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Effects of the CCK Receptor Antagonist MK-329 on Food Intake in Broiler Chickens

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COVASA, M. AND J. M. FORBES. *Effects of the CCK receptor antagonist MK-329 on food intake in broiler chickens.* PHARMACOL BIOCHEM BEHAV **48**(2) 479–486, 1994.—The cholecystokinin (CCK) receptor antagonist MK-329 (previously L-364,718) was administered intraperitoneally to free-feeding broiler chickens and tested for conditioning effects using the colored food paradigm. The 8.0, 16.0, and 32.0 μg/kg doses of MK-329 did not exert any effect on food intake and failed to condition a color preference or aversion. When higher doses were used (90, 180, and 360 μg/kg) MK-329 caused a significant increase in food intake during the 2-h test period. Intravenously injected MK-329 (70, 140, and 280 μg/kg) produced an increase in food intake, with maximum increases occurring at a dose of 70 μg/kg. CCK (14 μg/kg) caused a reduction in feeding, and this effect was not blocked by pretreatment with intraperitoneal injection of MK-329 (32, 90, 180, and 360 μg/kg). The results question the role of endogenous CCK in satiety in chickens.

Cholecystokinin MK-329 Chickens Conditioning Preference test Satiety

CCK has been reported to inhibit food consumption in a variety of species, including rat, mouse, hamster, dog, pig, sheep, wolf, chicken, monkey, and humans (1,15,20,26,28,29,37,40, 47,56). The mechanism mediating the satiety action of CCK has been extensively investigated in rats and, to a lesser extent, in chickens. Evidence indicates that CCK, released from the intestine after a meal, acts on receptors in the gut, relaying sensory information via the vagus nerves to brain regions regulating feeding behaviours (9,11,12,19,31,39,44,52,53,58).

Considerable debate has taken place on whether the effect of exogenous CCK on food intake is physiological or pharmacological, whether changes in food intake are secondary to CCK-induced malaise as opposed to satiety per se, and whether the effects are central or peripheral in origin (2,21, 41,55,57). If the hypothesis that CCK acts as a satiety factor is correct, it should follow that administration of a specific antagonist to CCK would block the effect of endogenous CCK released during a meal and, thus, increase the amount of food consumed. Recent studies with MK-329 (previously named L-364,718), a potent antagonist of the CCK-A receptor, which is found mainly in peripheral tissues, have demonstrated an increase in food intake in nonfasted rats (16,24,27), pigs (17), and humans (59). As with CCK itself, the effect of the antagonist is dependent upon the paradigm (dose, strain, age, type of food, time of day, fasted vs. nonfasted, prefed vs. no prefeeding) (51).

Several studies showed that chicks are capable of appropriate food selection (23) and that they associate general feeding-related behaviors with beneficial consequences (60) and aversion to substances associated with long-term aversive consequences (45). Kutlu and Forbes (30) showed that chicks are capable of adjusting their intake of ascorbic acid to meet their requirements by means of color. The use of color supports findings that revealed that chickens have a strong ability to employ color in learning situations and that obtaining shifts away from color is very difficult (5,14,33). In our previous studies, which involved intraperitoneal injections of CCK, we showed that chickens can associate injections of exogenous CCK with one colored food and develop an aversion for the food color paired with CCK (8). Furthermore, the association with color was reversed as a result of pairing injections with reversed colored foods.

No published studies have previously assessed the effect of MK-329 on food intake in chickens. Also, no studies have yet utilized the CCK antagonist MK-329 to investigate the possible physiological involvement of CCK using the conditioning colored food paradigm.

