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The cholecystokinin receptor antagonist L364,718 increases food intake in the rat by attenuation of the action of endogenous cholecystokinin

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1 To determine the role of endogenous cholecystokinin (CCK) in the regulation of food intake, the effects of the potent CCK receptor antagonist L364,718 were investigated on the intake of a palatable diet in non-deprived rats. The effect of a single dose of proglumide was also investigated for comparative purposes. In addition, the ability of L364,718 to antagonize the reduction in food intake produced by exogenous cholecystokinin-octapeptide (CCK8) or bombesin in food-deprived rats was determined.

2 L364,718 (10–100 $\mu g\,kg^{-1}$, i.p.) increased the intake of palatable diet during the 30 min test period. Proglumide (300 $mg\,kg^{-1}$, i.p.) also increased the intake of palatable diet. Conversely, CCK8 (0.5–5 $\mu g\,kg^{-1}$, i.p.) produced a reduction in the intake of the diet.

3 In fasted rats, L364,718 (100 $\mu g\,kg^{-1}$, i.p.) antagonized the reduction in food intake produced by CCK8 (10 $\mu g\,kg^{-1}$, i.p.) but not that produced by bombesin (50 $\mu g\,kg^{-1}$, i.p.). L364,718 did not increase food intake in these animals when measured over a 6 h period.

4 It is concluded that L364,718 is a potent, selective antagonist of the effects of CCK8 on food intake. The observation that L364,718 and proglumide increase the intake of a palatable diet provides some evidence that endogenous CCK is involved in the control of food intake in this model.

Introduction

Cholecystokinin (CCK) has been reported to reduce food intake and produce the behavioural syndrome of postprandial satiety in many species, including rats, sheep, rhesus monkeys and man (for review see Smith *et al.*, 1981a). In the rat, the reduction in food intake produced by intraperitoneal administration of cholecystokinin-octapeptide (CCK8) is abolished by abdominal vagotomy (Smith *et al.*, 1981b; Morley *et al.*, 1982). More specifically, destruction of vagal afferent fibres by surgical means (Smith *et al.*, 1985) or by treatment with the neurotoxin capsaicin (McClean, 1985; Ritter *et al.*, 1986) attenuates the reduction in food intake produced by CCK8, indicating that the initial site of action of this effect is in the periphery.

Studies showing that exogenous CCK produces satiety in the rat led to the suggestion that endogenous CCK released by ingested food is part of the negative feedback mechanism that terminates eating and elicits postprandial satiety (Gibbs *et al.*, 1973). If this hypothesis is correct, then a CCK receptor antagonist given alone should increase food intake. Studies using proglumide, a weak antagonist at CCK receptors, have yielded equivocal results (Collins *et al.*, 1983; Shillabeer & Davison, 1984; Schneider *et al.*, 1985). Thus, a reliable satiating effect of endogenous CCK remains to be demonstrated.

To determine the role of endogenous CCK in the regulation of food intake, the effects of the novel, potent peripheral CCK receptor antagonist L364,718 [3S(−)-N-(2, 3-dihydro-1-methyl-2-oxo-5-phenyl-1-H-1, 4-benzodiazepine-3-yl)-1H indole-2-carboxamide] (Evans *et al.*, 1986; Chang & Lotti, 1986) were investigated on the intake of a palatable diet in non-deprived rats. The effect of a high dose of proglumide was also investigated in this paradigm for comparative purposes. The palatable diet paradigm has previously been shown to be capable of detecting the hyperphagic effects of κ-opioid receptor agonists and benzodiazepines (Cooper *et al.*, 1985; Cooper & Yerbury, 1986). Using a different protocol, the ability of L364,718 to antagonize the reduction in food intake produced by CCK8 or bombesin was determined in fasted rats to verify that any effects on food intake were due to a specific antagonism of CCK. A preliminary account of this work has been presented to the British Pharmacological Society (Hewson *et al.*, 1987).

Methods

Animals

Male Wistar rats (Interfauna, Huntingdon) were used in all experiments. They were housed individually and maintained on a 12 h light-12 h dark cycle (lights on 07 h 00 min) and a room temperature of 21 ± 1°C.

Palatable diet studies

Rats (starting weight 175–200 g) were allowed free access to CRM pellet food (Labsure) and water. They were weighed daily to accustom them to being handled. The palatable diet used was very similar to that described by Cooper *et al.* (1985). It was freshly prepared each day and had the following ingredients and proportions: 50 ml Nestles sweetened condensed milk; 150 ml tap water; 200 g CRM powdered food (Labsure). After thorough mixing the diet set to a firm consistency.

