Pharmacology Biochemistry & Behavior, Vol. 19, pp. 577–582, 1983. © Ankho International Inc. Printed in the U.S.A.

The Effect of Peripherally Administered Satiety Substances on Feeding Induced by Butorphanol Tartrate

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Received 12 January 1983

MORLEY, J. E., A. S. LEVINE, J. KNEIP, M. GRACE AND C. J. BILLINGTON. *The effect of peripherally administered satiety substances on feeding induced by butorphanol tartrate.* PHARMACOL BIOCHEM BEHAV **19**(4) 577–582, 1983.—Endogenous opioid peptides appear to play a role in the initiation of feeding. Butorphanol, an exogenous opiate which preferentially generalizes to the kappa-sigma opiate receptors, is a potent initiator of feeding. In these studies, we examined the effect of peripherally administered putative satiety substances, cholecystokininoctapeptide, somatostatin, bombesin, gastrin-releasing peptide, thyrotropin-releasing hormone, calcitonin and glucagon on butorphanol induced feeding. With the exception of bombesin, all the other putative satiety factors required 2 to 32 times as high a dose to significantly suppress feeding following butorphanol compared to the dosages required to suppress starvation or tail pinch induced feeding. Bombesin appeared to be approximately equipotent in all systems tested. Haloperidol and atropine both suppressed butorphanol induced feeding supporting our previous hypothesis of an integral relationship between acetylcholinergic-dopaminergic and opioid mechanisms in the initiation of feeding. The findings reported here are compatible with an important role for opioid mechanisms in the initiation of feeding.

Bombesin Opiates Gastrin-releasing peptide GRP Butorphanol CCK Cholecystokinin TRH Glucagon Calcitonin Somatostatin

WE HAVE previously proposed an integrated hypothesis to explain the interactions of monoamines and peptides in the regulation of appetite [26, 34, 35]. We suggested that the hypothalamus acts as a neuroendocrine transducer with the control of food intake involving a delicate balance between a number of neuropeptides and monoamines. It was suggested that food intake is initiated by a dopamine-opioid mechanism and that this signal is governed by inhibitory inputs from the medial hypothalamic area. In addition, it is clear that at least some peptides produce their inhibitory effects on food intake by activating afferent fibers in the vagus [24, 36, 47]. In an attempt to more fully define these monoamine-peptide interactions involved in feeding, we have studied the interaction of a variety of pharmacological feeding inducers, including norepinephrine [31], muscimol [30] and insulin [16] with known satiety substances.

Endogenous opioid peptides appear to play a central role in the regulation of appetite [33,43]. Recent studies have shown that the endogenous opioid peptide, dynorphin, is a potent inducer of feeding after central administration [14, 32, 37]. Dynorphin appears to be the endogenous ligand for the kappa receptor [5, 12, 53]. A number of exogenous opiates which preferentially bind to the kappa receptor have been demonstrated to produce feeding after peripheral administration [7, 22, 38, 44]. The morphinan congener, butorphanol tartrate, has actions suggesting it to preferentially effect κ and σ opiate receptors [39,42]. Butorphanol is in our hands, the most potent feeding enhancer of all the exogenous opiates [20]. For these reasons we have begun to undertake a systematic investigation of the effects of a variety of satiety substances on butorphanol-induced feeding. This communication reports our findings with peripherally administered satiety agents.

GENERAL METHOD

Animals and Chemicals

Food consumption was studied in individually housed male Sprague-Dawley rats (150–200 g) kept under standard lighting conditions (12 hr/day artificial light—0700 to 1900 hr). All rats were given free access to a standard diet (Purina laboratory chow) and water until the beginning of the experiments. Butorphanol tartrate (Bristol Laboratories, Syracuse, NY) was injected subcutaneously at a dose of 8 mg/kg. This dose was chosen as it consistently produces a maximum effect on feeding. All animals received a second injection of vehicle or satiety agent. The maximum effect of butorphanol on feeding occurs between 1 to 3 hours, and, thus, in some experiments where short acting satiety substances were being given, the injection of satiety agent or vehicle was delayed for 1 hour after butorphanol administration. A

weighed quantity of food was presented to the animals immediately following the second injection and the quantity of food consumed measured at the intervals specified in individual experiments. Animals had access to water ad lib during the experiments. All experiments began between 0800 and 1000 hours.

