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Bombesin and its family of peptides: prospects for the treatment of obesity ☆

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Abstract

Bombesin, its family of bombesin-like peptides, and many other peptides/hormones modulate biological and behavioral functions in animals. Among the wide variety of functions influenced by bombesin/bombesin-like peptides, the most prominent may be their role in feeding-related behavior. Over many years, intensive psychopharmacological studies have addressed the mechanisms by which these peptides induce feeding suppression, and the results suggest the applicability of bombesin/bombesin-like peptides for the treatment of eating disorders and/or obesity in humans. Recent studies using gene-knockout mice also shed new light on the relationship between bombesin/bombesin-like peptides and feeding behavior. In addition, genetic analyses of the possible links between bombesin/bombesin-like peptides/receptors and human obesity have also been undertaken. Here, we briefly review the literature pertaining to the relationship between bombesin/bombesin-like peptides and feeding behavior—with particular attention to human subjects—and discuss the pharmacotherapeutic potential of bombesin/bombesin-like peptides with regard to obesity.

Keywords: Bombesin; GRP (gastrin-releasing peptide); GRP receptor; Bombesin BB_1 receptor; Bombesin BB_2 receptor; Bombesin bb_3 receptor; Feeding behavior; Obesity

1. Introduction

Bombesin was originally purified from the skin of the European frog *Bombina bombina* (Erspamer et al., 1970; Anastasi et al., 1971), while two bombesin-like peptides, gastrin-releasing peptide (GRP) and neuromedin B, were purified from mammalian tissues (McDonald et al., 1979; Minamino et al., 1983, 1988). These peptides exert their effects through G-protein coupled receptors such as the GRP receptor (bombesin BB_2 receptor, Battey et al., 1991), the neuromedin B receptor (bombesin BB_1 receptor, Wada et al., 1991; Ohki-Hamazaki et al., 1997a), or the bombesin receptor subtype-3 (bombesin bb_3 receptor, BRS-3; Fathi et al., 1993; Ohki-Hamazaki et al., 1997a). No specific endogenous ligand(s) have yet been identified for the bombesin bb_3 receptor. Table 1 summarizes the bombesin-like peptides and their antagonists.

Bombesin and bombesin-like peptides have a wide range of functions. These peptides promote cell growth, including that of carcinoma cell lines (Wiedermann, 1989; Lebacq-Verheyden et al., 1990; Johnson and Kelley, 1995), and are involved in smooth muscle contraction (Schjoldager et al., 1991; Battey and Wada, 1991) and the regulation of body temperature (Calisher and Avery, 1984; Itoh et al., 1995; Ohki-Hamazaki, 2000; Ohki-Hamazaki et al., 1999). Furthermore, bombesin/bombesin-like peptides mediate endocrine responses, such as the release of gastrin, cholesystokinin (CCK), and pancreatic polypeptide (Erspamer et al., 1974; Lu et al., 1986; Konturek, 1994). Similarly, psychopharmacological and other behavioral studies reveal that bombesin/bombesin-like peptides may elicit various behavioral responses. Exogenously administered peptides increase spontaneous activity, such as locomotion, grooming and scratching behavior (Schulz et al., 1984; Johnston and Meralli, 1988; Itoh et al., 1994), and regulate pain

☆ The animal experiments conducted in our laboratory were performed in strict accordance with the guidelines of the National Institute of Neuroscience, National Center of Neurology and Psychiatry (Japan), and were approved by the Animal Investigation Committee of the Institute.

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Table 1
Effects of bombesin-like peptides and antagonists on feeding behavior

		Note	References
Ligands			
BN		strongly suppress feeding	Gibbs et al., 1979
GRPs	GRP-(1–27)	strongly suppress feeding	Thaw et al., 1998
	GRP-(18–27)	alone: no effect on feeding	Thaw et al., 1998
	(neuromedin C)	combined with NMB-(23–32): positive effect on feeding	
NMBs	NMB-(1–32)	suppress feeding	Merali et al., 1999
	NMB-(2–32)	not determined	–
	NMB-(23–32)	no effect on feeding	Thaw et al., 1998
		effect on feeding	Merali et al., 1999
Antagonists			
[D-Phe^{12},Leu^{14}]BN		blocked BN-induced feeding suppression increased food intake	Heinz-Erian et al., 1987; Merali et al., 1988; Flynn 1991, 1993, 1997
[D-Phe12]BN		inhibited BN-induced amylase secretion	Heinz-Erian et al., 1987; Merali et al., 1988
[Tyr^4,D-Phe^{12}]BN		inhibited BN-induced amylase secretion	Heinz-Erian et al., 1987; Merali et al., 1988
[Leu^{14}, psi13–14]BN		increased food intake	Merali et al., 1993
[D-Phe^6]bombesin-(6–13)metyl ester		preferential GRP-R antagonist, increased food intake	Flynn, 1993; Stratford et al., 1995
[D-Phe^6]bombesin-(6–13)ethyl amid		blocked BN-induced feeding suppression	Flynn, 1997
BW2258U89		no effect on feeding	Stratford et al., 1995
		suppressed food intake as a partial agonist	Kirkham et al., 1995a
BIM23042		NMB-R > GRP-R, no effect on feeding	Flynn, 1993
BIM26226		specific GRP-R antagonist, increased food intake	Plamondon et al., 1998; Degen et al., 2001