The rats were familiarized with the palatable diet over a period of 10 weekdays (rats did not receive palatable diet at week-ends). Each rat was presented with a preweighed amount (30–40 g) of the diet in a Perspex petri-dish for 30 min each day in the home cage. Water and pellet food were removed during this 30 min period. Intake of the diet was measured by successive weighings of the food container on an electronic top-loading balance (Sartorius) and, after correction for any spillage, was recorded to an accuracy of 0.1 g. Any rat eating consistently less than 5 g at the end of this training period was excluded from further study. Before experiments were started the rats were also familiarized with the injection procedure. All experiments were performed between 10 h 00 min and 12 h 00 min.

On two separate experimental days rats were injected with either L364,718 (10–100 $\mu g\,kg^{-1}$, i.p.) or CCK8 (0.5–5 $\mu g\,kg^{-1}$, i.p.), 30 min or 5 min before presentation of the palatable food, respectively. In each experiment rats were randomly assigned to four groups ($n = 8$–10 per group). One group received vehicle and each of the remaining groups received one dose of drug. A third experiment investigated the effects of a single dose of proglumide on the intake of palatable diet. Proglumide (300 $mg\,kg^{-1}$, i.p.) or vehicle were administered 30 min before presentation of the diet ($n = 10$ rats per group). A period of two days separated experiments carried out in the same animals.

Statistical comparisons between the intake of palatable diet (grams of food eaten in 30 min) of treatment groups with the appropriate controls were made by use of the Kruskal-Wallis one-way ANOVA followed by the Mann-Whitney U-test (two-tailed). Significance was accepted for $P < 0.05$.

Antagonist studies in fasted rats

Rats (starting weight 75–100 g) were fasted for 18 h and allowed access to powdered CRM diet for 6 h between 10 h 00 min and 16 h 00 min each day. Water was available *ad libitum*. A period of 3 weeks was allowed for the animals to become accustomed to this feeding regime before experiments were started. At the start of the present experiments rats weighed between 175–200 g.

The ability of L364,718 to antagonize the reduction in the intake of powdered food produced by CCK8 or bombesin was investigated using a 2×2 factorial design. Rats were randomly assigned to treatment groups ($n = 7$ per group) and each rat received two injections. In the first experiment L364,718 (100 $\mu g\,kg^{-1}$, i.p.), or vehicle, was injected 30 min before CCK8 (10 $\mu g\,kg^{-1}$, i.p.), or vehicle. In the second experiment, bombesin (50 $\mu g\,kg^{-1}$, i.p.) was injected instead of CCK8. The doses of CCK8 and bombesin were selected on the basis of results from previous experiments (unpublished observations). Immediately after the second injection rats were given powdered food and the 30 min food intake measured. Results were analysed by two-way ANOVA for independent groups and individual group comparisons with the respective control groups were made with Dunnett's *t* test (two-tailed) (Winer, 1971).

To determine whether food intake was altered by L364,718 at any time point, additional measurements of cumulative food intake were made 1, 2, 3, 4, 5 and 6 h after food presentation. The food intake of the L364,718-treated groups were compared with control groups using the Mann-Whitney U-test (two-tailed).

Drugs

L364,718 (Merck, Sharp & Dohme) was prepared in 0.3 ml glycerol and 0.7 ml polyethylene glycol 400 per mg of L364,718 and diluted to the required concentration with distilled water. Proglumide (synthesized by Parke-Davis) was dissolved in 3% $NaHCO_3$ accompanied by gentle warming. This solution had a final pH of 9. CCK8 and bombesin (Bachem) were stored as frozen aliquots (corrected for peptide content) and diluted to the required concentration with sterile 0.9% w/v NaCl. All drugs were administered by the intraperitoneal route in a dose volume of 1 $ml\,kg^{-1}$, with the exception of proglumide where a dose volume of 4 $ml\,kg^{-1}$ was used.