All substances were injected in a 0.2 cc volume. Satiety substances were obtained from: cholecystokinin-octapeptide: Boehringer-Mannheim, Indianapolis, IN; bombesin: Sigma Chemical Co., St. Louis, MO; gastrin-releasing peptide: Peninsula Labs, San Carlos, CA; somatostatin: Ayerst Pharmaceuticals; thyrotropin-releasing hormone: Boehringer-Mannheim, Indianapolis, IN; calcitonin: Armour Pharmaceutical, Phoenix, AZ; haloperidol: McNeill Laboratories, Fort Washington, PA; atropine Sigma Chemical Co., St. Louis, MO; glucagon: Eli Lilly and Co., Indianapolis, IN.

Statistics

Food intake data was expressed as cummulative food intake. All results are expressed as the mean±SEM. Results were compared using repeated measures analysis of variance and the protected least significance test (BMDP statistics package). F values for each time point are given in the figure legends.

EXPERIMENT 1

Both cholecystokinin-octapeptide (CCK) and somatostatin are putative peripheral satiety factors that reduce feeding through a vagally mediated mechanism [19, 21, 36, 47]. CCK releases somatostatin from the perfused dog pancreas [13]; a fact that has been used to explain the close similarities in the satiety action of these two peptides [19]. The purpose of this experiment was to study the satiety effects of these two peptides over a range of doses known to be effective in suppressing feeding in other systems.

Method

Both CCK-8 and somatostatin were administered intraperitoneally (the preferred route of administration to demonstrate the satiety effect of these peptides), 1 hour after butorphanol was administered. Food intake was quantitated at 30, 60 and 120 minutes after the second injection. A total of 60 rats were used with 6–8 in each group.

Results and Discussion

CCK-8 suppressed feeding at both the 16 and 32 μg/kg dose but not at 8 μg/kg (Fig. 1). Somatostatin failed to statistically suppress feeding at any dose, although there was a tendency for suppression at higher doses. This suggests that cholecystokinin is a more potent inhibitor of feeding than somatostatin, particularly over the first 60 minutes after injection. Similarly, we have previously shown that somatostatin fails to inhibit feeding in 30 hr deprived animals, whereas CCK-8 is a potent inhibitor of feeding in this paradigm [19]. These data make it unlikely that CCK is producing its satiety effect through release of somatostatin. The failure of somatostatin to significantly suppress butorphanol induced feeding is compatible with our previous finding that it fails to inhibit dynorphin-(1–13) induced feeding [19] although the highest concentration of somatostatin just missed producing statisitcal significance at 120 minutes due to the slightly greater variance than that for CCK. We have