GENERAL METHOD

Day-old female broiler chicks were obtained from Mayfield Chicks Ltd. Rossendale, Lancs. They were fed standard

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TABLE 1
THE DESIGN OF EXPERIMENT 1

Group	Treatment	Foods	Number of Birds
1	8 μg MK	R+/G−	6
2	16 μg MK	R+/G−	6
3	32 μg MK	R+/G−	6
4	Vehicle	R+/G−	6
5	8 μg MK	R−/G+	6
6	16 μg MK	R−/G+	6
7	32 μg MK	R−/G+	6
8	Vehicle	R−/G+	6

starter crumbs (Dalgety Agriculture, Bristol, UK) ad lib and housed in a heated chick room (33°C reduced to 22° by week 3 and with 24 h lighting). At 3 weeks they were transferred to individual cages in another room and fed on a commercial pelleted grower food (Dalgety Agriculture Ltd, Bristol, UK). One week before the experiment started, the chicks were handled daily to become accustomed to the experimental conditions. At the beginning of the experiment, the chicks were weighed and divided into groups with equal mean body weight. The colored foods were prepared by mixing 10 ml of red or green food coloring (Gold Seal Liquid Colour, Clayton and Jowett Ltd., Runcorn, Chesire) with 40 ml water and spraying onto 1 kg of the food which was then allowed to dry at room temperature. To determine the conditioning effects, a preference test was carried out in which each bird was fasted for 1 h and then taken out of its cage and placed in a test box (180 mm high, 500 mm wide, and 340 mm deep) at the opposite end to two containers, one containing green food, the other red. The time to first peck was recorded; if a chick had not approached either food container within 1 min, no result was recorded. If a choice was towards the color which for that particular bird was associated with MK-329 injection, the time was recorded as positive; if the choice was for the colored food associated with saline, the time was recorded as negative. The reciprocal of the time was then calculated to give a value representing the speed with which a choice was made and the resulting data were subjected to *t*-test. The test preference was always carried out on nontreatment days and, therefore, the chickens were not under the direct influence of the blocker during behavioral testing.

Drugs Used

Sulphated CCK octapeptide (CCK-8), purchased from Bachem Ltd., Essex, UK, was reconstituted in pyrogen-free distiled water and stored as frozen aliquots (corrected for the peptide content). Before each injection it was diluted with physiological saline to the required concentration. The concentration of CCK used was 10 μg per 1 ml of solution. The volume injected varied from 0.4–2.8 ml, depending on body weight and dose used.

MK-329, a CCK antagonist, donated by Merk Sharp and Dohme Research Laboratories, Essex, UK, was dissolved using different vehicles according to the administration route. When injected intraperitoneally, 1 mg MK-329 was dissolved in 0.3 ml glycerol and 0.7 ml polythylene glycol 400 and then diluted to the required concentration with distilled water. For control injections, the same concentration of glycerol and polythylene glycol 400 dissolved in distilled water was used. When injected intravenously, MK-329 was dissolved in a solution consisting of 80% propylene glycol and 20% dimethyl sulfoxide (Sigma Chemical Co. Ltd, Dorset, UK). For control, a stock solution containing 80% propylene glycol and 20% dimethyl sulfoxide was used. All solutions were prepared daily prior to injection. Drug and vehicle solutions were injected either intraperitoneally or intravenously using different doses according to the experiment. The concentration of MK-329 used was 1 mg per 10 ml of solution. The volume injected varied from 0.4 to 3.7 ml per bird, according to their body weight and dose administered.

The data were analyzed using the analysis of variance in SAS (46) with repeated measures, followed by Duncan's multiple range test unless otherwise specified.

EXPERIMENT 1

Showing that exogenous CCK produces satiety in chickens 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. If this hypothesis is correct, then a CCK receptor antagonist given alone should increase food intake. Studies using CCK receptor antagonist proglumide have yielded equivocal results (6,48,50).

To determine the role of endogenous CCK in the regulation of food intake, the present experiment aimed to test two hypotheses: a) Whether MK-329 exerts any effect on food intake using three different doses (8, 16, and 32 μg/kg); b) Whether MK-329 could condition a colored food preference or aversion in free feeding chickens.