Results

Palatable diet studies

CCK8 produced a dose-dependent reduction in the

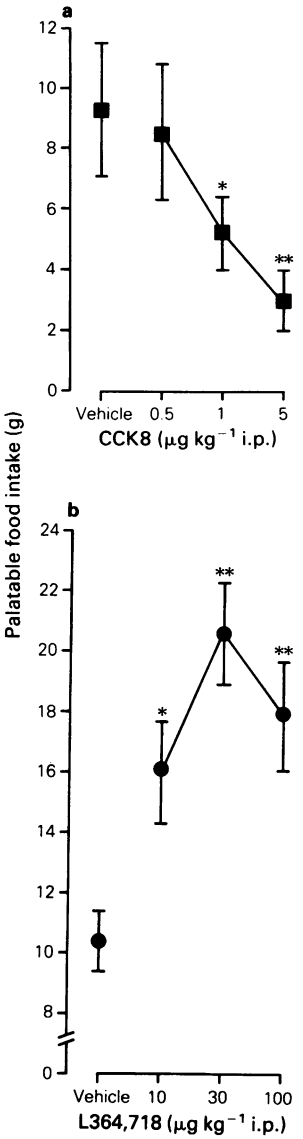

Figure 1 Effect of (a) cholecystokinin-octapeptide (CCK8) or (b) L364,718 on the intake of a palatable diet. On two separate experimental days, rats were injected with either CCK8 (0.5–5 μg kg^{-1}, i.p.; $n = 8$ per treatment group or < 364,718 (10–100μg kg^{-1}, i.p.; $n = 10$ per treatment group), 5 min or 30 min before presentation of the palatable diet, respectively. CCK8 produced a dose-related reduction, whereas L364,718 increased the intake of the palatable diet over the 30 min period compared to the control groups treated with the appropriate vehicle. *$P < 0.05$; **$P < 0.01$; Mann-Whitney U-test (two-tailed) following a significant difference between all groups using Kruskal-Wallis one-way ANOVA ($P < 0.01$).

intake of the palatable diet (Figure 1a). Significant effects were seen at doses of 1 μg kg^{-1} and 5 μg kg^{-1} CCK8 which reduced food intake by 44% and 68% respectively, when compared to control intake. The potent CCK receptor antagonist L364,718, however, produced the opposite effect to CCK8, in that it significantly increased the intake of the palatable diet at all doses tested (Figure 1b). The effect was maximal at a dose of 30 μg kg^{-1} L364,718, which doubled food intake compared to that of the control group. Proglumide, at a dose of 300 mg kg^{-1}, also produced an increase in the intake of the palatable diet from a control value of 9.2 ± 1.4 g to 15.1 ± 1.6 g ($P < 0.05$).

Antagonist studies in fasted rats

In rats fasted for 18 h, CCK8 (10 μg kg^{-1}) produced a significant reduction in the amount of food eaten in the 30 min period immediately after food presentation $F(1,24) = 12.34$, $P < 0.005$]. Figure 2 shows that L364,718 significantly antagonized the reduction in

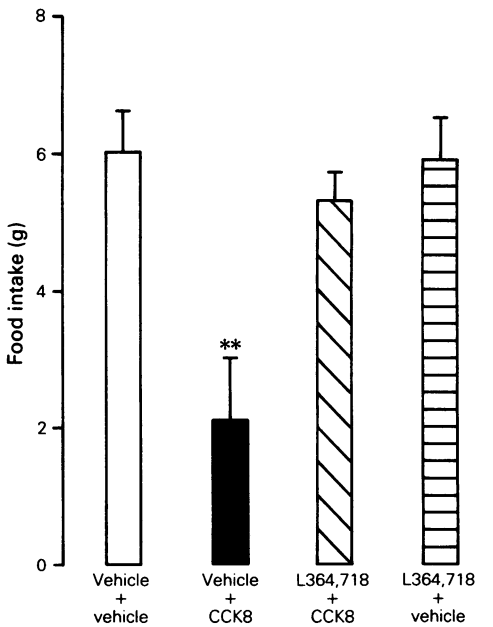

Figure 2 < 364,718 antagonizes the reduction in food intake produced by cholecystokinin-octapeptide (CCK8). Rats fasted for 18 h were injected with L364,718 (100 μg kg^{-1} i.p.) or L364,718 vehicle 30 min before presentation of food. A second injection of CCK8 (10 μg kg^{-1}, i.p.) or vehicle was given immediately before presentation of food. Pretreatment with L364,718 antagonized the reduction in 30 min food intake produced by CCK8. **$P < 0.01$, significantly different from control group, Dunnett's t test. $n = 7$ rats per treatment group.

food intake produced by CCK8 [drug-interaction term $F(1,24) = 6.65$, $P < 0.05$]. Bombesin (50 $\mu g\,kg^{-1}$) also produced a reduction in food intake in the fasted rats [$F(1,24) = 14.45$, $P < 0.001$]. In contrast to its effect on the response to CCK8, L364,718 did not antagonize the reduction in food intake produced by bombesin [drug-interaction term $F(1,24) = 0$, NS] (Figure 3). In neither of the drug-interaction experiments did L364,718 given alone increase food intake over the 6 h period (Table 1).