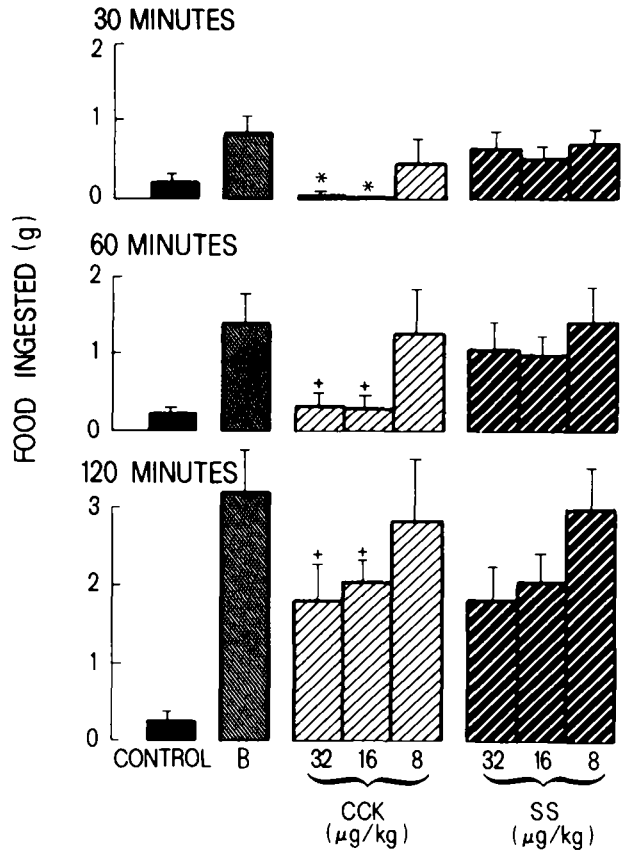

FIG. 1. The effect of cholecystokinin-octapeptide (CCK) and somatostatin on butorphanol induced feeding. *$p<0.01$, †$p<0.05$, $F(9,66)$, 30 min=2.0, 60 min=2.37, 120 min=4.58. Butorphanol induced significant feeding compared to controls at all times ($p<0.01$).

also found that CCK-8 (10 μg/kg) did not suppress dynorphin induced feeding [37] and the need for higher doses of CCK to suppress butorphanol induced feeding is again compatible with this observation. Doses of CCK-8 as low as 0.1 μg/kg have been shown to suppress feeding [46], suggesting that butorphanol is a potent feeding inducer. The high doses of CCK-8 needed to suppress butorphanol induced feeding are at a level where less specific effects of CCK-8 such as gut contraction and nausea may be playing a role in the suppression observed [6].

EXPERIMENT 2

Bombesin, a frog skin peptide, has been shown to inhibit feeding in a variety of models [10, 28, 48]. The mammalian counterpart of bombesin is gastrin-releasing peptide (GRP) [2] which also inhibits feeding after peripheral administration [49]. In this experiment, we examined the effect of bombesin and gastrin-releasing peptide on butorphanol induced feeding.

Method

Both bombesin and GRP were administered intraperitoneally 1 hour after butorphanol was administered. Food intake was quantitated at 30, 60 and 120 minutes after adminis-

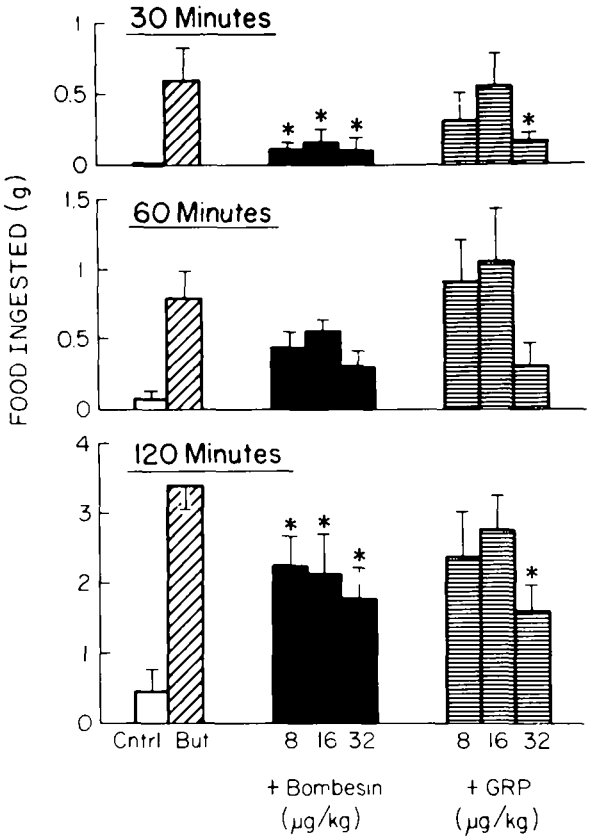

FIG. 2. The effect of bombesin and gastrin releasing peptide (GRP) on butorphanol induced feeding. *p< 0.01, F(7,52), 30 min = 2.15, 60 min = 1.21 and 120 min = 2.45. Butorphanol induced significant feeding compared to controls at 30 and 120 minutes (p<0.01). No significance is shown for 60 minutes as ANOVA was not significant.