BN: bombesin, GRP: gastrin-releasing peptide, NMB: neuromedin B, -R: receptor.

response (Pert et al., 1980; Cridland and Henry, 1992). Furthermore, post-training administration of bombesin and GRP can improve learning and memory (Flood and Morley, 1988; Williams and McGaugh, 1994; Rashidy-Pour and Razvani, 1998; Santo-Yamada et al., 2001). However, the most pronounced effect of bombesin/bombesin-like peptides is on the modulation of feeding behavior. Gibbs et al. (1979) first demonstrated that feeding behavior was suppressed in rats given exogenous bombesin. Thereafter, an intensive effort was undertaken to clarify the mechanisms by which bombesin/bombesin-like peptides control feeding behavior.

Here, we briefly review the investigations relevant to the mechanisms of bombesin/bombesin-like peptide-dependent control of feeding behavior, and discuss the pharmacotherapeutic potential of these peptides with respect to obesity.

2. Feeding suppression induced by bombesin/bombesin-like peptides

Feeding suppression by bombesin/bombesin-like peptides has been reported in a variety of species including humans. Peripheral and/or central administration of bombesin/bombesin-like peptides reduces meal size in a dose-dependent manner that is behavior-specific (e.g., meal size, licking behavior, meal pattern) in rats (see Gibbs et al., 1979, 1981; Martin and Gibbs, 1980) and other species (reviewed in Yamada et al., 2000b). Peripherally administered peptides affect food intake exclusively, whereas central administration affects both feeding behavior and spontaneous activity (e.g., increased grooming behavior, Masui et al., 1993). Moreover, food deprivation and subsequent re-feeding correlate with rapid changes in the concentration of GRP-like peptides that can be detected by immunoassay in the hippocampus and hypothalamus (Merali and Kateb, 1993). These results support the hypothesis that these peptides modulate satiety via the central as well as the peripheral nervous systems.

2.1. Effects of bombesin-like peptides and their antagonists on feeding behavior

The effects of bombesin/bombesin-like peptides, synthetic analogs, and their antagonists on feeding behavior are summarized in Table 1. Bombesin has a more potent effect on feeding than do GRP (Thaw et al., 1998) or neuromedin B analogs (Thaw et al., 1998; Merali et al., 1999). While neuromedin B/analogs alter food intake (Kirkham et al., 1995b; Ladenheim et al., 1994, 1996; Rushing et al., 1996; Thaw et al., 1998), their effects are less potent than GRP or bombesin (Ladenheim et al., 1994, 1996). Despite the effectiveness of full-length GRP (GRP-(1–27)) on feeding, the C-terminal decapeptide GRP-(18–27) (neuromedin C) fails to extend the inter-meal interval (Thaw et al., 1998). The neuromedin B analog neuromedin B-(1–32) is more potent than the C-terminal decapeptide neuromedin B-(23–32) (Merali et al., 1999). Suppression of feeding by neuromedin B-(23–32) is relatively weak, and the results for this

analog have not been consistent. Administration of neuromedin B-(23–32) alone fails to extend the inter-meal interval, but the combination of GRP-(18–27) and neuromedin B-(23–32) produces an intermediate prolongation of the interval (Thaw et al., 1998). The effect of neuromedin B-(2–32) (Minamino et al., 1988) on feeding has not yet been determined.