Method

Forty-eight, 3-week-old female broilers with a mean body weight of 590 g were used in a 2 × 4 factorial design experiment. They were divided into eight groups of six birds each with equal mean body weight. Two colored food combinations (R+/G−; R−/G+) and four treatments were given (8,

TABLE 2
MEAN COLOURED FOOD INTAKE (±SEM) AFTER 2 h FOLLOWING INJECTION (g/BIRD)

	Time after Injection (min)			
Treatment (μg/kg)	30	60	90	120
Vehicle	11.6 ± 1.5	14.1 ± 1.6	17.0 ± 1.7	19.9 ± 2.0
8 MK	9.8 ± 1.4	12.8 ± 1.7	16.5 ± 1.9	21.0 ± 2.1
16 MK	9.9 ± 1.5	13.9 ± 1.9	17.2 ± 2.0	20.6 ± 2.2
32 MK	11.0 ± 1.4	14.9 ± 1.8	17.7 ± 1.9	21.2 ± 2.9

16, 32 μg/kg MK-329 and vehicle solution). The first half of the birds (four groups) received injection of MK-329 paired with red food (conditioning stimulus) and vehicle paired with green food (R+/G−). For the other four groups, green food was paired with injection of MK-329 and red food with injection of vehicle (R−/G+) (Table 1).

One day the birds were given one color in association with MK-329 and on the following day the other color in association with vehicle. On the third day, a preference test was carried out to see whether birds could associate the colored food with the internal consequences of the drug. Colored food was given for the 2 h following injection, and measurements of intake were taken every half an hour for 2 h. The birds were not fasted prior to injection and they received uncolored food ad lib for the rest of the day. The experiment lasted 9 days, during which each bird received three intraperitoneal injections of MK-329 and three of vehicle. Every third day birds were tested for their colored food preference, so that the speed of association the injection with a particular colored food could be determined.

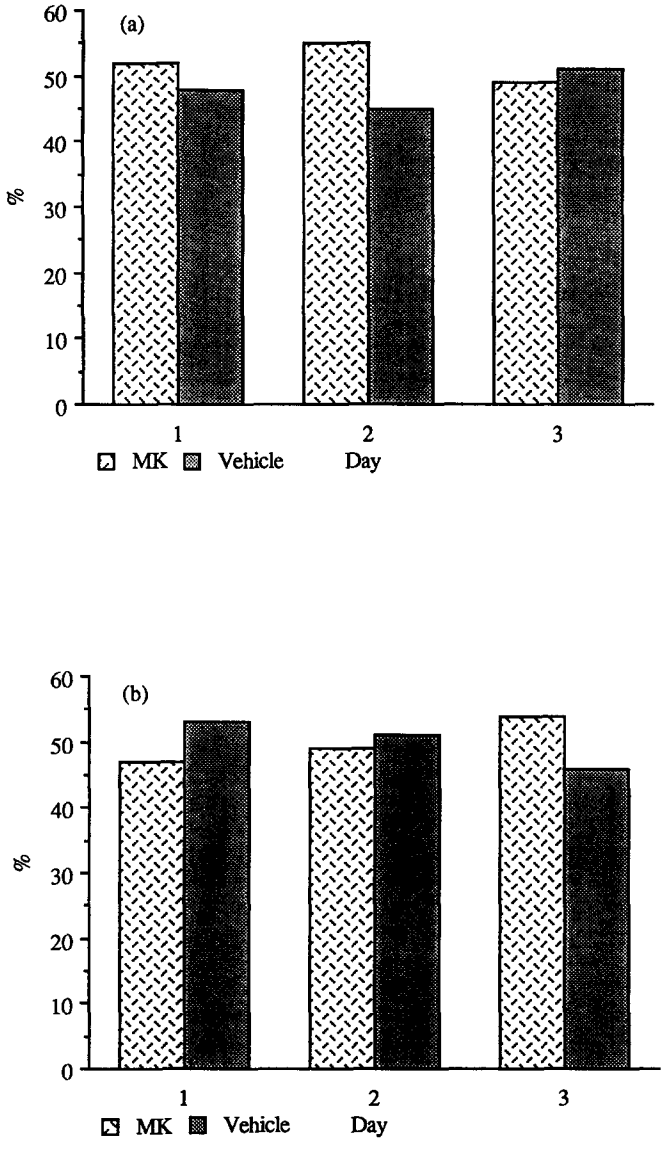

FIG. 1. Preference of birds following injection of MK-329 and vehicle. The graph shows a random preference for both food associations: R+/G− in a and R−/G+ in b ($p < 0.05$).

Results

Intraperitoneal injections of MK-329 had no effect on food intake of free-feeding chickens following 2 h after injection ($p > 0.05$) (Table 2).

