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BRIEF COMMUNICATION

Cholecystokinin and Bombesin Suppress Operant Responding for Food Reward

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BABCOCK, A. M., M. LIVOSKY AND D. D. AVERY. *Cholecystokinin and bombesin suppress operant responding for food reward.* PHARMACOL BIOCHEM BEHAV 22(5) 893–895, 1985.—The effects of intraperitoneal injections of cholecystokinin (CCK) and bombesin (BBS) on food-rewarded operant responding were investigated. Response rates were significantly suppressed following administrations of CCK (0.7, 1.4, and 2.9 μg/kg). The effects appeared to be dose dependent. Responding was also suppressed following injections of BBS (6 and 16 μg/kg). These results confirm and extend previous findings concerning the possible function of these peptides.

Cholecystokinin Bombesin Operant responding Satiety

BOMBESIN (BBS) is an oligopeptide isolated from the skin of the European frog, *Bombina bombina* [1]. Analogs of BBS have been found in the gastrointestinal tract of several mammals including the rat and are released from the G.I. tract with feeding [9]. Peripheral injections of BBS produce a decrease in food intake in food-deprived [10] and sham-feeding rats [17]. Central administrations of BBS suppress food [3,15] and water intake [7]. In addition, central BBS produces a potent hypothermic effect [3,5]. Cholecystokinin (CCK) was first described as a humoral mechanism for stimulation of gallbladder contractions initiated by the presence of fat in the intestine [14]. Food-satiety has been reported following administration of CCK to intact rats [11], sham-fed rats [12] and genetically obese mice [18]. These findings suggest that BBS and CCK act as satiety signals.

The motivational aspects of these peptides can be demonstrated with operant responding paradigms. We have found that central administration of BBS suppresses operant responding for food and water reward in the rat (to be published). Similar findings have been reported in the pig [19]. Central and peripheral CCK suppress operant responding for food in the rat [16]. Glick *et al.* [13] were unable to demonstrate a significant effect on operant responding for food reward when administering CCK at a dose greater than that which produces a maximal physiological response and concluded that feeding behavior was unaffected by this peptide. Responding levels were shown to have substantially decreased, however, clearly suggesting a trend.

To our knowledge, no experiments have established the effects of peripheral BBS on operant responding for food reward. A significant reduction of operant responding for food reward following CCK administration has been demonstrated in only one study [16] suggesting the need for further confirmation of this finding. These relationships were investigated in the present experiments.

METHOD

Subjects

A total of 10 female Sprague-Dawley rats weighing 200–300 g were individually housed. Animals were gradually reduced to 85% of free feeding weight during a two week period. This was maintained throughout the experiment by weighing the animals and feeding them up to their individual reduced weights following each operant session. Tap water was available at all times.

Apparatus

Standard lever boxes were programmed to deliver a 45 mg food pellet (Noyes Co, NH) for every 10 depressions of the lever. The bombesin (Sigma Co, NV) and cholecystokinin (gift from Salk Institute, La Jolla, CA) were reconstituted with distilled water and diluted to the appropriate concentration with 0.9% saline.

Procedure

Animals were randomly divided into two equal groups and trained to lever press for food reward. One group (n=5) received intraperitoneal injections of 0.9% saline and BBS at doses of 4, 6, and 16 μg/kg weight. The second group (n=5) received intraperitoneal injections of 0.9% saline and CCK at a dose of 0.4, 0.7, 1.4, and 2.9 μg/kg weight. These doses are similar to those used by others to demonstrate the proposed satiety effects of CCK [2, 11, 12] and BBS [10,15]. The injection volumes were 0.2–0.35 ml. Treatments were randomly presented and all treatment days were separated by a non-treatment session. Sessions were 30 minutes in length.

The number of lever-press responses for both groups was evaluated separately using analysis of variance. A Newman-Keuls *post hoc* test was used to determine differences among individual means.

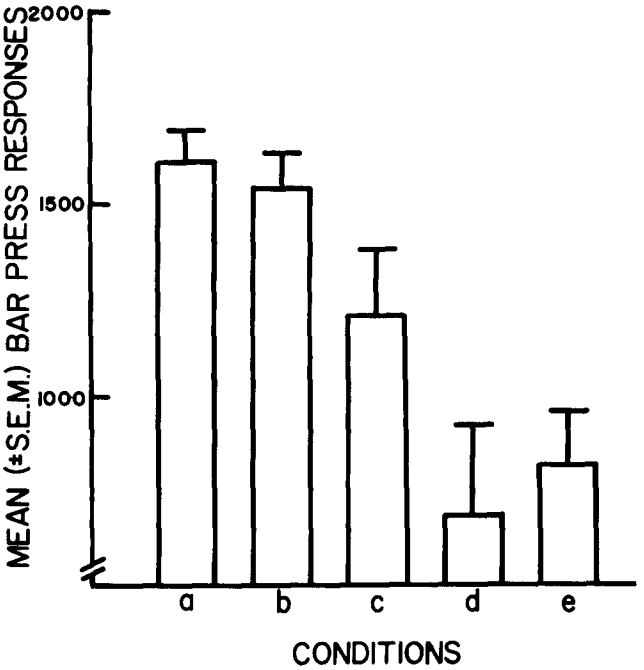

FIG. 1. Mean (±S.E.M.) bar press responses during a 30 minute period following CCK and saline treatments. Symbols represent saline (a), 0.4 μg CCK (b), 0.7 μg CCK (c), 1.4 μg CCK (d), and 2.9 μg CCK (e).