Specific receptor antagonists can attenuate the anorectic actions of exogenously administered bombesin-like peptides, and the blockade of bombesin receptors within the central nervous system (CNS) can induce a significant elevation in food intake. Analogs of bombesin were developed by substituting histidine-12 with D-amino acids, along with other substitutions ([D-Phe^{12}]bombesin, [D-Phe^{12}, Leu^{14}]bombesin, and [Tyr^{4}, D-Phe^{12}]bombesin; Heinz-Erian et al., 1987). Administration of these peptides inhibits bombesin-stimulated amylase secretion as well as the binding of bombesin to rat brain slices (Merali et al., 1988). Administration of [D-Phe^{12}, Leu^{14}]bombesin in the 4th ventricle blocks the bombesin-induced decrease in food intake (Flynn, 1991, 1997), and also enhances feeding in rats (Flynn, 1993). [Leu^{14}, psi13–14]bombesin also increases food intake in satiated rats (Merali et al., 1993). Similarly, administration of [D-Phe^{6}]bombesin-(6–13) methyl ester (Flynn, 1993; Stratford et al., 1995), the preferential antagonist for GRP receptor (binds GRP receptor > neuromedin B receptor), as well as [D-Phe^{12}, Leu^{14}]bombesin (Flynn, 1993) into the 4th ventricle enhances food intake. Flynn (1997) demonstrated that [D-Phe^{12}, Leu^{14}]bombesin (binds GRP receptor > neuromedin B receptor) and [D-Phe^{6}]bombesin-(6–13) ethyl amide (binds GRP receptor > neuromedin B receptor) attenuate the ability of bombesin to suppress food intake whereas BIM-23402 (somatostatin octapeptide analogue: D-Nal-*cyclo*[Sys-Try-D-Trp-Lya-Val-Cyc]-Nal-NH_2, binds neuromedin B receptor > GRP receptor) does not attenuate the ability of bombesin. These results suggest that exogenously administered bombesin may exert its effect on food intake primarily through GRP receptor (Flynn, 1997). Administration of BW2258U89 (GRP analogue: [(de-NH_2)Phe^{19}, D-Ala^{24}, D-Pro^{26} psi(CH_2NH)Phe^{27}]-GRP-(19–27)) in the 4th ventricle does not increase food intake (Stratford et al., 1995), but when administered peripherally attenuates food intake by acting as a partial agonist (Kirkham et al., 1995a,b). BIM26226 ([D-F_5Phe^{6} D-Ala^{11}]bombesin-(6–13) OMe); an octapeptide analogue of bombesin), a potent and specific GRP receptor antagonist, also facilitates feeding in rats (Plamondon et al., 1998); and further, this compound antagonizes the physiological function of endogenous GRP in human subjects (Degen et al., 2001).

2.2. Studies using knockout mice

There are two reports that employ bombesin-like peptide receptor knockouts to investigate feeding suppression in mice (Hampton et al., 1998; Ohki-Hamazaki et al., 1999). Intraperitoneal (i.p.) administration of GRP reduces the intake of glucose solution in wild-type mice but not in GRP-receptor-deficient mice (Hampton et al., 1998). On the other hand, neuromedin B-(23–32) (i.p.) does not suppress glucose solution intake either in wild-type mice or in neuromedin B receptor-deficient mice (Ohki-Hamazaki et al., 1999). Although the effect of neuromedin B-(23–32) on feeding behavior is relatively weak (Thaw et al., 1998; Merali et al., 1999), the lack of feeding suppression in both wild-type and neuromedin B receptor-deficient mice supports the hypothesis that bombesin-like peptides suppress feeding mainly via the GRP/GRP receptor pathway and that the neuromedin B/neuromedin B receptor pathway may be secondary in this respect (Flynn, 1997).

A major concern in studies of bombesin/bombesin-like peptides/receptors is that the action of exogenously administered peptides on satiety simply reflects a pharmacological effect (Gibbs, 1985). Although antagonists for bombesin-like peptide receptors promote food ingestion in some cases (see above), the contribution of endogenous bombesin-like peptides on the normal regulation of food intake remains unknown. However, studies using knockout mice provide new avenues for such research. Deficiency in one bombesin-like peptide receptor, either GRP receptor or neuromedin B receptor, does not affect daily/normal feeding (Wada et al., 1997; Ohki-Hamazaki et al., 1999; Yamada et al., 2000b). Furthermore, mice with double knockouts of GRP receptor and neuromedin B receptor also exhibit normal body weight even after a year of observation (Fig. 1). These results suggest that exogenously administered bombesin/bombesin-like peptides may not necessarily reflect the function of endogenous GRP/neuromedin B with respect to food intake. In contrast to the result for these single/double knockouts,