Also, MK-329 failed to condition any color preference or aversion ($p > 0.05$) as the birds showed a random approach to colored food (Fig. 1).

Experiment 2

Experiment 1 failed to demonstrate any effect of MK-329 using doses of 8, 16, or 32 μg/kg, and it is possible that the doses used were too low to counteract endogenous CCK release and produce enhanced feeding. Therefore, the present experiment was designed to test the effect of MK-329 on food intake, when injected intraperitoneally using three higher doses (90, 180, and 360 μg/kg).

Method

Twenty-four, 5-week-old female broilers of 800 g mean body weight were used in a 4 × 4 Latin square arrangement. The birds were divided into four groups of six birds each with equal mean body weight and were subjected to four treatments (90, 180, 360 μg/kg MK-329 and vehicle solution). Each group received each of these treatments according to the Latin square design. The experiment was repeated once. The birds were not food deprived. The injections were given at around 1100 and food intake was measured every half an hour for the following 2 h. Food and water were available ad lib throughout. The analysis of variance was done for repeated measurements using the GLM (General Linear Model) procedure.

Results

MK-329 caused a progressive increase in food intake that became significant with every dose ($p < 0.05$) after 2 h following injection (Table 3).

No differences were observed between doses used. A group × dose effect was noticed throughout the experiment at each time interval ($p < 0.05$).

The drug did not produce any observed short- or long-term behavioral effects that could be interpreted as abnormal.

EXPERIMENT 3

MK-329 has been shown to produce a dose-related increase in food intake in pigs when injected intravenously with a maximal increase of 50% above control (17).

The purpose of this experiment was to investigate the effect of MK-329 on food intake in chickens using the intravenous site of administration.

Method

Five female broilers with similar body weight (mean 1157 g) and 5 weeks of age were used in a 5 × 5 Latin square experimental design. They received five treatments, four doses of MK-329 (35, 70, 140, and 280 μg/kg) and one of vehicle solution. Every bird was injected into the brachial vein using a 25 mm butterfly catheter needle with each of the five treatments once, in a random order according to the Latin square

TABLE 3

MEAN CUMULATIVE FOOD INTAKE (±SEM) DURING 2 h FOLLOWING IP INJECTION OF MK-329 (EXPERIMENT 2)

Treatment Dose (μg/kg)	Time after Injection (min)			
	30	60	90	120
Vehicle	4.9 ± 0.5	7.6 ± 0.8	10.8 ± 0.8	13.2 ± 0.9
90 MK	6.2 ± 0.8	9.8 ± 1.1	13.8 ± 1.2	17.0 ± 1.4*
180 MK	5.9 ± 0.6	10.1 ± 0.8	13.3 ± 1.0	16.7 ± 1.2*
360 MK	6.5 ± 0.9	9.8 ± 1.0	13.8 ± 1.1	16.0 ± 1.1*

*Indicates significant differences ($p < 0.05$).

design. The birds were allowed at least 48 h between treatments for the vein to recover. Food and water were given ad lib. Food intake for 2 h following the injection and total daily food intake were measured during the experiment.

Results

MK-329 caused an increase in food intake after 2 h but total daily food intake was not affected (Table 4).

Maximal increases in food intake (approximately 70% above control) were observed at a dose of 70 μg/kg. A low dose (i.e., 35 μg/kg) had no effect. Interestingly, the 280 μg/kg dose of MK-329 produced a smaller increase in feeding to the 70 μg/kg dose, but not sufficient to be significant. A similar bell-shaped curve for MK-329 has been reported in the rat (24), and in the pig (17).

EXPERIMENT 4

On the basis of previous work with exogenous CCK (8) and MK-329, one of the assumptions underlying the design of this experiment was that MK-329 would antagonize the satiating effect of exogenous CCK-8 in free-feeding chickens. Therefore, the following experiment aimed to test the effect of MK-329 on the inhibition of food intake produced by exogenous CCK.

Method

Ten 6-week-old female broilers with a similar body weight (mean 1016 g) were used in this experiment. A 5 × 5 Latin square design was employed with two replicates. The birds were injected intraperitoneally using five treatments consisting of the following pairs of injections: a) vehicle followed by another injection of saline; b) vehicle followed by injection of CCK-8 (14 μg/kg); 3-5) MK-329 (90, 180, 360 μg/kg) followed by injection of CCK (14 μg/kg).