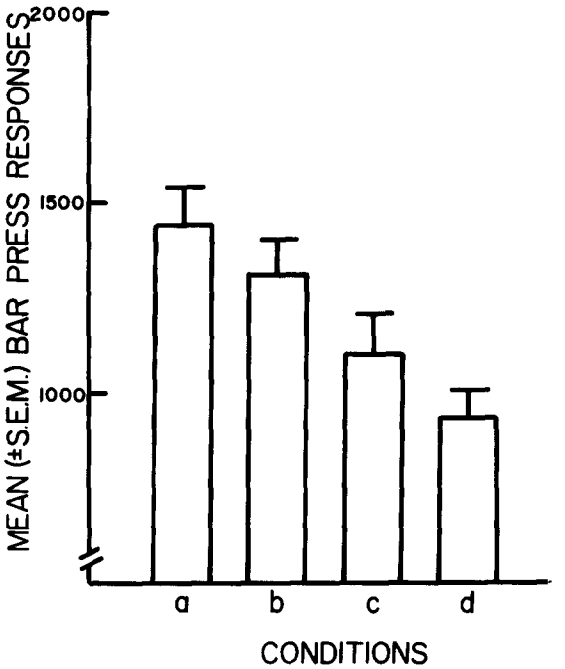

FIG. 2. Mean (±S.E.M.) bar press responses during a 30 minute period following BBS and saline treatments. Symbols represent saline (a), 4.0 μg BBS (b), 6.0 μg BBS (c), and 16 μg BBS (d).

RESULTS

Figure 1 shows the mean number of bar press responses following saline and CCK injections. All doses except 0.4 μg significantly suppressed responding for food reward when compared to baseline, $F(2,20)=11.50$, $p<0.05$. The highest dose (2.9 μg) produced greater suppression than the 0.4 μg and 0.7 μg doses ($p<0.05$). The 1.4 μg dose suppressed responding more than the 0.4 μg dose ($p<0.05$). The suppression appeared to be dose dependent.

Mean number of bar press responses following saline and BBS is illustrated in Fig. 2. The 6 μg and 16 μg doses significantly suppressed responding for food reward when compared to baseline, $F(5,20)=5.46$, $p<0.05$. Non-treatment sessions, saline control injections, and baseline levels did not significantly differ from each other for both CCK and BBS groups ($p>0.05$).

DISCUSSION

The results of the present study indicate that peripheral injections of BBS and CCK suppress operant responding for food reward. These findings are consistent with the proposed hypophagia effect of these peptides [2, 10, 11]. Our findings are also in agreement with those of Maddison [16], who reported suppression of operant responding for food reward following peripheral injections of CCK in the rat, and those of Parrott and Baldwin [19], who demonstrated operant suppression for food with peripheral injections of BBS in the pig. Our results support those findings of Glick *et al.* [13] in that a similar dose of CCK (4 μg) failed to suppress responding.

Dog plasma levels of CCK increase following BBS administrations [4] suggesting that the satiety following BBS is a result of CCK release. However the satiety effects of CCK and BBS diverge depending on the physical characteristics of the food [9]. In addition, CCK-induced hypophagia, but not BBS-induced hypophagia, can be blocked by vagotomy [21,22]. Identification of separate binding sites for BBS and CCK in pancreatic tissue has been reported [20]. These data suggest the existence of separate mechanisms for the production of hypophagia with CCK and BBS.

Recent work in this laboratory has demonstrated suppression of operant responding for food and water reward following central injections of BBS (to be published). Central injections of CCK have also been shown to suppress operant responding for food [16]. These findings suggest that both BBS and CCK are capable of influencing motivational systems concerned with food intake within the central nervous system.

Intravenous injections of CCK affect electrical activity of several areas of the rat brain including the hypothalamus [6] suggesting that CCK may in part act on the central nervous system to produce satiety. Since central administrations of BBS suppress food intake, it is reasonable to suggest that peripheral BBS may also in part act on the central nervous system to produce a satiety effect. Banks [4] has demonstrated that CSF levels of CCK are not increased following peripheral infusion of CCK suggesting that this peptide is incapable of passing the blood-brain barrier. However high plasma levels of CCK were inversely related to CSF levels of CCK, and BBS appeared to suppress or modulate this action. Further investigation is needed to clarify this functional relationship and the effects of BBS and CCK on feeding behavior.

The present results do not demonstrate whether the effects of these peptides on operant responding for food repre-

sent a satiety or an aversion. However the present study employed doses of CCK (approximately 8–63 Ivy Dog Units) that were similar to the dose used (40 Ivy Dog Units) to demonstrate that CCK elicits a complete behavioral sequence of satiety [2]. Malaise has also been suggested to explain the suppression of food intake following BBS [8], but this has been challenged by others [15].

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