose tissue and is regulated by changes in energy balance. It is proposed [36•] that because of NMB's know anorectic effect centrally, this association may form a part of a new adipose tissue-hypothalamic axis regulating food intake. The importance of BB_3-receptor in satiety was discussed above on the section dealing with this receptor.

III.F.BB receptors-Recent advances-Tumor growth/differentiation

Activation of each of the Bn receptor classes can have growth effects in both normal and neoplastic tissues [3••,18••,19••]. Furthermore, Bn receptors are one of the most frequent receptor classes that are overexpressed/ectopically expressed by human cancers [8,18••,19••, 50,51]. Both NMB and GRP have been shown to have autocrine growth effects in a number of human tumors including tumors of the lung, head and neck, CNS, pancreas, prostate and colon [3••,18••,19••]. In addition activation of BB_2-receptors can have pro-angiogenic effects [3••,52]

Recent studies provide evidence that activation of each of the Bn receptor family can have growth-promoting effects in some tumors [3••,18••,19••]. Recent studies demonstrate in some tumors the growth effects of BB_2-receptor activation are mediated by transactivation of the EGF receptor, which is dependent on Src-mediated cleavage and release of TGF-α and amphiregulin with stimulation of the PI3K pathway [3••,53,54•,55]. However, detailed studies of the effect of ectopic expression of the BB_2-receptor and GRP by human colon cancers provide evidence in this tumor their primary effect is to function as a morphogen or differentiating factor rather than as a mitogen or growth-stimulating factor [56], This morphogenic effect is mediated by activation of $p125^{FAK}$, which enhances cell attachment and is caused by upregulation of ICAM-1 [57,58].

Studies of the growth effects of Bn-related peptides on human tumors using Bn receptor inhibitors either alone or with other agents [3••,55,59-62] demonstrate prominent inhibition of tumor growth in many cases, resulting in the proposal that these compounds either alone or with other anti-tumor treatment could be used as a possible novel therapeutic approach [3••, 59,63]. Recently a phase I trial of a BB_2-receptor antagonist, RC-3095 was reported in patients with advanced solid tumors [64•]. No toxicity was seen and no objective responses were seen, however the targeted plasma level was not achieved even with dose-escalation, and it was proposed newer drug delivery systems would need to be developed to fully evaluate this approach.

III.G.BB receptors-Recent advances-Tumor imaging and receptor-targeted cytotoxicity of tumors

The overexpression/ectopic expression of Bn receptors by human tumors is being investigated to use in their localization and to target cytotoxic agents [3••,18••,63,65,66•]. This approach

is now widely used clinically with many neuroendocrine tumors using ^{111}Indium-labeled somatostatin analogues [67•] and is also being used with promising results for cytotoxic treatment of patients with advanced malignant neuroendocrine tumors using ^{111}Indium, ^{90}Yttrium or ^{177} Lutetium-labeled somatostatin analogues [67•,68]. Unfortunately, many common tumors lack somatostatin receptors, however they possess Bn receptors. Therefore the development of labeled Bn analogues for imaging or targeted cytotoxicity is a very active area of investigation at present. Numerous radiolabeled [^{111}Indium, ^{68}Gallium, ^{177} Lutetium,^{64}Copper, ^{86}Yttrium, ^{18}F, ^{99m}Tc] GRP analogues with enhanced stability that bind with high affinity to BB_2-receptors are reported, as well as there ability to image various human tumors in vivo using gamma detectors or PET imaging [10, 69-77]. In some preliminary studies in humans, tumors were imaged in the majority of patients, and in some cases, tumors were detected using radiolabeled Bn analogues that were not seen on other commonly used imaging modalities [75,78-80]. At present no study has established the value of imaging using radiolabeled Bn analogues.

A number of Bn analogues coupled to radiolabeled compounds [^{177}Lutetium] [69,70,81,82•] as well as to cytotoxic agents (camptothecin-a topoisomerase inhibitor, doxorubicin analogues, paclitaxel) [65,66•,83-85,86•,87,88] have been described which retain high affinity for Bn receptors. They are internalized by Bn-receptor-bearing tissues and are being evaluated for the possibility of delivering Bn-receptor mediated tumoral cytotoxicity. Many of these compounds have been shown to cause tumor cytotoxicity in animal studies and one study has provided evidence that it is due to specific interaction with the BB_2-receptors overexpressed on the tumor [66•]. At present it is unclear whether this approach will be effective in vivo in human tumors whether alone or in combination with other anti-tumor treatments.

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