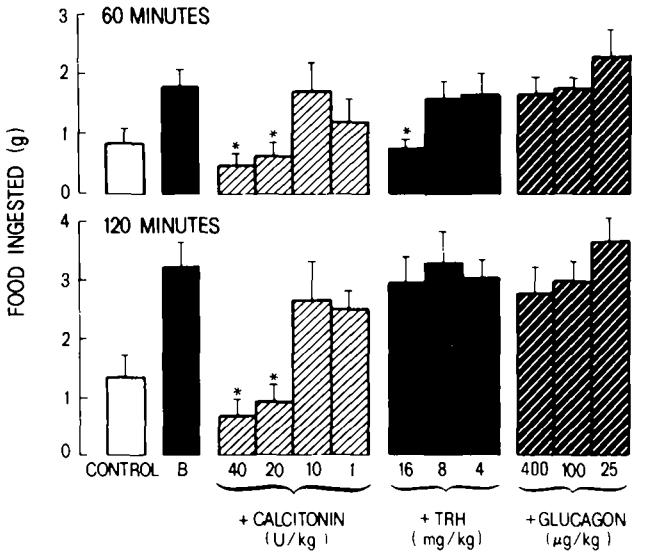

FIG. 3. Effect of calcitonin, throtropin releasing hormone (TRH) and glucagon on food intake, F(7,52), 30 min = 2.15, 60 min = 1.21 and 120 min = 2.45. Butorphanol induced significant feeding compared to the controls, *p< 0.01.

tration of the second injection. A total of 64 rats were used with 8 in each group.

Results and Discussion

Bombesin significantly suppressed feeding at all doses at 30 and 120 minutes (Fig. 2). GRP was only effective at the highest dose tested. GRP has been shown to be 30% less potent than bombesin on a molar basis in other feeding paradigms [49]. Bombesin was at least twice as potent as CCK-8 in suppressing feeding which is of interest as it has been shown to be 5 times less potent than CCK in suppressing feeding after a 3 hour food deprivation period during the day [10,11]. Bombesin produces its effect by a different mechanism to CCK as its effect is not vagally dependent [11,36]. Bombesin has also been shown to inhibit dynorphin-(1–13) induced feeding whereas CCK does not [37]. The findings here further support the concept that bombesin is more potent than CCK in suppressing opiate induced feeding.

EXPERIMENT 3

Calcitonin is a potent inhibitor of feeding when given either peripherally or centrally [8, 18, 41]. TRH suppresses feeding after both peripheral and central injection [27], possibly by different mechanisms [36]. Both calcitonin and TRH are more potent after central than peripheral administration [27,41]. Glucagon suppresses feeding after peripheral injection [9,17]. The experiment reported here examined the effect of peripherally administered calcitonin, TRH and glucagon on butorphanol induced feeding.

Method

The methods were similar to those described in Experiments 1 and 2 except that food was quantitated only at 60 and 120 minutes after the second injection. A total of 93 rats were used with 7 to 8 in each group.

Results and Discussion

Calcitonin decreased butorphanol induced feeding at a dose of 20 units/kg, a dose double that which has been shown to be effective after peripheral administration in other feeding systems [27] (Fig. 3). Calcitonin is released following a meal [40] and by a number of gastrointestinal peptides [1,3] and as such is a candidate peripheral satiety factor. Our findings here neither confirm nor detract from the status of calcitonin as a putative peripheral satiety agent.

TRH at the highest dose tested decreased feeding at the 60 minute but not at the 120 minute time point (Fig. 3). Although TRH is widely distributed throughout the gastrointestinal tract [23] and has a variety of effects on gastrointestinal function [25], the doses necessary to suppress feeding after peripheral administration appear to be too high to be physiological. This feeling is supported by the fact that vagotomy blocks peripheral TRH-induced satiety but not satiety after central administration [36]. High concentrations of peripherally administered TRH have been demonstrated to suppress exogenous and endogenous opiate actions in other systems [25].