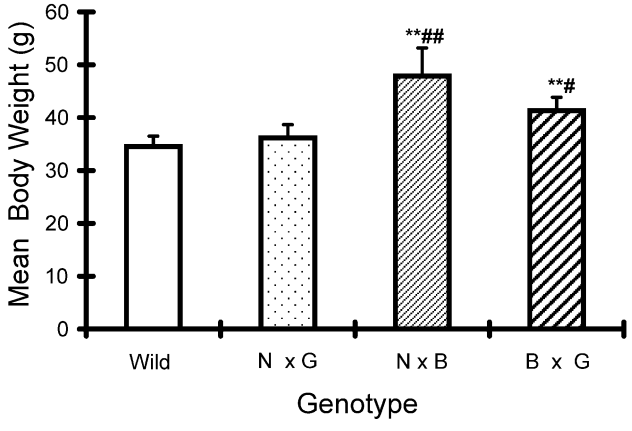

Fig. 1. Summary of the body weight of mice carrying double knockouts of bombesin-like peptide receptors. Body weight was measured as previously described (Yamada et al., 2000b). Data represent mean body weight + S.E.M. Wild: wild-type mice ($n=8$); N × G: neuromedin B receptor/GRP receptor double knockout mice ($n=8$); N × B: neuromedin B receptor/BRS-3 double knockout mice ($n=5$); B × G: BRS-3/GRP receptor double knockout mice ($n=10$). Symbols represent statistical differences compared to either wild-type mice (** $P<0.01$) or N × G mice (## $P<0.01$, # $P<0.05$). Statistical analyses were conducted using one-way ANOVA and Duncan's multiple comparison method.

BRS-3-deficient mice exhibit increased food consumption during daily/normal feeding (Ohki-Hamazaki et al., 1997b). This BRS-3 result suggests that the BRS-3 pathway may mediate the effect(s) of endogenous bombesin/bombesin-like peptides on the control of food intake, and that BRS-3 and its endogenous ligand(s) may function in a manner that is distinct from that of the GRP/GRP receptor and neuromedin B/neuromedin B receptor pathways. Although the efficacy of the bombesin-like peptide knockout strategy (and perhaps other peptide/hormone knockouts as well) in studies of the mechanisms of feeding behavior control has not yet attained broad consent (see Merali et al., 1999; Beck, 2001), this strategy may prove quite useful when used in conjunction with traditional experimental paradigms.

3. Mechanisms by which bombesin-like peptides induce feeding suppression

3.1. Motivational mechanisms of feeding suppression by bombesin-like peptides

The mechanisms by which bombesin/bombesin-like peptides affect feeding have been studied extensively. Still, the question of whether feeding suppression is induced by 'satiation' or 'aversion' after exogenous peptide administration has long been a subject of vigorous debate. Bombesin/bombesin-like peptides suppress the spontaneous feeding behavior of animals under a variety of experimental conditions including deprivation of food (see Kulkosky et al., 1982; Stuckey and Gibbs, 1982), administration of feeding-inducing drugs such as insulin, norepinephrine or neuropeptide Y (NPY) (see Levine and Morley, 1981a,b; Morley et al., 1982a,b, 1987), and/or stress stimuli (e.g., tail pinch) (see Morley and Levine, 1981; Morley et al., 1982a,b; Levine and Morley, 1981a,b). Bombesin/bombesin-like peptides also alter the meal patterns of animals (Stuckey and Gibbs, 1982; Flynn, 1991; Lynch and Babcock, 1993; Kirkham et al., 1995a,b; Rushing et al., 1996; Thaw et al., 1998). Results from these studies suggest that the termination of spontaneous feeding, the change in the meal pattern, and the decrement in the amount of food intake may be attributable to 'satiety.' When meals are terminated following peptide administration, animals show the normal behavioral sequence associated with postprandial satiety: they engage in non-feeding activities such as grooming and exploration, then rest or sleep (Smith and Gibbs, 1984). Further, animals terminate feeding soon after administration of bombesin-like peptides, but they eat or drink the same food(s) when it is presented in the absence of peptides. This result supports the tenet that feeding suppression observed after the administration of bombesin/bombesin-like peptides is not attributable to any sickness and/or adverse sensation caused by these peptides.

