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Peripherally Administered Somatostatin Reduces Feeding by a Vagal Mediated Mechanism

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LEVINE, A. S. AND J. E. MORLEY. *Peripherally administered somatostatin reduces feeding by a vagal mediated mechanism.* PHARMAC. BIOCHEM. BEHAV. 16(6) 897–902, 1982.—Somatostatin (SS) is considered to be an important regulator of nutrient homeostasis. As such, we felt it would be of use to study in detail its effects on feeding. Intraperitoneal administration of SS (10 μg/kg) reduces spontaneous nocturnal feeding (3.6±0.6 g/2 hr vs 1.6±0.5 g/2 hr, $p<0.025$). In a separate study we found that SS also reduced spontaneous feeding in sham operated animals, but not in vagotomized animals (1.2±0.7 g/2 hr vs 3.8±0.3 g/2 hr, $p<0.05$). SS inhibited stress (tail-pinch) induced eating at 10 and 1, but not 0.1 μg/kg and also inhibited insulin (10 U/kg) induced feeding over a 3 hour period at the 10 μg/kg dose. SS failed to inhibit feeding induced by either the intracerebroventricular administration of norepinephrine, the GABA agonist muscimol, or the endogenous opioid, dynorphin. SS (10 μg/kg) failed to suppress water intake or ingestion of a 2% sucrose solution suggesting that somatostatin does not suppress feeding by a generalized disruption of behavior or due to the aversiveness of SS. However, food intake also was not suppressed following food deprivation, suggesting a possible aversive effect of SS. We conclude that somatostatin may play a role as one of the physiological signals involved in short-term appetite regulation. Like CCK, the effects of SS would appear to be mediated through the vagus.

Somatostatin Feeding Vagal mediated Satiety factors

THE tetradecapeptide somatostatin (SS), which was originally isolated from sheep and pig hypothalamic tissue [6,36], possesses a wide variety of activities, most of which are suppressive [3]. Included in these inhibitory activities are endocrine and exocrine functions of the gastrointestinal tract. SS inhibits (1) basal acid [14, 33, 38, 39], pepsin and intrinsic factor output in humans [38]; (2) release of insulin [2], glucagon [10], pancreozymin [37], gastric inhibitory polypeptide [8], motilin [42], enteroglucagon [35], and secretin [9]; and (3) absorption of glucose [11], xylose [44], galactose [34], lactose [34], triglycerides [40] and amino acids [13]. As SS is released following ingestion of food [3] and as SS has suppressive actions on gastrointestinal function, it appears that this gut hormone may play a role in feeding behaviors. Vijayan and McCann [43] demonstrated that intracerebroventricular administration of 3 nmoles of SS suppressed both water and food ingestion in rats. More recently, Lotter *et al.* [21] have reported that intraperitoneal administration of SS decreases food intake in rats and baboons, apparently by acting selectively on food intake rather than by inducing nausea or illness.

We have previously proposed an integrated hypothesis to explain the monoaminergic-peptidergic regulation of appetite [23]. It was suggested that food intake was initiated by a tonic signal produced by a dopamine-enkephalinergic mechanism in the area of the lateral hypothalamus and that this signal is governed by inhibitory inputs from the medial hypothalamic area, including a serotonergic-cholecystokinin (CCK) and a noradrenergic-thyrotropin releasing hormone (TRH) system. The current study was undertaken to evaluate the ability of SS to suppress food intake induced by various pharmacological agents and procedures in order to gain a better understanding of SS's role in the complex monoaminergic-peptidergic regulation of appetite.

GENERAL METHOD

Animals and Chemicals

Male Sprague-Dawley rats (250–300 g), kept under standard lighting conditions (12 hr/day artificial light, 6 a.m. to 6 p.m.) and given free access to Purina rat chow and water were used in all experiments. In the rats receiving intraventricular peptides or saline, stainless steel guide tubes were stereotactically implanted into the lateral ventricle under

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nembutal anesthesia at least 5 days prior to the commencement of the experiments. Drugs and peptides were administered in a 5 μl volume of saline when given intraventricularly, or in a 0.5 cc volume of saline subcutaneously.

All substances were purchased commercially: Insulin (Iletin U-100, Eli Lilly and Co.), muscimol, norepinephrine and dynorphin (Sigma Chemical Co., St. Louis, Missouri), and somatostatin [14] (donation from Ayerst Pharmaceuticals).