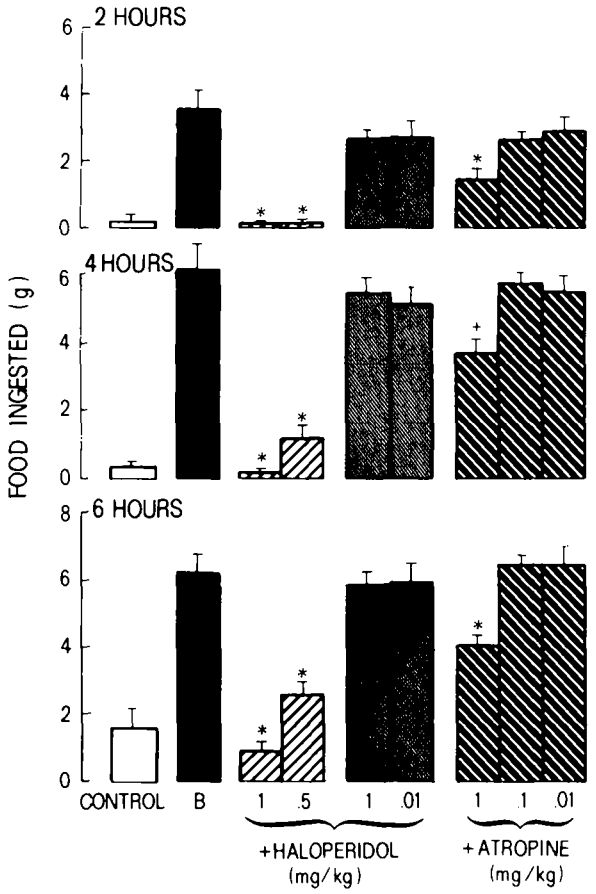

FIG. 4. Effect of haloperidol and atropine on butorphanol induced feeding. *$p<0.05$, †$p<0.05$, F(8,62), 2 hr=13.23, 4 hr=30.75 and 6 hr=23.46. Butorphanol induced significant feeding compared to the controls.

We conclude that the satiety effect of peripherally administered TRH represents a pharmacological effect in the rat. This may not be true in the dog [45]. Species differences in TRH effect have been demonstrated for gastric acid secretion in the dog and rat [24,29].

Pancreatic glucagon has been proposed as a mechanism for postprandial satiety because exogenous glucagon inhibits food intake [9], antibodies to glucagon elicit feeding [15] and endogenous glucagon is released during feeding [51]. We found no effect of glucagon in doses up to 400 μg/kg on butorphanol induced feeding.

EXPERIMENT 4

Dopaminergic antagonism with haloperidol and acetylcholine antagonism with atropine have both been shown to decrease feeding, presumably via central mechanisms [4,52]. In this experiment we examined the effects of atropine and haloperidol on butorphanol induced feeding.

Method

Butorphanol and the test agents were injected simultaneously subcutaneously at time zero in separate syringes. Food intake was quantitated at 2, 4 and 6 hours. A total of 78 rats were used with 7–8 rats in each group. An additional 52 rats were given access to either a 2 g/dl solution of glucose or water for 4 hours in order to assess whether the atropine and haloperidol were inhibiting mastication and swallowing by inhibiting salivary secretion. There was no food present during this experiment.

TABLE 1

EFFECT OF BUTORPHANOL (8 mg/kg) WITH AND WITHOUT HALOPERIDOL AND ATROPINE ON INTAKE OF WATER AND 2 g/dl OF GLUCOSE

Treatment	Water Intake n	Water Intake (ml)		Glucose (2%) Intake n	Glucose (2%) Intake (ml)	
Vehicle	6	2.80	0.95	6	3.30	0.53
Butorphanol (8 mg/kg)	8	1.97	0.23	8	2.74	0.30
Butorphanol + Haloperidol (0.5 mg/kg)	6	1.42	0.07*	6	2.60	0.90
Butorphanol + Atropine (1 mg/kg)	6	1.00	0.21*	6	2.67	0.13

*$p<0.05$ vs. butorphanol.