Several studies, however, report that aversive effects of bombesin/bombesin-like peptides may be responsible for feeding suppression (Vanderweele et al., 1985). The question of whether administration of bombesin/bombesin-like peptides may cause animal sickness has been addressed using a conditioned taste aversion (CTA) learning paradigm. Conditioned taste aversion is a potent learning mechanism that controls feeding behavior in animals and humans (Scarborough and McLaurin, 1961; Garcia and Koelling, 1967; Smith and Roll, 1967). Once an animal experiences sickness and/or nausea after ingesting a novel food or drink, they exhibit a strong avoidance of the same food/drink in the future (Garcia and Koelling, 1967). If bombesin/bombesin-like peptides cause sickness, then affected animals may undergo conditioned taste aversion. Several studies examined whether bombesin/bombesin-like peptides could bring about conditioned taste aversion, but results from these studies were not consistent relative to LiCl administration (Kulkosky et al., 1981; Deutsch and Parsons, 1981; Billington et al., 1983; Vanderweele et al., 1985; Flynn, 1989; Ervin et al., 1995). In our laboratory, we used GRP-receptor-deficient mice to examine whether GRP promotes conditioned taste aversion learning. If administration of GRP has any effect on conditioned taste aversion learning, then we would expect to observe different responses between GRP-receptor-deficient and wild-type mice since the knockout mice should not be affected by GRP. However, even though conditioned taste aversion was induced by LiCl in both GRP-receptor-deficient and wild-type mice (Fig. 2), conditioned taste aversion learning was not observed in either animal group after peripheral administration of GRP. Although there are methodological differences between feeding suppression studies and conditioned taste aversion studies, there is an abundance of data (including our study) that does not support

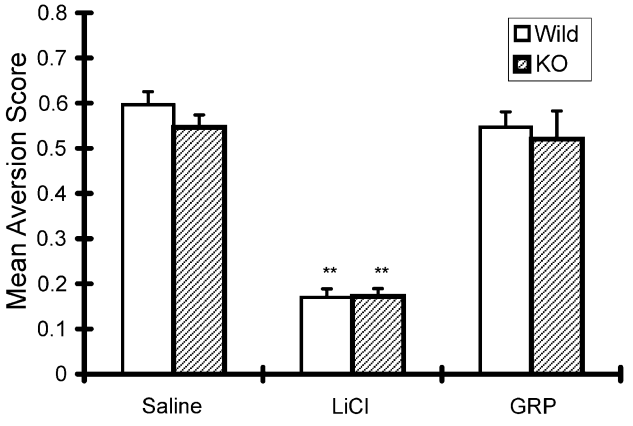

Fig. 2. Summary of the conditioned taste aversion test in GRP-receptor-deficient mice. Data represent mean aversion score + S.E.M. Experimental procedures and the calculation of the aversion score were as previously described (Yamada et al., 1999, 2000b). Each experimental group consisted of eight subjects. Wild: wild-type mice; KO: GRP-receptor-deficient mice. Saline: mice administered physiological saline (64 μl/10 g body weight, i.p.); LiCl: mice administered LiCl (0.3 M, 64 μl/10 g body weight, i.p.); GRP: mice administered GRP (32 nmol/kg, 64 μl/10 g body weight, i.p.). Symbols represent statistical differences compared to saline groups (** $P < 0.01$). Statistical analyses were conducted using one-way ANOVA and Turkey's multiple comparison method.

the "aversion hypothesis" of bombesin/bombesin-like peptide-induced feeding suppression. However, this hypothesis cannot be completely excluded at present because there are several animal and human studies that report that bombesin/bombesin-like peptides cause a sick sensation and form conditioned taste aversion. Clearly, if bombesin/bombesin-like peptides are to undergo therapeutic trials in the future, then a detailed assessment of the potential toxicity of these peptides must first be conducted.

3.2. Neural mechanisms of feeding suppression by bombesin-like peptides

The interaction of bombesin/bombesin-like peptides with CCK and other peptides/hormones has been the subject of considerable investigation (reviewed in Smith and Gibbs, 1984), and the feeding-related effects of bombesin/bombesin-like peptides have been compared with those of CCK. While both bombesin and CCK suppress food intake rapidly after administration, CCK suppresses liquid food intake more potently than solid food while bombesin suppresses both liquid and solid food intake equally (Gibbs et al., 1979). Peripheral administration of bombesin/bombesin-like peptides prompts CCK release in animals and humans (Erspamer et al., 1974; Jansen and Lamers, 1983, 1984), and therefore it has been postulated that bombesin/bombesin-like peptides act indirectly through CCK. However, administration of CCK receptor antagonists such as proglumide, L364,718 or loxiglumide do not affect bombesin/bombesin-like peptide-induced feeding suppression (Collins et al., 1983; Hewson et al., 1988; Lieverse et al., 1993b,c). Given that the effects of bombesin/bombesin-like peptides and CCK can be distinguished and that antagonists to the CCK receptor do not affect bombesin/bombesin-like peptide-induced feeding suppression, it is reasonable to propose that the mechanisms of feeding suppression by bombesin/bombesin-like peptides may be, at least in part, independent of CCK (Stein and Woods, 1981; Ladenheim et al., 1999; Lieverse et al., 1993b,c).