Each bird received each of the treatments once according to the Latin square design. The second injection was given 5 min after the first injection and food was measured every half hour for the following 2 h.

Results

The results are given in Table 5.

CCK-8 (14 μg/kg) caused a significant decrease in feeding in the first half an hour. Pretreatment of the chickens with MK-329 did not abolish the inhibitory effects of CCK (14 μg/kg) on feeding. Although there was a tendency for 180 μg/kg of MK-329 to equalise the intake in the first half hour to the level of the control group, the increase was not sufficient to be statistically significant. After 2 h the food intake following 180 MK-CCK was almost similar to the control group (vehicle-saline), whereas the 90 and 360 μg/kg dose of MK followed by CCK still maintained food intake at a similar level to the vehicle-CCK treatment.

TABLE 4

MEAN FOOD INTAKE (±SEM) OF BIRDS FOLLOWING IV INJECTIONS OF MK-329 (EXPERIMENT 3)

Treatment Dose (μg/kg)	Food Intake (g/Bird)	
	2 h	24 h
Vehicle solution	12.2 ± 1.1*	144.0 ± 14.4 NS
35 MK-329	13.8 ± 1.9*†	142.4 ± 11.0 NS
70 MK-329	21.2 ± 2.3‡	158.0 ± 13.0 NS
140 MK-329	19.6 ± 4.2†‡	127.6 ± 9.6 NS
280 MK-329	16.6 ± 3.2*†‡	140.0 ± 11.8 NS

*†‡Values with different superscript were significantly different ($p < 0.05$); NS, nonsignificant.

EXPERIMENT 5

Unlike in mammals, the results from Experiment 4 showed that the CCK antagonist MK-329 did not block the response to exogenous CCK-8 in broiler chickens.

One reason for the failure of MK-329 to block exogenous CCK-8 in this study may be that the antagonist was given too close to the time of CCK administration. In similar work with rats, MK-329 was administered 30 min prior to exogenous CCK and/or food presentation to allow more time for adequate distribution and antagonism of the appropriate receptors (11,36,54). In addition, our results from the previous experiments indicate that the effect of MK-329 does not appear clearly until 120 min after administration.

Another reason for the failure of MK-329 to prevent the effect of CCK in Experiment 4 could be that the dose of MK-329 used was too high and some authors suggest that blockade of exogenous CCK must be achieved with a dose of MK-329 which, by itself, does not increase food intake (36,54). Otherwise, an apparent blockade could simply be the result of summation of two opposing actions on different systems.

To eliminate these possible effects and interactions the

TABLE 5

MEAN FOOD INTAKE (±SEM) DURING 2 h FOLLOWING IP INJECTION (EXPERIMENT 4)

Treatment Dose (μg/kg)	Time after Injection (min)			
	30	60	90	120
Vehicle-saline	6.3 ± 2.3*	12.5 ± 2.4*	15.0 ± 2.5*	19.5 ± 2.7*
Vehicle-14 CCK	2.4 ± 1.3†	7.5 ± 1.9*	10.6 ± 2.2*	15.6 ± 3.3*
90 MK-14 CCK	2.2 ± 1.0†	7.5 ± 2.0*	10.6 ± 2.4*	14.4 ± 2.7*
180 MK-14 CCK	4.7 ± 1.6†	8.8 ± 2.5*	13.7 ± 2.6*	18.5 ± 2.9*
360 MK-14 CCK	3.2 ± 1.1†	7.6 ± 2.2*	11.3 ± 3.1*	14.3 ± 3.0*

*†Values in the same column with different superscripts were significantly different ($p < 0.05$).

present experiment investigated the effect of MK-329 on the inhibitory effect of CCK-8 on intake during normal feeding. Two new elements have been introduced: a) a control treatment in which the dose of MK-329 chosen does not increase food intake, and b) the injection of the antagonist 30 min prior to CCK administration.