Statistics

All results are expressed as mean ± SEM. Results were compared by one-way analysis of variance followed by a two-tailed unpaired Student's t-test.

EXPERIMENT 1

The purpose of this study was to study the effect of SS on spontaneous feeding in rats and to evaluate whether SS affects food intake via the vagus nerve.

Method

The effect of intraperitoneal administration of SS on food intake was measured following a two hour period during which time rats normally ingest food (2000–2200 hr). SS was administered 5 min prior to the start of the feeding trial. Approximately 7–10 g of Purina rat chow was placed into the home cage of each animal with animals having free access to water. Following the two hour period the remaining food, including spillage, was measured.

For vagotomy, rats (n=8) were anesthetized with nembutal, a midline incision was made, and vagal trunks were visualized. Bilateral vagotomy was performed according to the method of Smith *et al.* [41]. Briefly, each vagal trunk was ligated and transected between two sutures. The gastric branches were transected in a similar manner. All vagotomies were verified anatomically (with the assistance of a 5× hand lens) after testing was completed. Shams were prepared (n=7) using the above procedure except for transection of the vagus. Animals were allowed to recover at least 7 days before being used in the study. The effect of SS on spontaneous eating in the vagotomized rats and the sham controls were then conducted as described above.

Results and Discussion

Spontaneous feeding from 2000–2200 hr was suppressed by intraperitoneal administration of SS (Fig. 1A). Lotter *et al.* [21] have previously shown that SS administered prior to a meal reduces food intake in rats and baboons. Thus SS suppresses feeding in animals acclimated to a meal feeding regimen and in rats ingesting food during the normal nocturnal feeding phase. Whereas Lotter *et al.* [21] reported that 10 ng/kg SS suppressed food intake during meal eating, we found that 1 μg/kg SS was not sufficient to suppress food intake in spontaneously feeding rats. This discrepancy in dosage may be due to the different sources of SS or to the strength of stimuli used to induce feeding.

Food intake was also measured in vagotomized animals during the nocturnal feeding period. SS (10 μg/kg) markedly suppressed spontaneous feeding in the sham animals, however, did not alter food intake in the vagotomized rats (Fig. 1B). This suggests that peripherally administered SS reduces food intake via gastric vagal fibers. Recently, Smith *et al.* [41] reported that peripherally administered CCK-8 acts in the abdomen through gastric vagal fibers and not directly on the brain to produce satiety in the rat. The similar action of CCK-8 and SS may be due to CCK-induced increase in SS secretion [12] (although SS itself depresses pancreozymin release [37]).

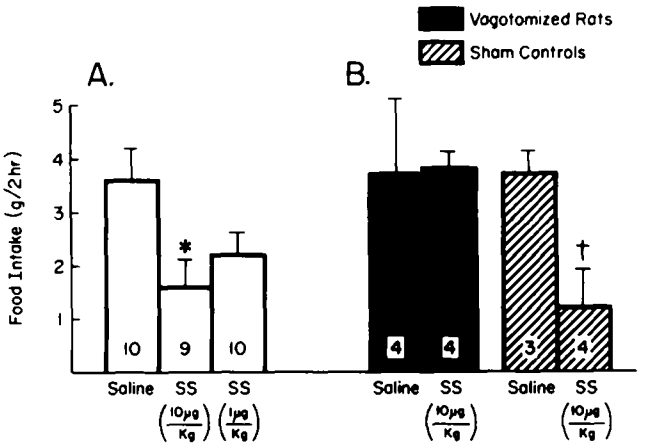

FIG. 1. Effect of somatostatin on spontaneous feeding (2000–2200 hr). (A) Normal rats not receiving surgery. (B) Vagotomized rats and their sham controls (*$p<0.025$, †$p<0.05$).

EXPERIMENT 2

Mildly pinching the tail of rats reliably induces a syndrome of gnawing, eating and licking in the presence of food. This model of stress induced oral behavior is believed to be dopamine dependent [2] and to involve activation of the endogenous opiates [22,24]. The purpose of this study was to evaluate the effect of SS on tail-pinch induced feeding.

