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Bombesin Inhibits Stress-Induced Eating

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MORLEY, J. E. AND A. S. LEVINE. *Bombesin inhibits stress-induced eating.* PHARMAC. BIOCHEM. BEHAV. **14**(2) 149–151, 1981.—Bombesin administered both intracerebroventricularly and parenterally suppressed stress-induced eating in the rat (using the mild tail pinch model). Intraventricular administration of bombesin resulted in hyperglycemia, which was abolished by adrenalectomy. The satiety-inducing effect of bombesin was independent of the hyperglycemia it produces as suppression of stress-induced eating was still present in adrenalectomized animals.

Bombesin Stress-induced eating Neurotensin Satiety Tail pinch eating Glucose

BOMBESIN, a tetradecapeptide originally isolated from amphibian skin [7], has been reported to suppress food intake when administered peripherally [9]. Bombesin-like immunoreactivity is present in large quantities in the brain as well as throughout mammalian gut [4, 22, 24]. Intraventricular administration of bombesin has been reported to produce a prompt and sustained hyperglycemia, hyperglucagonemia, and relative or absolute hypoinsulinemia, all of which can be reversed by prior adrenalectomy [5]. In this study we report on the effects of centrally administered bombesin on short term appetite regulation as quantitated in Antelman's mild tail-pinch model [1].

Mild tail pinch reliably induces a syndrome of eating, gnawing and licking behavior [1,18]. Having demonstrated ingestive behavior on one trial, a rat will reliably show enhancement of food ingestion on subsequent trials at 15-minute intervals. We chose the mild tail-pinch model to study the effects of bombesin on centrally mediated satiety for several reasons: (1) it correlates well with starvation induced eating [17,18] (and unpublished observations); (2) it avoids depriving adrenalectomized animals of food and water; and (3) this response is of particular interest in view of the parallel it displays with stress-induced eating in humans [12].

METHOD

For these studies we used the mild tail pinch method of Antelman [1] as modified by us [16,18]. Tail pinch behavior was induced by applying minimal pressure to the rat's tail using a plastic hemostat. Behavioral testing was carried out in a 22×17 cm plastic box containing 3 pellets of Purina rat chow (6–10 g). In our experiments we used naive, non-food deprived male Sprague-Dawley rats, weighing 150–250 g, all of whom had been shown to ingest food over a 2-min period of tail pinch. All testing was done between 12 noon and 4 p.m.

In the rats receiving intraventricular peptides or saline, stainless steel guide tubes were stereotactically implanted into the lateral ventricle under methoxyflurane anesthesia (Pitman-Moore, NJ) at least 7 days before experiments commenced. Mild tail-pinch was applied to induce gnawing and continued for 2 minutes after the onset of the gnawing behavior. Food consumption was obtained by weighing the food before and after the 2-min period. Chewing was quantitated by weighing the remainder of the pellets left behind after the food had been passed through a metal grid with pores 2 mm². Peptides were administered in a 5 μl volume of saline. In the control experiments 5 μl of saline alone was administered. All animals were pre-tested 5-min before peptide administration and then ten minutes after peptide administration. For the parenteral studies, bombesin, neurotensin or saline were administered subcutaneously after the first 2-min tail-pinch trial and the animals were re-tested at 15 and 30 min. Bilateral adrenalectomies were performed under ether anesthesia. Blood glucose was measured using a glucose analyzer (Beckman, Fullerton, CA).

Results were compared using the two-tailed Student's *t*-test. All results are expressed as the mean ± SEM. Bombesin was obtained from Boehringer-Mannheim (Indianapolis, IN) and neurotensin from Calbiochem (San Diego, CA).

RESULTS

Intraventricular administration of bombesin produced a dose dependent suppression of food ingestion (Fig. 1). Intraventricular saline was associated with the expected enhancement of food intake seen in untreated animals. Neurotensin failed to suppress food intake at an equivalent dose to the bombesin. Intracerebroventricular bombesin (1 μg) also suppressed food ingestion in the adrenalectomized animals (39 ± 20%, $p<0.05$). Intraventricular administration of bombesin produced a rise in blood sugar (188 ± 9 vs

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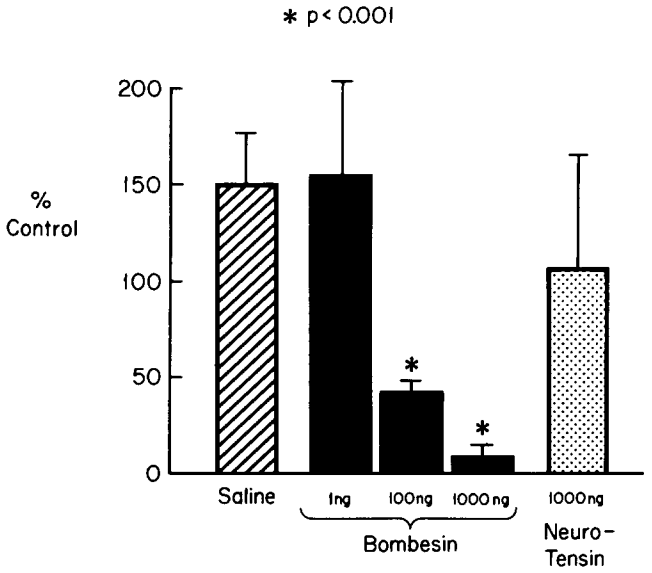

FIG. 1. Effect of intraventricular bombesin and neurotensin on stress-induced eating. This shows that bombesin, but not neurotensin, inhibits tail-pinch induced eating in a dose related manner. Results are expressed as a ratio of food ingested after peptide administration to food ingested prior to peptide administration (% control). Basal food ingestion over the 2-minute control period was 0.6 ± 0.1 g. The 1000 ng bombesin dose was significantly lower than the 100 ng dose ($p<0.05$).