Bombesin/bombesin-like peptide-mediated satiety has also been investigated with respect to neural connections between the gastrointestinal tract and the brain (see Savory and Hodgkiss, 1984; Stuckey et al., 1985), and it has been shown that disconnection of this neural pathway blocks feeding suppression by exogenous bombesin-like peptides (Stuckey et al., 1985). The visceral nerves that mediate satiety signals elicited by bombesin/bombesin-like peptides or CCK can be clearly distinguished: bombesin/bombesin-like peptides require both vagal and spinal visceral input while CCK requires gastric branches of the vagus. Furthermore, the fact that peripheral administration of bombesin suppresses sham-feeding as well as feeding implies that bombesin interacts with facets of the gastrointestinal tract other than the gut (Gibbs, 1985).

It is likely that the neurotransmission mechanisms that mediate the effects of bombesin/bombesin-like peptides on feeding behavior are quite complex and thus beyond the scope of this review. However, the central neurocircuitry involved is discussed in detail by Merali et al. (1999).

4. Feeding-related effects of bombesin/bombesin-like peptides in humans

While bombesin/bombesin-like peptide-induced feeding suppression has been studied principally in animals, several

Table 2
Human pre-clinical assessment of the effects of bombesin-like peptides on feeding behavior and endocrine response

Authors	Subjects	Drugs and dosage (i.v.)		Results[1]
Muurahainen et al., 1983a	8 lean healthy men	BN	4 ng/kg/min	decreased
Muurahainen et al., 1983b	8 lean healthy men	BN	4 ng/kg/min	decreased
Lieverse et al., 1993b	9 healthy lean women	BN	412.5 ng/kg/165 min	slight effect
		BN + loxiglumide	(27.5 ng/kg/165 min)	decreased
Lieverse et al., 1993c	9 lean subjects	BN	0.23 nmol/kg/150 min	decreased
	6 of above subjects	BN + loxiglumide	(5 mg/kg/h)	decreased
Muuraheinen et al., 1993	12 healthy non obese men	BN	1.33 ng/kg/min	no effects
			4 ng/kg/min	decreased
Gutzwiller et al., 1994	20 healthy men	GRP	10, 40, 160 pmol/kg/h	decreased[a]
	8 healthy men	GRP(160) + loxiglumide	(22 μmol/kg/h)	decreased[a]
Lieverse et al., 1994a	9 healthy lean women and	BN	0.23 nmol/kg/150 min	decreased
	9 healthy obese women			no effects
Lieverse et al., 1994b	15 healthy lean subjects and	BN	46 pmol/kg/30 min	CCK/PP[b]
	14 healthy non-diabetic obese subjects			
Lieverse et al., 1998	7 lean and 7 healthy obese women	BN	0.09 nmol/kg/h	decreased
				no effect
Degen et al., 2001	22 healthy men	GRP antagonist (BIM26226)	5–500 μg/kg/h	CCK, etc.[c]

BN: bombesin, GRP: gastrin-releasing peptide, CCK: cholecystokinin, PP: pancreatic polypeptide.

[1] Results represent the amount of food intake except where footnoted. [a]Calorie intake, [b]blood CCK/PP concentration, [c]blood CCK concentration and gallbladder contraction.

studies have been conducted using human subjects (Table 2). The first such human studies by Muuraheinen et al. (1983a,b, 1993) showed that a relatively high dose of bombesin (4 ng/kg/min) administered intravenously to healthy lean subjects suppresses food intake in a single meal, with few side effects except a sensation of sickness. Lieverse et al. (1993b,c) also reported bombesin-induced feeding suppression in healthy lean human subjects using a combination of loxiglumide and bombesin. As seen in animals, they found that bombesin-induced feeding suppression in humans may occur via a CCK-independent mechanism (Lieverse et al., 1993c). As mentioned above, bombesin was originally purified from the skin of a frog and does not exist in mammalian tissue. Therefore, feeding-related effects of bombesin/bombesin-like peptides in mammals/humans should, of course, be examined using endogenous bombesin-like peptides. Gutzwiller et al. (1994) reported that systemic administration of synthetic human GRP reduces calorie intake and the rate of eating in a dose-dependent manner without side effects. Again, the possibility that GRP-induced feeding suppression in human subjects might be independent of CCK was put forth by these investigators. The effects of blocking bombesin/bombesin-like peptide receptors on feeding-related behavior using antagonists have been studied in animals (Table 1), and the effect of the GRP-receptor antagonist (BIM26226) has also been examined in humans (Degen et al., 2001). Intravenous administration of BIM26226 inhibits both gallbladder contraction and CCK release induced by endogenous or exogenous GRP, respectively, in a dose-dependent manner.