Method

We used the tail-pinch method as previously described by us [16]. Briefly, behavioral testing was carried out in an unfamiliar plastic box containing 2 pellets of Purina rat chow (6–10 g). Tail-pinch behavior was induced by squeezing the rat's tail with a plastic towel clamp (Mac Bick, Murray Hill, NJ). Pressure was increased until the animal began to chew, at which stage pressure was maintained constant for a 2 min period with the exception that if the animal stopped chewing, pressure was slightly increased. Food ingestion was quantitated by weighing the pellet before and after the experimental period. Food spillage was defined as the quantity of uningested food removed from the whole pellet. If tail-pinch behaviors could not be induced within 2 min, the animal was deemed to be refractory to tail-pinch and food ingestion was recorded as 0 g.

The experimental protocol consisted of a 2 min basal tail-pinch trial after which SS was administered intraperitoneally and the animal was retested 15 min later with a second 2 min tail-pinch trial. Animals were allowed to remain in the testing arena during the interval between the tail-pinch trials. All results are expressed as:

$$\frac{\text{g/2 min of food eaten 15 min after drug administration}}{\text{g/2 min of food eaten during the basal period}} \times 100$$

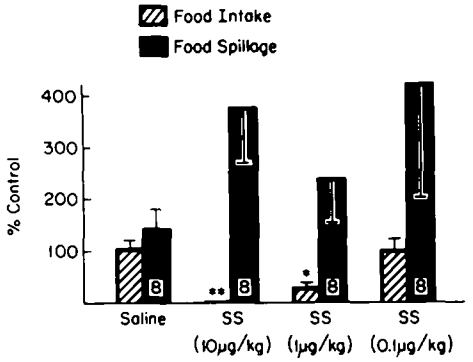

FIG. 2. Effect of somatostatin on tail-pinch induced feeding (*$p<0.01$, **$p<0.001$).

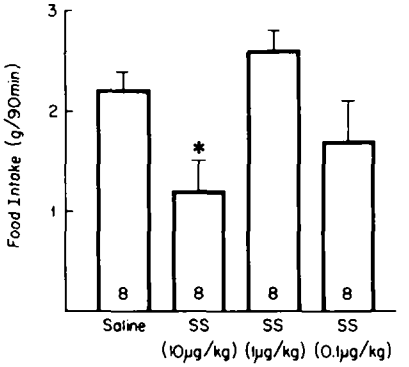

FIG. 3. Effect of somatostatin on insulin induced feeding (10 units/kg) (*$p<0.025$).

Results and Discussion

SS had an inhibitory effect on TP-induced feeding at the 10 and 1 μg/kg dose (Fig. 2). We [19] and others [31] have previously shown that CCK-8 (1, 5 and 10 μg/kg) also suppressed tail-pinch induced eating when administered peripherally, further suggesting a relationship between SS and CCK-8. In addition, the satiety factors bombesin (10 and 1 μg/kg) and TRH (4 and 8 mg/kg), which like CCK-8 and SS have peripheral effects, have been shown to suppress tail-pinch induced feeding [25,26]. Calcitonin (10 units/kg) which is released by CCK-8 also has been reported to suppress tail-pinch induced eating [17]. However, calcitonin appears to produce its satiety effect centrally, since intraventricularly administered calcitonin is a thousand-fold more potent than parenterally administered calcitonin [17].

EXPERIMENT 3

It is well established that peripheral administration of insulin will induce eating in rats consistently, with a resultant increase in body weight. This study was conducted to evaluate the effect of SS on insulin induced feeding.

Method

Eating was stimulated by subcutaneous administration of 10 U/kg of insulin. Insulin was administered and followed 90 min later by intraperitoneal injection of SS or saline. Rats were then placed in unfamiliar plastic boxes containing 6–10 g of rat chow for a further 90 min period following which food intake was quantitated.

Results and Discussion

SS administration suppressed insulin induced feeding over a 90 min period at the 10 μg/kg dose (Fig. 3). We have previously reported that CCK-8 (5 μg/kg) and bombesin (5 μg/kg) also suppressed insulin induced feeding [18].

EXPERIMENT 4

Intraventricular administration of the GABA agonist, muscimol, has been shown to induce feeding in rats, possibly by binding to GABA receptors within satiety areas, exerting an inhibitory effect on the system [32]. Norepinephrine has also been implicated as an important hypothalamic factor in the activation of feeding, although it has been demonstrated that its function after injection into some areas of the lateral hypothalamus can produce the opposite effect [15]. The purpose of this study was to evaluate the effect of SS on muscimol and norepinephrine induced feeding.