TABLE 1

EFFECT OF PARENTERAL BOMBESIN AND NEUROTENSIN ON STRESS-INDUCED EATING

			Food Ingested (% Control)	
		n	15 Minutes	30 Minutes
Saline		8	170 ± 51	116 ± 13
Bombesin	10 μg/kg	8	31 ± 13*	31 ± 10*
	1 μg/kg	8	19 ± 7*	23 ± 10*
	0.1 μg/kg	8	142 ± 27	167 ± 55
Bombesin (in adrenalectomized)	10 μg/kg	6	38 ± 18*	40 ± 15†
Neurotensin	10 μg/kg	6	122 ± 20	105 ± 25

*$p<0.01$, †$p<0.05$.

136 ± 5 mg/dl, $p<0.05$) and the effect was abolished by adrenalectomy (118 ± 14 vs 115 ± 14 mg/dl, $p<0.1$).

In a separate series of studies we showed that parenteral administration of bombesin inhibits stress induced eating at doses of 1 and 10 μg/kg (Table 1). Following parenteral administration of bombesin (1 μg/kg) there was an enhancement of chewing activity (341 ± 90%; $p<0.001$). As was found with intraventricular administration of bombesin, parenteral administration of bombesin resulted in a rise in blood glucose (209 ± 11 vs 121 ± 2; $p<0.01$). The increase in glucose was reduced by adrenalectomy, but was still significantly higher than that observed in adrenalectomized controls (159 ± 6 vs 110 ± 3; $p<0.01$). Animal behavior (exploration, grooming, apparent sleep) after both intraventricular and parenteral administration of bombesin was qualitatively similar to that observed in the control animals.

DISCUSSION

We have shown that both intraventricular and parenteral administration of bombesin suppresses stress-induced eating. As all animals demonstrated normal chewing behavior and behavior patterns after administration of bombesin, this suggests that bombesin did not reduce food intake simply by causing a generalized disruption of behavior but rather that it produced a selective suppression of feeding, a quality that may be anticipated in a natural satiety signal. The failure of neurotensin to suppress eating makes a non-specific effect of intraventricularly administered peptides unlikely.

Centrally administered bombesin has been reported to produce a prompt and sustained hyperglycemia, hyperglucagonemia, and relative or absolute hypoinsulinemia; all of which may be linked to centrally induced satiety [5]. We eliminated the above effects of bombesin by adrenalectomy [5]. Since food ingestion was suppressed by bombesin in the adrenalectomized animals without an increase in blood glucose, it appears that bombesin may have a direct effect on the central nervous system. In contrast, we cannot conclude that the satiety inducing effect of parenterally administered bombesin is not secondary to alterations in glucose homeostasis. The failure of adrenalectomy to lower blood glucose levels after parenteral bombesin is most probably due to bombesin's direct effect on the pancreas as shown by Martindale *et al.* [11] in the isolated perfused rat pancreas. It should be noted that food ingestion after 1 μg bombesin in the adrenalectomized animals was greater (39 ± 20% of control) than in the intact animals (7 ± 5%) suggesting the possibility that the bombesin induced hyperglycemia may have played a minor role in the suppression of food ingestion.

Another potential mechanism by which bombesin may inhibit stress-induced eating is by its ability to produce hypothermia [3]. Local cooling of the pre-optic area of the anterior hypothalamus has been shown to depress feeding in rats [23]. Our data do not allow us to comment on whether or not a disruption of body temperature control produced by intraventricular bombesin was partially responsible for the observed suppression in food intake.

The physiological actions of bombesin are unknown. Bombesin in pharmacological doses has been reported to increase blood pressure, to stimulate the secretion of gastric acid, gastrin and cholecystokinin, to stimulate exocrine pancreatic secretion and to produce contraction of the gallbladder [2,21]. It has been shown to lower body temperature [3] and produce a variety of effects on anterior pituitary hormonal release [14,19]. We now conclude that bombesin is a putative satiety signal. Two other peptides, cholecystokinin and thyrotropin releasing hormone, which have also been shown to be present in both the gastrointestinal tract and the brain [13,15], have been postulated to play a role as satiety factors [8, 16, 20, 25]. Present methodology does not allow

us to distinguish between effects produced by these peptides acting locally in the hypothalamus in a paracrine fashion from those they produce as circulating hormones in the classical sense. Thus whether or not bombesin is one of the unidentified gastric satiety signals that have been demonstrated in the rat [6,10] or acts predominantly as a central neuromodulator of appetite control (see [17] for a review of this concept) remains to be determined.

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