Table 1 Failure of L364,718 to increase food intake over a 6 h period in fasted rats

Treatment	*Hours after food presentation*			
	1	*2*	*3*	*6*
Vehicle	8.3 ± 0.9	11.0 ± 1.0	11.6 ± 0.8	20.2 ± 0.9
L364,718	8.6 ± 0.9	10.7 ± 0.9	11.8 ± 0.5	19.6 ± 1.2

Values are mean (± s.e.mean) cumulative food intake (g) at 1, 2, 3 and 6 h after food presentation. No significant difference was observed between the L364,718-treated and vehicle control groups at any time with the Mann-Whitney U-test (two-tailed). $n = 7$ rats per group. The data were taken from the L364,718–CCK8 antagonist study.

Discussion

The present results have confirmed that intraperitoneal administration of CCK8 was capable of producing a reduction in food intake in the palatable diet paradigm. Although many previous studies have demonstrated a reduction in food intake after administration of exogenous CCK to rats (Gibbs *et al.*, 1973; Morley *et al.*, 1982; Smith *et al.*, 1985 McClean, 1985, Ritter *et al.*, 1986), it was important to demonstrate such an effect in the palatable diet paradigm in view of the observation that the CCK antagonists L364,718 and proglumide themselves had an effect on the intake of the diet.

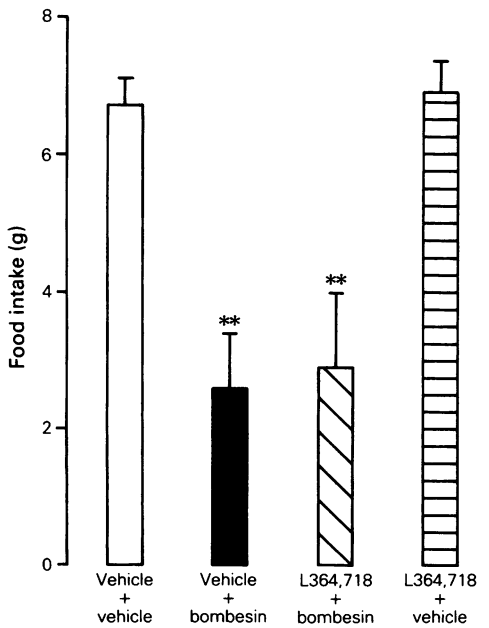

Figure 3 Failure of L364,718 to antagonize the reduction in food intake produced by bombesin. Rats fasted for 18 h were injected with L364,718 (100 $\mu g\,kg^{-1}$, i.p.) or L364,718 vehicle 30 min before presentation of food. A second injection of bombesin (50 $\mu g\,kg^{-1}$, i.p.) or vehicle was given immediately before presentation of food. The reduction in food intake produced by bombesin was not antagonized by L364,718. $^{**}P < 0.01$, significantly different from the control group, Dunnett's t test. $n = 7$ rats per treatment group.

In fasted rats, L364,718 potently antagonized the satiety effect of exogenously-administered CCK8. This result is in agreement with the high affinity shown by L364,718 for the peripheral CCK receptor and its antagonism of the contractile effects of CCK8 on the guinea-pig gall bladder *in vivo* (Chang & Lotti, 1986). The antagonism by L364,718 of the reduction in food intake produced by CCK8 thus provides pharmacological support for the studies which have demonstrated that intraperitoneal administration of CCK8 reduces food intake by an initial action in the periphery (Smith *et al.*, 1985; McClean, 1985; Ritter *et al.*, 1986). In view of the observation that CCK8 inhibits gastric emptying in mice and that L364,718 potently antagonizes this effect (Lotti *et al.*, 1986), it is tempting to speculate that this may be the mechanism by which peripherally administered CCK8 produces a reduction in food intake. However, as CCK reduces sham feeding in rats with gastric fistulae (Gibbs *et al.*, 1973) its effects on food intake appear to be independent of those on gastric emptying rate.

The failure of L364,718 to antagonize the reduction in food intake produced by another putative satiety peptide, bombesin, in fasted rats gives some indication that it is selective for the effects of CCK on food intake. This finding also provides further evidence that CCK8 and bombesin act via different mechanisms to reduce food intake, as suggested by previous studies (Smith *et al.*, 1981c; Collins *et al.*, 1983). Collins *et al.* (1983) also reported that proglumide partially antagonized the effects of high doses of bombesin (4–16 $\mu g\,kg^{-1}$, i.p.) and further suggested that these doses

of bombesin reduce food intake by the release of CCK. The results of the present study, which also used a high dose of bombesin (50 $\mu g\,kg^{-1}$, i.p.), do not support this conclusion.