Method

Eight, 4-week-old female broiler chickens with similar body weight (mean 930 g) were used in a 4 × 4 Latin square design experiment. Chickens were not deprived of food and they were injected intraperitoneally using four treatments consisting of the following pair of injections: vehicle + saline; MK-329 + saline; vehicle + CCK-8; MK-329 + CCK-8.

A repeated measures design was used, with each bird receiving all treatments in a random fashion; a period of at least 2 days was allowed between successive tests. Food intakes were recorded over 2 h as in Experiment 4, and analysis of variance was done for cumulative intake over each time period. The dose of MK-329 used was 32 μg/kg, which did not increase food intake when administered by itself in our previous experimental conditions (Experiment 1). The dose of CCK-8 was 14 μg/kg; the concentration and volume injected were similar to those used in Experiment 4.

Results

Administration of CCK-8 + vehicle caused a decrease ($p < 0.05$) in feeding starting 30 min after injection. However, this inhibitory action of CCK was relatively short lived, lasting until 60 min (Table 6).

Administration of MK-329 (32 μg/kg) followed by saline produced no effect on feeding although food intake at 60 min after saline injection was increased compared to the vehicle + saline treatment, but did not reach the significance level ($p > 0.05$).

Pretreatment with MK-329 did not prevent the feeding responses that were present following administration of CCK-8 ($p > 0.05$).

Discussion

Reference has already been made in the Introduction to the hypothesis put forward by Gibbs et al. (22), namely, that CCK released from the small intestine during a meal acts in a negative feedback manner to induce satiety. Although this hypothesis was based on the observation that exogenous CCK reduces food intake in a number of species, there was very little evidence to support a role for endogenous CCK in satiety. It was suggested that a reasonable way to approach this question was to use drugs that block the action of CCK, the reasoning being that if endogenous CCK is involved in the termination of eating, then antagonists of CCK should produce an increase in meal size by blocking its inhibitory effect on feeding. However, experiments with a relatively weak CCK antagonist (proglumide) produced contradictory results. In the present study we have found that MK-329, a potent and specific peripheral CCK-receptor antagonist, increases food intake in free-feeding chickens. Thus, these results confirm

TABLE 6

MEAN FOOD INTAKE (±SEM) DURING 2 h FOLLOWING IP INJECTION (EXPERIMENT 5)

Treatment Dose (μg/kg)	Time after Injection (min)			
	30	60	90	120
Vehicle + Saline	5.1 ± 1.5*	5.8 ± 1.6*†	9.9 ± 2.6*	14.1 ± 3.2*
Vehicle + CCK	1.5 ± 0.8†	4.1 ± 1.5†	11.5 ± 3.6*	14.1 ± 3.6*
MK + Saline	6.1 ± 2.0*	10.7 ± 1.8*	14.2 ± 2.7*	19.0 ± 2.5*
MK + CCK	1.5 ± 1.2†	3.4 ± 1.7†	9.0 ± 2.4*	12.8 ± 2.0*

*†Values in the same column with different superscript were significantly different ($p < 0.05$).

those already described in the rat (16,24) and pig (17), and also demonstrate that a CCK antagonist can enhance feeding in a species other than rat and pig.

The significant increase in food intake produced by MK-329 provides pharmacological support for the studies that have demonstrated that intraperitoneal administration of CCK-8 reduces food intake by an initial action in the periphery (35,43,52). In view of the observation that CCK-8 inhibits gastric emptying in mice and that MK-329 potently antagonises this effect (32), it is tempting to speculate that this may be the mechanism by which peripherally administered CCK-8 produces a reduction in food intake. However, as CCK reduces sham feeding in rats with gastric fistulae (22), its effect on food intake appears to be independent of that on gastric emptying rate. It was also noted in humans that changes in gastric emptying rates were not responsible for the changes in appetite (59).

The observation that CCK antagonists can increase food intake is in agreement with the findings of Shillabeer and Davison (50) 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. (48) could not replicate the findings of Shillabeer and Davison (50) under similar experimental conditions. Similarly, Crawley et al. (13) failed to observe an increase in intake of palatable food in fasted mice following the administration of either proglumide or another CCK receptor antagonist, benzotript.