Results and Discussion

Both haloperidol (1 and 0.5 mg/kg) and atropine sulfate (1 mg/kg) decreased feeding due to butorphanol at all the time points tested (Fig. 4). We have previously found that dopamine blockade will decrease dynorphin-(1–13) induced feeding [37] and have suggested that dopamine is involved primarily in the initiation of chewing whereas the opiates are involved in the hunger drive [34]. Acetylcholine involvement in feeding appears to be linked to the nigro-striatal tracts and dopaminergic mechanisms [52], and as such it is not surprising that atropine acted similarly to haloperidol. Butorphanol failed to increase the intake of either water or the intake of 2 g/dl glucose confirming the specificity of butorphanol for solid food intake (Table 1). Neither haloperidol nor atropine inhibited the intake of 2 g/dl glucose after butorphanol, however, both decreased the intake of water when given in combination with butorphanol. These data suggest some specificity of both haloperidol and atropine towards both food and water ingestion.

GENERAL DISCUSSION

This study confirms that butorphanol is a potent stimulator of feeding in the rat. Table 2 compares the effects of the satiety agents used in this study to the effects of these agents on feeding induced by a variety of agents. As can be seen, the minimal effective dose required to suppress feeding induced by butorphanol was from 2 to 32 times greater than the dose required to suppress starvation and/or tail pinch induced eating for all the putative satiety peptides with the exception of bombesin. In addition, much higher doses of CCK-8 were required to suppress the butorphanol induced feeding than were necessary to suppress norepinephrine and insulin induced feeding. At least threefold lower doses of somatostatin were required to suppress insulin induced feed-

TABLE 2

EFFECT OF PERIPHERALLY ADMINISTERED SATIETY AGENTS ON FEEDING INDUCED BY A VARIETY OF METHODS

Agents	Minimal Effective Dose				
	Starvation (24–30 hr)	Tail pinch (2 min)	Norepinephrine (2 μg ICV)	Insulin (10 units/kg)	Butorphanol (8 mg/kg)
CCK-8	1 μg/kg	< 5 μg/kg	< 10 μg/kg	< 5 μg/kg	16 μg/kg
Somatostatin	10 μg/kg	1 μg/kg	10 μg/kg	10 μg/kg	32 μg/kg
Bombesin	5 μg/kg	1 μg/kg	< 10 μg/kg	< 5 μg/kg	< 8 μg/kg
GRP	(1 μg/kg)	—	—	—	32 μg/kg
TRH	8 mg/kg	< 4 mg/kg	—	—	16 mg/kg
Calcitonin	10 U/kg	10 U/kg	—	—	20 U/kg
Glucagon	(25 μg/kg)	< 1 mg/kg	—	—	400 μg/kg
Haloperidol	< 0.5 mg/kg	< 0.5 mg/kg	—	< 0.5 mg/kg	0.5 mg/kg
Atropine	< 2.5 mg/kg	< 2.5 mg/kg	—	< 2.5 mg/kg	1 mg/kg

All data except when in parenthesis has been obtained in our laboratory.
Greater and less than signs indicate lower or higher dose response data is not available.

ing. Thus, based on this data, bombesin appears to be unique among the putative satiety peptides in that the dose of it required to suppress butorphanol induced feeding after peripheral administration is similar to that required to reduce feeding induced by other feeding inducers. In this regard, the recent report localizing the site of bombesin in action on feeding to the lateral hypothalamus is of interest [50] although there is no evidence that this is also the site of action of peripherally administered bombesin.

It needs to be pointed out that, although both dynorphin and butorphanol have actions on the kappa receptor, butorphanol induced feeding is resistant to naloxone whereas dynorphin induced feeding is naloxone sensitive [32] suggesting that these two ligands may not induce feeding by a similar mechanism. It would seem that the fact that both butorphanol- and dynorphin-induced feeding are blocked by bombesin and haloperidol implies more about putative common final pathways than it does about a similar mechanism for the initiation of feeding. In addition, it should be pointed out that the same dose of butorphanol produces a different magnitude of feeding in different groups of rats necessitating that controls are always run simultaneously on the experimental day.

These studies are supportive of the concept that opiates play an important role in the initiation of feeding [26, 33, 43]. They demonstrate the utility of pharmacological approaches to unraveling the complex interplay of monoamines and neuropeptides in the regulation of feeding responses. The differing effects of satiety agents in different feeding paradigms suggests more than one site of action for some of these agents, e.g., bombesin and also the possibility that more than one feeding initiation system exists.

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