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**Bombesin**

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Gene symbol: [GRP](#)

**1. General Information**

Peptides of the bombesin family were first isolated from frog skin in the early 1970s. Bombesin, a 14 amino acid peptide was isolated from the skin of the amphibian *Bombina bombina* (**Figure 1**) by Vittorio Erspamer and colleagues, in Parma, Italy.



**Figure 1.** *Bombina bombina* also known as the European fire-bellied toad. Image from [en.wikipedia.org](https://en.wikipedia.org).

Its amino acid sequence was determined and it was shown to contain blocked amino and carboxyl terminals (1). Related peptides termed alytensin, ranatensin and litorin were isolated from other frogs (18). In the 1980s bombesin like peptides

were identified in mammals. The first mammalian bombesin like peptide was isolated from pig gastric tissue and named gastrin-releasing peptide (GRP) because it had a potent action to release gastrin (53). GRP is a 27 amino acid peptide and results from the processing of a 148 amino acid precursor (85). Other subsequently identified related mammalian molecules include Neuromedin B (NMB) isolated from porcine spinal cord (54, 62) and Neuromedin C (NMC) also isolated from pig spinal cord (55) but which is now known to be GRP 18-27 (37). Bombesin, GRP, and NMC share a common carboxyl terminal sequence as shown in **Table 1**. NMB has a different precursor and one amino acid difference in the consensus heptapeptide. Using cDNA cloning the frog bombesin precursor was shown to contain 107 amino acids (76). The precursor contained a signal peptide sequence and one copy of bombesin followed by a typical processing site. The mammalian peptides GRP and NMB also have a similarly structured prohormone.

**Table 1**

1	14	
pGlu—Glu—Arg—Leu—Gly—Asn—Glu	—Trp—Ala—Val—Gly—His—Leu—Met—NH <sub>2</sub>	Bombesin
—Met—Tyr—Pro—Arg—Gly—Asn—His	—Trp—Ala—Val—Gly—His—Leu—Met—NH <sub>2</sub>	GRP
Gly—Asn—His	—Trp—Ala—Val—Gly—His—Leu—Met—NH <sub>2</sub>	NMC

**Table 1. The entire structure is shown except for GRP which has 27 amino acids (the first 13 amino acids are not shown).** The GRP sequence shown is for human, pig, and dog. The other bombesin related peptides have similarity but not identity to the carboxy-terminal sequence.

Bombesin family members are neuropeptides that are broadly located in the CNS and peripheral nervous system especially the parasympathetic nerves. They have also been shown to be present in organs such as the pancreas, urinary bladder, and uterus and in the enteric nervous system where their cell bodies are present in the myenteric plexus. Bombesin and bombesin like peptides (BLP) in the GI tract regulate gastric acid and pancreatic secretion. In the stomach, GRP is the most potent known stimulator of gastrin release in dogs and humans and thereby stimulates gastric acid secretion (6). Bombesin also stimulates CCK release (9, 19) as well as directly regulating pancreas cells as described later. BLPs also stimulate smooth muscle contraction in the intestine, stomach, and gall bladder. They can also regulate uterine and ureter contraction. In all these actions BLPs act in concert with other regulatory systems and are in some cases species dependent.

In the CNS, BLPs are located in specific neurons. BLPs play roles in satiety, thermoregulation, energy balance, circadian rhythm, and behavior (26, 75). A recent important discovery is the role of GRP neurons in the dorsal horn of the spinal cord in relaying the itch response to the brain (67, 73). Another interesting site is the participation of NMB in the sighing response of the respiratory system (46).

**Bombesin Receptors**

Mammals express three types of bombesin receptors all of which are 7 transmembrane cell surface receptors and signal through heterotrimeric G proteins of the Gq family. Properties of these receptors as determined by ligand binding and molecular cloning are only summarized here but have been reviewed extensively in several publications (26, 37, 42, 73, 75). The most common type is the GRP-R or BBR-2 which responds with high affinity to bombesin, GRP and NMC and was first characterized by the high affinity binding of radioiodinated bombesin to pancreatic acini and brain membranes (38, 57). The second is the NMB-R which responds preferentially to NMB and was originally described in the rat esophagus (92). The third type is an orphan receptor without a known natural ligand identified by homology and termed bombesin receptor subtype 3 (BRS-3) that is present in brain, muscle and islet beta cells and may play a role in glucose homeostasis (21). A fourth receptor has been described in amphibian brain (58). Agonists, antagonists, and radioligands have been identified for the three mammalian receptors and reviewed (37, 75). The receptors appear to internalize agonist peptides but not antagonists although the functional importance of this is unclear. Receptors can also be desensitized and internalized. Bombesin receptors are increased on many tumor cells, and this has been used for ligand imaging and to deliver chemotherapeutic agents particularly in prostate cancer (4, 70). Further properties of the GRP-R and its actions will be

considered as studied using pancreatic acinar cells.

