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Comparison of the Actions of Bombesin, Gastrin-Releasing Peptide-27, Neuromedin B, and Gastrin-Releasing Peptide-10 in Causing Release of Gastrin and Gastric Inhibitory Peptide in Rats[1] (42398)

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Abstract. The objective of this study was to compare the gastrin- and gastric inhibitory peptide (GIP)-releasing actions of bombesin, gastrin-releasing peptide (GRP)-27, neuromedin B, and GRP-10 in rats. Both bombesin and GRP-27 are potent stimulants of gastrin and GIP release, whereas neuromedin B and GRP-10 are less effective, on a molar basis.

Neuromedin B and gastrin-releasing peptide (GRP)-10 are two novel decapeptides which have been isolated and characterized recently from extracts of porcine spinal cord and canine duodenum, respectively (1–3). Neuromedin B and GRP-10 resemble the C-terminal structure of bombesin and GRP-27.

Although bombesin and GRP-27 have been shown to release gastric inhibitory peptide (GIP) and gastrin in several species (4–10), their stimulatory actions on the release of gastrin and GIP have never been compared to those of neuromedin B and GRP-10. The objective of this paper, therefore, was to compare the potencies of bombesin, GRP-27, GRP-10, and neuromedin B on the release of gastrin and GIP in rats.

Materials and Methods. *Animals.* Male rats (200–225 g) were obtained from Texas Animal Specialties (Humble, Tex.) and maintained in an air-conditioned (25 ± 2°C) and light-regulated (lights on, 0500–1700 hr) animal quarters for at least 7 days before the following experiments were done. All rats had free access to rat chow and tap water unless stated otherwise.

Radioimmunoassays (RIA): Gastrin. A double-antibody RIA procedure was utilized to measure serum gastrin levels as reported earlier (10). *GIP.* Serum GIP levels were measured using a double-antibody RIA procedure according to Kuzio and colleagues (11). GRP-27, bombesin, and neuromedin B do not cross-react in either RIA.

Experimental design. Synthetic GRP-27, bombesin, neuromedin B, GRP-10 (18.0, 3.6, 0.4, 0.04, 0.02, 0.01, 0.004 nmole/200 g body wt; prepared in 0.1% bovine serum albumin, 0.9% saline, and 0.05 *M* acetic acid) or vehicle alone (0.2 ml) were given intravenously to 24-hr fasted rats ($N = 6$ rats/dose) under light ether anesthesia. All peptides were supplied by Peninsula Laboratories (San Carlos, Calif.) or BACHEM (Torrance, Calif.). Ten minutes after administration of the peptide or vehicle alone, blood was collected after decapitation for determination of serum gastrin and GIP. Serum was separated and stored at −20°C until it was processed in the RIAs. Blood was collected 10 min after administration of each peptide since we determined in previous studies that the maximal GIP and gastrin responses occur at 10–15 min after peptide administration.

Statistics. Data are expressed as means ± SEM. The serum GIP responses to bombesin and GRP were compared by linear regression analysis and Student's *t* test (12). The gastrin responses to bombesin and GRP were evaluated by analysis of variance followed by a Newman–Keuls test (13). Differences with a *P* value of <0.05 were considered significant.

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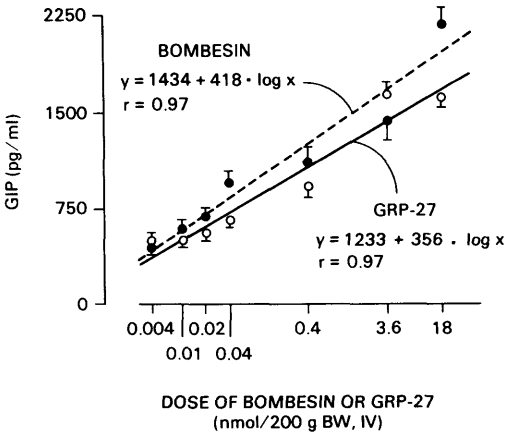

FIG. 1. Linear regression lines of the serum GIP responses to bombesin and GRP-27.

Results. Administration of graded doses of bombesin and GRP-27 resulted in dose-related elevations in serum GIP levels (Fig. 1). The average slopes (±SEM) of the bomesin and GRP-27 regression lines are 418 (±29) and 356 (±26), respectively. Statistical evaluation of the slopes reveal that the serum GIP responses to graded doses of bombesin and GRP-27 do not differ significantly ($P > 0.05$).