The increase in the intake of palatable diet produced by the CCK receptor antagonists L364,718 and proglumide in this study is consistent with the hypothesis that endogenous CCK terminates food intake. The antagonist studies in fasted rats provide evidence that the increase in the intake of palatable diet produced by L364,718 could be due to a specific blockade of the effects of endogenously released CCK. Thus, the results of the palatable diet study provide good pharmacological evidence for a role of endogenously released CCK in the regulation of food intake, complementing the observations that there is a rise in plasma CCK after a meal in rats (Liddle *et al.*, 1984), and in normal and obese human subjects (Burhol *et al.*, 1984).

The observation that CCK antagonists can increase food intake is in agreement with the findings of Shillabeer & Davison (1984) who reported that proglumide increased the intake of liquid food in rats fasted for 18 h and then given a preload of 10 ml liquid food before the test. However, other workers have failed to observe an increase in food intake after the administration of CCK receptor antagonists. For example, Schneider *et al.* (1985) could not replicate the findings of Shillabeer & Davison (1984) using proglumide under similar experimental conditions. Similarly, Crawley *et al.* (1986) failed to observe an increase in palatable food intake in fasted mice following the administration of either proglumide or another CCK receptor antagonist, benzotript.

The inconsistent effects on food intake obtained by previous workers using proglumide or benzotript may reflect the low potencies of these compounds as antagonists of the effects of CCK8 when tested *in vitro* (Hahne *et al.*, 1981; Chang *et al.*, 1985), necessitating the use of large doses of these compounds *in vivo*. For example, proglumide was routinely used at a dose of 150 $mg\,kg^{-1}$ in the earlier studies discussed above. This, in turn, increases the possible occurrence of non-specific effects which may influence the outcome of the experiment. However, the potency and selectivity of the CCK antagonist used was unlikely to be the major reason for the inconsistent results of previous studies, since in most cases it was demonstrated that proglumide or benzotript, at the doses used, effectively blocked the effects of exogenously-administered CCK8 (Collins *et al.*, 1983; Schneider *et al.*, 1985). In addition, proglumide increased the intake of palatable food in the present study. Alternatively, the conflicting results on food intake obtained previously with weak CCK antagonists may in part by explained by the choice of feeding paradigm. Thus, the earlier experiments investigated the effects of CCK antagonists on food intake in animals fasted for 18–20 h (in some cases a preload of liquid food was given before the test). In the present study it was observed that L364,718 did not increase food intake in rats fasted for 18 h and hence the use of animals deprived of food may prevent the expression of the hyperphagic effects of CCK antagonists. The present study overcame the possible problems associated with the *in vivo* use of weak antagonists and paradigms involving food deprivation by the use of L364,718, which is a highly potent and selective peripheral CCK receptor antagonist both *in vitro* and *in vivo* (Chang & Lotti, 1986; Lotti *et al.*, 1986), and the use of non-deprived animals trained to eat a palatable diet in a paradigm that has been shown to be sensitive to the hyperphagic effects of other drugs (Cooper *et al.*, 1985; Cooper & Yerbury, 1986).

It is not clear why L364,718 failed to increase food intake in fasted rats in this study, as although control rats eat at a maximal rate initially and may therefore be unable to increase their food intake, they do stop eating about 2 h after receiving food. If CCK was involved in terminating eating at this time, food intake would be expected to increase in animals treated with L364,718. This substance is an effective antagonist of the effects of CCK8 on gastric emptying in the mouse for up to 5 h after its administration (Lotti *et al.*, 1986) and therefore the failure to increase food intake in the fasted rat model cannot be attributed to its duration of action. We have also failed to observe an increase in food intake in fasted rats following proglumide administration at a dose that clearly antagonized the reduction in food intake produced by CCK8 (Davies & Hewson, unpublished observations).

It therefore appears possible that endogenous CCK does not play a major role in terminating food intake in the fasted rat. Furthermore, these results indicate that the mechanisms involved in the termination of eating behaviour may differ in non-deprived animals eating a palatable food and those eating following a period of fasting.

It is concluded that L364,718 is a potent, selective antagonist of the effects of CCK8 on food intake. The observation that L364,718 and proglumide increase the intake of palatable food provides some pharmacological evidence that endogenous CCK is involved in the control of food intake in this model.

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