## 2. Bombesin and the Pancreas

In the pancreas, endogenous GRP, the mammalian equivalent of bombesin is primarily located in neurons. Immunofluorescence has localized it to preganglionic vagal fibers, pancreatic ganglia and in beaded neurons running between acini (13, 24, 40, 56, 83). The pig however, was the only species to have a high concentration of immunoreactive GRP in the pancreas (56). Using rat pancreatic lobules, GRP was shown to stimulate acetylcholine release and about half of the effect on amylase release was blocked by neuronal or ganglionic blockers (23). This suggests GRP may act both on neurons and acinar cells. Studies in the pig have shown that electrical stimulation of the vagus nerve releases GRP and its active fragment, GRP (18-27) both in vivo and in the perfused pancreas (40, 41). Furthermore, bombesin receptor antagonists inhibited secretion induced by vagal stimulation by 33% (33). Thus, in the pig, GRP plays a role in endogenous pancreatic secretion although the role in other species may be less.

### Pancreatic Enzyme Secretion

Early studies indicated that bombesin administration could stimulate pancreatic secretion in a variety of species including humans, dogs, rats and guinea pigs (2, 5, 14, 34, 59, 66, 91) with the biggest effect being on digestive enzyme secretion. Subsequent studies showed a similar action induced by mammalian GRP and NMC. Moreover, a prominent role was found in the perfused pig pancreas (41). Bombesin peptides also stimulated gastrin, CCK, and acetylcholine release (5, 9, 19, 52). The secretion induced was enzyme rich and poor in bicarbonate. Thus, an initial question was whether bombesin stimulated the pancreas directly or through a neural or hormonal intermediate. However, studies using antrectomized dogs to remove gastrin, CCK antagonists, and atropine have shown in multiple

species including humans that the effect of bombesin was primarily direct (2, 30, 31, 47). This was confirmed by the finding of specific bombesin receptors on human pancreatic membranes (82), isolated rodent pancreatic acini (38, 98) and pancreatic AR42J cells (48, 84). The major form in the pancreas is the GRP-R also known as the BB<sub>2</sub> receptor (63). In its native state this receptor on mouse acini is an 80 kDa glycoprotein (36). A number of bombesin receptor antagonists have also been developed most of which are modified bombesin peptides some having a reduced peptide bond (12, 29, 93). One of the most potent is [D-Phe<sup>6</sup>]BN-(6-13) ethyl ester with a K<sub>i</sub> of 5nM to inhibit pancreatic amylase secretion stimulated by bombesin. The use of a specific receptor antagonist has shown that bombesin stimulation through these receptors does not play a role in meal stimulated digestive enzyme secretion in vivo (91).

### Actions of Bombesin on isolated pancreatic acini

Even after the discovery of mammalian GRP, bombesin continued in common use for the study of cellular mechanisms using isolated acini because of its ready availability. Bombesin and related peptides showed a slight biphasic dose response with reduced ability to stimulate in vitro amylase release from isolated guinea pig acinar cells at supramaximal concentrations; maximal secretion was observed at 100 nM (51, 88). Similar results but with maximal secretion at 100 pM were seen in mouse acini (35). By contrast in rat acini, bombesin induced a monophasic dose response with a maximal response at 1 nM (50, 60). Thus, there is a difference from CCK stimulation which induces a pronounced biphasic dose-response curve in all species studied. Stimulation of amylase release by bombesin and GRP has also been reported from human isolated acini (86).

Bombesin activated IP<sub>3</sub> and diacylglycerol production and intracellular calcium release in rodent acini (15, 50, 72). Thus, bombesin activates signaling pathways through heterotrimeric G<sub>q/11</sub>

protein similar to CCK although by different receptors. Other actions of bombesin shared with CCK have included activation of protein synthesis mechanisms, protein tyrosine kinases, Src family kinases, PKC, calcineurin, phospholipase A<sub>2</sub>, p125FAK, ERK, JNK, p70 S6K, eEF2K, PAK2 and PAK4, and downregulation of c-Met (7, 10, 32, 39, 60, 61, 74, 78-80). Other differences between bombesin and CCK on acini are that bombesin induces less damage and ER stress (43). In some studies, bombesin is used as an alternative agonist to show that an event is not initiated by a single receptor (8). Other studies have looked at the properties of bombesin receptors to internalize bombesin (98), their ability to induce residual stimulation (35), to desensitize (50), and to be regulated by CCK (97).