Seminal studies on the treatment of obesity by bombesin/bombesin-like peptides were conducted by Lieverse et al. (1994a, 1998). They compared the effects of peripheral administration of bombesin in healthy lean women and healthy non-diabetic obese women. They found that bombesin suppresses food intake and increases satiety only in lean women, but found no differences between lean and obese subjects with respect to plasma CCK and pancreatic polypeptide secretion. However, following a meal the plasma pancreatic polypeptide level was markedly diminished in obese subjects (Lieverse et al., 1994b). Their results are quite significant with respect to the prospect of treating obesity with bombesin/bombesin-like peptides, and it is therefore important for future studies to clarify the efficacy of using these peptides to modulate food intake and manage body weight in obese persons.

5. Prospects for treating obesity with bombesin/bombesin-like peptides

The principle of using bombesin/bombesin-like peptides to treat obesity and/or eating disorders in humans has been discussed since the 1980s. Articles that review this putative pharmacological approach are summarized in Table 3. In the following section, two different viewpoints are discussed: that bombesin/bombesin-like peptides may act as anorectic agents; and the prospects for the development of novel anorectic agents.

Table 3
Review articles on bombesin-like peptides relevant to therapeutics and/or treatment of obesity

References	Journal (Vol.)
Lombardi et al., 1984	Min. Med. 75
Smith and Gibbs, 1984	Fed. Proc. 43
Thomas, 1986	Rev. Med. Interne. 7
Powers and Pappas, 1989	Ann. Surg. 209
Smith and Gibbs, 1992	Am. J. Clin. Nutr. 55
Lieverse et al., 1993a	Scand. J. Gastroenterol. Suppl. 200
Cheah, 1996	Singapore Med. 37
Weiser et al., 1997	J. Clin. Pharmacol. 37
Wechsler, 1998	Acta Med. Austrica 25
Merali et al., 1999	Neuropeptides 33
Halford and Blundell, 2000	Prog. Drug Res. 54
Beck, 2001	Neurosci. Biobehav. Rev. 25

5.1. Bombesin/bombesin-like peptides as anorectic drugs

Although a number of review articles refer to the applicability of bombesin/bombesin-like peptides for the treatment of obesity, the feasibility of this approach remains unclear. Bombesin-like peptides (especially bombesin and GRP) can strongly suppress feeding in animals and humans. Furthermore, these peptides generally do not cause sickness and/or other harmful side effects in humans (references cited in Table 2). Therefore, it is plausible that these peptides may act as anorectic agents for the treatment of obesity, although some difficult issues remain with respect to such pharmacotherapy. First, regardless of whether bombesin/bombesin-like peptide-induced feeding suppression is attributable to satiation or aversion, the effect of these peptides is temporal and transient. A single administration of GRP suppresses spontaneous feeding for only 15 to 30 min in partially food-deprived mice (Yamada et al., 2000b). Although most studies involving these peptides report a suppression of spontaneous feeding, few report long-lasting suppression by bombesin/bombesin-like peptides either in animals or humans. A few animal studies examined chronic/continuous administration of CCK and bombesin with osmotic minipumps, but no weight loss was achieved owing to the rapid development of tolerance to the satiety peptides (Crawley and Beinfield, 1983; Morley, 1987). There have been no human studies involving chronic treatment with bombesin/bombesin-like peptides, and therefore no data exist on the efficacy of this approach with respect to feeding behavior and body weight control (or possible side effects). Thus, a detailed assessment of the effects of multiple and long-term administration of these peptides on feeding-related behavior, body weight change, and toxicity is required if bombesin/bombesin-like peptides are to be utilized for the purpose of curbing appetite. Second, bombesin/bombesin-like peptides suppress food intake in a single meal, and the