TABLE 1

EFFECT OF SOMATOSTATIN ON MUSCIMOL AND NOREPINEPHRINE INDUCED FEEDING IN RATS*

	n	Food Intake (g/30 min)
Muscimol (500 ng ICV) + saline	12	2.9 ± 0.5
+ SS (10 μg/kg)	10	2.7 ± 0.6
+ SS (1 μg/kg)	8	3.6 ± 0.9
+ SS (0.1 μg/kg)	5	3.2 ± 0.4
Norepinephrine (2 μg ICV)		
+ saline	10	1.4 ± 0.4
+ SS (10 mg/kg)	10	1.7 ± 0.3
+ SS (1 mg/kg)	8	2.4 ± 0.5

*During this time period rats receiving saline ICV ingested no food (n=5).

Method

Eating was stimulated by intracerebroventricular (ICV) administration of muscimol (500 ng/5 μl saline) or norepinephrine (20 μg/5 μl slightly acidified saline). Muscimol or norepinephrine was administered followed immediately by an intraperitoneal injection of SS or saline. Rats were then placed in unfamiliar plastic boxes containing 6–10 g of rat chow and food intake was quantitated for a 30 min period.

Results and Discussion

SS failed to suppress muscimol and norepinephrine induced feeding (Table 1). We have previously reported [27] that many known satiety factors fail to inhibit muscimol induced feeding, including CCK-8, bombesin, quipazine, TRH, isoproterinol and phentolamine. However, bombesin and CCK-8 do reduce norepinephrine induced eating [28]. Thus, although SS acts similarly to CCK-8 and bombesin in most feeding models, SS does not appear to be as potent a satiety factor in norepinephrine induced feeding.

TABLE 2

EFFECT OF SOMATOSTATIN ON DYNORPHIN INDUCED FEEDING*

	n	Food Intake (g/60 min)
Dynorphin (10 μg ICV)	7	1.6 ± 0.3
+ SS (10 μg/kg)	7	1.2 ± 0.5
+ SS (1 μg/kg)	5	1.5 ± 0.6

*During this time period rats receiving saline ICV ingested 0.2 ± 0.2 g (n=8).

TABLE 3

EFFECT OF SOMATOSTATIN ON WATER AND SUCROSE (2%) INGESTION IN WATER DEPRIVED RATS

	Fluid Intake (ml/60 min)	
	Water	Sucrose
Saline	4.4 ± 1.0	5.4 ± 0.6
SS (10 μg/kg)	5.4 ± 0.7	6.6 ± 0.8
SS (1 μg/kg)	4.7 ± 0.8	5.2 ± 0.6

EXPERIMENT 5

The potent opioid peptide, dynorphin-(1-13), has recently been demonstrated to stimulate food ingestion in sated rats [30]. The purpose of this study was to evaluate the effect of SS on synorphin-(1-13) induced feeding.

Method

Animals were housed in individual cages and all testing was carried out in their home cages. Use of the home cage is important for dynorphin-(1-13) induced eating, as in a previous experiment [30] only one of eight animals given 10 μg of dynorphin-(1-13) ICV ate when placed in a novel environment. All testing was carried out between 1400 and 1600 hr. Immediately after drug or vehicle administration, animals were returned to their cage together with 2 pellets of preweighed Purina rat chow (6–10 g) and food intake was measured for 60 min.

Results and Discussion

Dynorphin-(1-13) induced feeding was not suppressed by SS (Table 2). We have recently observed that CCK (10 μg/kg) does not suppress dynorphin-(1-13) induced feeding, whereas bombesin (10 μg/kg) markedly suppressed dynorphin-(1-13) induced feeding (unpublished observation).

EXPERIMENT 6

SS has been shown to have a generalized depressant effect and has been reported to cause nausea in humans [5]. In the present experiment we evaluated the effect of SS on ingestion of water or a sucrose solution (2%) to observe whether SS suppresses oral behaviors in general, which might suggest a generalized disruption of behavior.