The present findings showed that the dose of MK-329 necessary to inhibit the action of endogenously released CCK varies according to the site of administration. When the drug was administered intraperitoneally, the effective dose in increasing food intake was higher (90 and 180 μg/kg) than that required for the antagonism of endogenous CCK when MK-329 was given by intravenous injection (70 μg/kg). The difference in the effective dose is likely to be due to the poor absorption from the peritoneal cavity because the compound has been reported to have a short half life.

Studies carried out in pigs and in a number of other species have shown that systemic administration of the CCK-A receptor antagonist devazepide, but not the CCK-B receptor antagonist L356,260, increased food intake (7) and this has been taken as evidence that endogenous CCK acts on peripheral CCK-A receptors; hence, its involvement in satiety. However this can be confounded, because devazepide crosses the blood–brain barrier (42) and it is possible that the increased food intake observed following its administration is due to a central effect rather than to antagonism of endogenous peripheral CCK. The present study suggests that the satiety effect of endogenous CCK could be mediated either peripherally by the CCK-A receptor subtype, located predominantly in the periphery, or centrally by similar receptors found in discrete regions of the central nervous system (25,38). Therefore, the stimulatory effect of MK-329 on feeding does not provide conclusive evidence that CCK is acting on CCK-A receptors because MK-329 can antagonize the CCK binding to the CCK-B receptors at high concentrations (49).

The mode of action of CCK in mediating meal-induced responses cannot be determined precisely from studies using administration of MK-329 or other antagonists because possible widespread effects of these antagonists on gastrointestinal transit and digestion of food may alter a particular response by mechanisms not involving a direct action of CCK. Furthermore, interpretation of the results of these studies requires consideration not only of the relative affinities of these antagonists for the various CCK receptor subtypes but also of their pharmacokinetic properties (time-dependent processes of absorption, distribution, tissue localisation, biotransformation, and clearance).

It is unlikely that the time elapsed between administration of the drugs could affect the outcome of the results. In Experiment 4, CCK-8 was injected immediately after administration of the blocker, whereas in Experiment 5, 30 min were allowed between injections and the effects were similar in both experiments. Injections of A70104, a CCK-A receptor antagonist, 10 min before the administration of exogenous CCK-8 abolished the inhibitory effect of CCK on feeding in pigs (18).

Further investigation is necessary to determine whether comparisons of the dose–response effects and the time of administration of the antagonist before the CCK injection will be generally useful in defining physiological actions of CCK on the receptor subtype involved in specific CCK actions.

Unlike in rats, the present work with chickens did not clearly demonstrate that administration of CCK inhibits food intake by an action at CCK-A receptors and questions the role of endogenous CCK as a satiety factor. A recent study on gastroduodenal motility and coordination in chickens that used infusion of CCK-A (L364,718) and CCK-B (L365,269) receptor antagonists to antagonize the action of exogenous CCK-8 has given similar results (34). Studies carried out in the pig and other species have shown that administration of the CCK-A receptor antagonist devazepide, but not the CCK-B receptor antagonist L356,260, increases food intake, and this has been interpreted as evidence that endogenous CCK is acting on the peripheral CCK-A receptors and, therefore, it is involved in satiety (17). However, recent studies, using a new CCK-A receptor antagonist A70104, believed not to enter the CNS from the systemic circulation, had no stimulatory effects on food intake but abolished the effect of intravenous CCK on operant food intake in pigs. This suggests that endogenous CCK released from the small intestine does not act as a satiety factor in the pig (18). Because these results are different from those found in rats, studies using local peripheral and central administration of CCK antagonists directed at specific CCK receptor populations would be useful in defining mechanisms of CCK actions in control of feeding behavior in chickens. It would be of interest to see the action of A70104 both centrally and peripherally, in chickens.

The inability of the CCK antagonist MK-329 to block the response to CCK-8 shows that there are differences in CCK receptors between birds and mammals. In agreement with this, the antagonist L364,718 was unable to block CCK-induced pancreatic secretion in turkeys (4).

In conclusion, these results support the evidence that CCK-A receptor antagonist MK-329 increases food intake in chickens but question the involvement of endogenous CCK as a satiety agent. Whether the effect of MK-329 is central or peripheral remains to be clarified.

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