Neuromedin B (18 nmole) caused a significant elevation in serum GIP levels (1132 ± 69 pg/ml) whereas lower doses were ineffective. A higher dose of neuromedin B (90 nmole) did not cause a greater elevation in serum GIP levels when compared to 18 nmole (data not given). The serum GIP response to neuromedin B (18 nmole) is significantly less than the serum response to identical molar doses of bombesin and GRP-27. GRP-10, at 3.6 and 18 nmole, caused a dose-related elevation in serum GIP levels of 842 ± 36 and 1125 ± 47 pg/ml, respectively. Lower doses of GRP-10 were ineffective and a higher dose of GRP-10 did not elevate serum GIP levels significantly above the effect of 18 nmole. The serum GIP responses to 3.6 and 18 nmole of GRP-10 were significantly lower than the respective responses to identical molar doses of bombesin and GRP-27.

The serum gastrin responses to 0.4 and 3.6 nmole of bombesin and GRP-27 were significantly greater than the gastrin responses to immediately lower doses of bombesin and GRP-27 (Fig. 2). Neuromedin B failed to cause a significant elevation of serum gastrin levels when compared to the serum gastrin level after administration of intravenous vehicle alone (data not shown). Intravenous administration of GRP-10 (90 nmole) resulted in a significant elevation in the serum gastrin level (299 ± 23 pg/ml), whereas lower doses were ineffective.

Discussion. The results of the present study show that bombesin and GRP-27 stimulate release of gastrin and GIP in rats equipotently. In contrast, neuromedin B failed to stimulate the release of gastrin at the doses tested, and GRP-10 is significantly less, on a molar basis, in comparison to that of GRP-27 and bombesin.

In dogs, McDonald and colleagues (7) have found that bombesin and GRP-27 are equipotent in the stimulation of the release of numerous gut and pancreatic peptides, including gastrin and GIP. Other laboratories have also shown that bombesin and GRP-27 are equipotent in stimulating neurotensin release in rats (14), and gastrin and pancreatic polypeptide (PP) release in dogs (15, 16). Orloff and co-workers (16) have reported that GRP-10 is less potent than GRP-27 and bombesin, on a molar basis, in the stimulation of gastrin re-

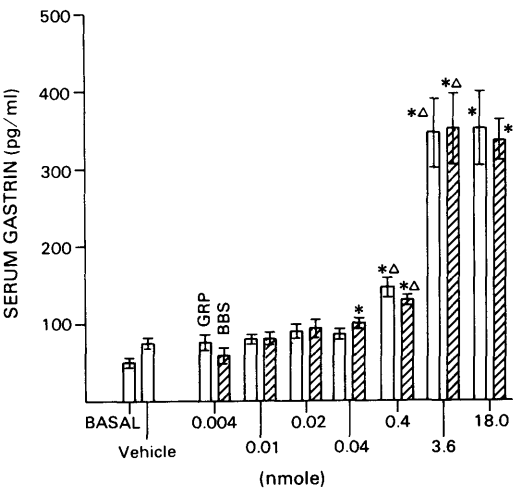

FIG. 2. Serum gastrin levels 10 min after various doses of bombesin (BBS) or GRP-27 in 24-hr fasted rats. (*, $P < 0.05$ vs basal or intravenous vehicle alone; Δ, $P < 0.05$ vs immediately lower dose of respective peptide).

lease. Vagne and colleagues (17) have shown, however, that GRP is significantly less potent than bombesin in stimulating gastric acid secretion in cats. In any case, bombesin and GRP-27 are potent stimulatory factors of gastrointestinal and pancreatic peptide release, but whether they function as physiologic regulators remains to be established. Brown and co-workers (18) have suggested that GRP-27 is the mammalian equivalent of the amphibian peptide, bombesin. Several studies have shown, however, that several forms of bombesin-like immunoreactivity exist in the mammalian gastrointestinal tract (2, 19–23) and it is conceivable that each form may play a unique role in the regulation of gastrointestinal and pancreatic function.

It is worth mentioning that differences in the catabolism of bombesin, GRP-27, neuromedin B, and GRP-10 might explain the differences in their potencies on GIP and gastrin release. Although the half-lives ($T_{1/2}$) of neuromedin B and GRP-10 have not been reported, the disappearance half-life of bombesin is 3.1 ± 0.6 min in man (6), whereas the disappearance of GRP-27 from the circulation is characterized by slow and fast components ($T_{1/2}$ = 1.4 and 6.6 min) (24).

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