resultant weight loss is nearly identical to that achieved with restricted feeding. There is no evidence that bombesin/bombesin-like peptides reduce body weight (or curb weight gain) by via metabolism of body mass (in particular, fat). Third, orally administered bombesin/bombesin-like peptides show no activity (Smith and Gibbs, 1992) and thus are at a distinct disadvantage as anti-obesity drugs. Finally, some studies report that obese subjects may be insensitive to the effects of bombesin/bombesin-like peptides on feeding-related behavior (Lieverse et al., 1994a, 1998). In genetically obese Zucker rats, which are less sensitive to CCK-induced satiety relative to their lean littermates, decreased binding of CCK to its pancreatic receptor is observed (McLaughlin and Baile, 1980a,b; McLaughlin et al., 1984). However, satiety in BRS-3-deficient mice exhibits normal sensitivity to exogenously administered GRP (Yamada et al., 2000b). These discrepancies suggest that, with respect to satiety, the sensitivity to bombesin/bombesin-like peptides may differ among species and/or with different types of obesity. Therefore, sensitivity to bombesin/bombesin-like peptides should be assessed in many types of obese subjects including humans.

The above discussion on the applicability of bombesin/bombesin-like peptides as anorectic drugs reveals that these peptides have potency as anti-obesity drugs. At present, however, the aforementioned difficulties may limit such implementation.

5.2. Molecular basis of bombesin/bombesin-like peptides' effect on obesity, and development of a new class of anti-obesity agents

The BRS-3 receptor has no known endogenous ligand(s). Studies with BRS-3-deficient mice demonstrate that the BRS-3 pathway is involved in a somewhat different aspect of feeding behavior. Although GRP-receptor- and neuromedin B receptor-deficient mice exhibit normal feeding-related behavior and body weight gain (Wada et al., 1997; Ohki-Hamazaki et al., 1999), BRS-3-deficient mice exhibit moderate obesity caused by increased daily/normal food intake and decreased energy expenditure (Ohki-Hamazaki et al., 1997b; Wada et al., 1998; Yamada et al., 2000a). These results indicate that the role played by the BRS-3 pathway in feeding-related behavior may differ from those of the GRP/GRP receptor and neuromedin B/neuromedin B receptor pathways (Yamada et al., 2000b). BRS-3-deficient mice show decreased glucose and insulin tolerance (Ohki-Hamazaki et al., 1997b), and thus the BRS-3 pathway may be primarily involved in glucose metabolism. The metabolic defects and obesity observed in BRS-3-deficient mice prompted a recent study of the contribution of bombesin-like peptides to human obesity. However, neither deletion nor mutation of the BRS-3 gene has any effect on obesity, at least among the Japanese population involved in this study (Hotta et al., 2000). In addition, while a human chromosomal translocation with a breakpoint within the GRP receptor gene has been reported in a patient with autism (Ishikawa-Brush et al., 1997), no such translocation has been observed in an obese patient. Thus, to date there is no evidence that directly links obesity with dysfunction in bombesin-like peptides/receptors systems. However, only a few such studies have been undertaken, and further investigation should either confirm or refute any contributions that bombesin/bombesin-like peptide/receptor systems might make to human obesity.

From a therapeutic perspective, BRS-3-deficient mouse may also be a useful tool for the development of drugs for the treatment of obesity. BRS-3 expression is limited to hypothalamic nuclei (paraventricular nucleus: PVN) and medial/central amygdaloid nuclei (MePD, CeA) (Ohki-Hamazaki et al., 1997a; Yamada et al., 1999). However, the fact that the potential drug targets are limited may offer a salient advantage when developing new compounds as therapeutics. Specific ligand(s) for BRS-3, whether they are endogenous or synthetic, represent a new class of potential anorectic and/or anti-obesity agents that may strongly suppress feeding. Furthermore, such agents may also promote energy expenditure. Therefore, further studies with bombesin/bombesin-like peptides using both traditional psychopharmacological as well as gene-targeting (knockout) strategies may well contribute to the development of new therapeutics for the treatment of obesity.

6. Concluding remarks

In this review, research demonstrating the modulatory function of bombesin/bombesin-like peptides in feeding behavior was presented along with a discussion of the aspects involved with the feasibility of pharmacotherapy of obesity using these peptides. Studies toward the application of bombesin/bombesin-like peptides to the treatment of obesity have just begun, but owing to the aforementioned difficulties in duration of action and route of administration, the efficacy of these peptides as anorectic (anti-obesity) agents may be quite limited at present. However, recent studies using gene-targeted animals reveal the unexpected function of a bombesin/bombesin-like peptide/receptor pathway (especially, the BRS-3 pathway) in feeding and body weight regulation. Further studies of the relationship between these peptides and feeding/satiety from both psychopharmacological and genetic/molecular biological perspectives may be fruitful in the development of new therapeutics for the treatment of obesity.

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