Method

Water intake was stimulated by water-depriving the animals for 15 hr prior to the experiments (food given ad lib). At the time of each study rats were removed from their home cages and placed into plastic boxes unfamiliar to the rats. Water bottles were equipped with sipping tubes and were weighed to the nearest 0.1 g before and after each study. During the experiment the animals had free access to either water or sucrose (2%) for a 60 min period following administration of SS. Forty-four rats were used in the study and all rats received at least 3 training days prior to the study.

Results and Discussion

SS failed to suppress water intake or ingestion of a 2% sucrose solution (Table 3). It has been reported that intraventricular administration of SS (3 nmoles) suppressed water intake at 1 hour [43]. Lotter *et al.* [21] demonstrated that peripheral SS did not reduce ingestion of water or a saccharin solution. We have previously reported that flavor can alter the effective dose of a given antidopsinogen [20,29]. In the present study SS did not alter fluid intake of either water or a sucrose solution, suggesting that SS does not suppress feeding by a generalized disruption of behavior or due to the aversiveness of SS.

EXPERIMENT 7

In this experiment we attempted to provide a corresponding feeding test for the drinking test (Experiment 6). A 30 hr food deprivation trial was used, since in our hands a 15 hr deprivation schedule results in extreme variability in food intake between rats.

Method

Food intake was stimulated by depriving the rats of food for 30 hr (water given ad lib). At the time of each study rats were removed from their home cages, given an intraperitoneal injection of SS or saline, and placed into plastic boxes unfamiliar to the rats (containing 6–10 g of rat chow). Food intake was measured for the ensuing 30 min period. Sixty rats were used in the study (15/group) and all rats received three training days prior to the study.

Results and Discussion

SS failed to suppress food intake following food deprivation (Table 4). As SS failed to suppress intake of water, a 2% sucrose solution or rat chow following fluid or food deprivation, it appears that SS may have some slightly aversive qualities which may have been overcome by increasing the strength of the stimulus.

GENERAL DISCUSSION

Somatostatin appears to have an important general function in nutrient homeostasis. In addition to retarding nutrient absorption [11, 34, 44], inhibiting insulin [1], glucagon [10], and suppressing gut hormones in general [3], it now seems clear that SS also suppresses food intake under various con-

TABLE 4

EFFECT OF SOMATOSTATIN ON FOOD INTAKE IN FOOD DEPRIVED RATS

	Food Intake (g/30 min)
Saline	1.6 ± 0.1
SS (10 μg/kg)	1.7 ± 0.1
SS (1 μg/kg)	1.4 ± 0.2
SS (0.1 μg/kg)	1.6 ± 0.1

ditions. SS suppresses nocturnal feeding, meal feeding [21], and two types of stress related feeding, i.e., tail-pinch and insulin induced feeding in the rat. Lotter *et al.* [21] have demonstrated that SS also suppresses meal feeding in the baboon.

The finding in the present study suggests that as has been reported for CCK [41], the satiety effect of SS works via the vagus nerve. Lotter *et al.* [21] found that SS was ineffective as a satiety agent when administered centrally, whereas Vijayan and McCann [43] reported significant suppression of feeding when 3 nmoles of SS was administered centrally. SS may suppress feeding under certain circumstances when given centrally (as has been reported for CCK-8 [19]); however, probably it is more potent when administered peripherally. As drinking behavior was not suppressed following administration of parenteral SS, it appeared that SS did not decrease food intake due to generalized disruption of behavior or due to illness. Also, Lotter *et al.* [21] reported that SS did not lead to a conditioned taste aversion. However, it should be noted that in the present study food intake also was not suppressed following food deprivation, suggesting a possible aversive effect of SS.

There appear to be many similarities between SS and CCK-8: (1) both reduce the size of a subsequent meal; (2) both suppress food intake in insulin induced and tail-pinch induced feeding; (3) neither suppress muscimol or dynorphin induced feeding (although CCK does suppress norepinephrine induced feeding, whereas SS does not); (4) both seem to act via the vagus; (5) neither appear to result in a generalized disruption of behavior; (6) both are secreted during a meal; and finally, as is true for many peptides, (7) they are both found in the brain and the GI tract. CCK increases the release of SS [12], which may explain the close relationship between CCK and SS. However, CCK and glucagon (which also suppresses feeding) both release the potent anoretic peptide, calcitonin [4,7]. Thus, it is clear that only a complex series of interactions between many neuroregulatory agents can explain control of food intake.

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