### **Bombesin and Experimental Pancreatitis**

Bombesin by itself does not induce experimental pancreatitis in vivo or acinar cell damage in vitro in contrast to what is produced by caerulein (71, 96). Bombesin increases the activation of intracellular trypsin and the processing of procarboxypeptidase A1 in isolated acini (25). However, the activated enzyme was secreted from the cell following bombesin stimulation thus plausibly explaining the lack of cell damage (25). By contrast, when bombesin stimulation was combined with pancreatic duct obstruction, retention of active enzymes and pancreatitis resulted (65). Another difference from caerulein is that bombesin failed to activate NF- $\kappa$ B (28).

### **Pancreatic Ductal Secretion**

There is some evidence that bombesin peptides can influence the ductal secretion of fluid and electrolytes. This is somewhat species dependent, and in most cases may not be of physiological importance. Most bombesin immunoreactive neurons in the pancreas are located near acinar cells with a lesser innervation of ducts (83). Injection of bombesin can stimulate fluid secretion especially in rats and guinea pigs (2, 66). Most directly, bombesin stimulates fluid secretion by

isolated rat and guinea pig ducts and this effect is blocked by a GRP-R antagonist (3, 87). The maximum rate of secretion in response to bombesin was similar to the response to secretin or CCK. While the machinery is present to support secretion there is little evidence that this occurs physiologically. There is no published data that a GRP-R antagonist or gene deletion of the receptor reduces pancreatic juice secretion except for a partial effect in the pig.

### **Trophic Function of Bombesin Peptides**

In addition to stimulating pancreatic enzyme and ductal secretion, bombesin injection stimulates the growth of the pancreas in both adult and newborn rodents (44, 69, 89, 90). Both hyperplasia (increased cell number) and hypertrophy (increased cell size) have been reported. Exogenous GRP also has effects similar to bombesin (11). Bombesin administration can release CCK but blocking CCK action does not reduce the bombesin-induced pancreatic growth (81). In addition, bombesin can preserve exocrine pancreatic function that is reduced in parenteral nutrition (68). Bombesin can also stimulate the mRNA and protein content of specific digestive enzymes (77) and increase polyamine synthesis (89).

Bombesin can also stimulate cell growth pathways in primary cultures of rodent acinar cells (45) and activate expression of early response genes in isolated rat acini (49). However, the importance of bombesin as a trophic factor for the exocrine pancreas is unclear, similar to effects on physiological secretion discussed earlier as bombesin stimulation activates growth pathways normally activated by CCK. Deletion of GRP or its receptor has not been reported to alter pancreatic size.

Bombesin like peptides can also affect the growth of pancreatic cancer cells. This has been studied the most in pancreatic cancer derived cell lines. Similar to effects in some lung cancer, bombesin can act as an autocrine stimulator in cell lines such

as Mia PaCa-2 and HPAF (17, 95) although it inhibits growth of H2T cells (20). Pathways involved in growth stimulation include tyrosine kinases, tyrosine phosphatases and MAP kinases (16, 17). However, in a study localizing bombesin receptors in distinct tissue compartments, bombesin receptors were not found in the tumor tissue of pancreatic cancer although they were found in chronic pancreatitis (22). Thus, the role of bombesin in pancreatic cancer requires further study.

### 3. Tools to study bombesin and GRP

#### a. Synthetic Peptide

Bombesin can be obtained from multiple sources including Sigma-Aldrich, Research Plus, Bachem, Anaspec and Abbtotec.

#### b. Antibodies

Antibodies against bombesin are available from Genway and Phoenix Pharmaceuticals.

#### c. ELISA and RIA

An RIA kit for GRP is available from Phoenix Pharmaceuticals. An ELISA kit against Bombesin is available from My BioSource and against mouse GRP from Antibodies-online.

#### d. Antagonists

Peptide antagonists against the Bombesin receptor are available from Sigma-Aldrich and Tocris. One of the most potent against the GRP-R is [D-Phe<sup>6</sup>] BN-(6-13) ethyl ester.

#### e. Gene deleted mice

Preparation of GRP-R gene deleted mice have been reported (27, 94). Mice have also been prepared with the NMB-R gene deleted (64).

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