THE ROLE OF OROSENSORY CUES IN THE MEDIATION OF CHOLECYSTOKININ-INDUCED SATIETY

by

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STATEMENT BY AUTHOR

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Date
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ABSTRACT

Cholecystokinin (CCK), a gastrointestinal hormone, is regarded by some to be a mediator of short-term satiety that interacts with orosensory cues to produce normal satiety. In these studies, the effects of CCK on hunger in the absence of orosensory cues are investigated. In Experiment 1, 16 rats were injected with either CCK Octapeptide (1.5 µg/kg) or NaCl (0.9%) and allowed to bar-press for food for one hour. The CCK group bar-pressed for 30% fewer pellets (relative to baseline) than the NaCl group. Experiment 2 was identical to Experiment 1 except that after injection, there was a one hour extinction trial. Experiment 3 was identical to Experiment 2 except that the first 50 responses were reinforced (10 pellets on a 5:1 fixed ratio) before the extinction began. In Experiments 2 and 3, no differences were found in the rate or number of bar-presses to extinction. It had been hypothesized that the 10-pellet "priming" procedure would allow a CCK-orosensory interaction to reduce responses to extinction. Further study using varying amounts of "priming" might yield useful information about the nature of this interaction. The similarity between the CCK and NaCl groups under extinction was interpreted as evidence that CCK alone is not a sufficient central mediator of short-term satiety.
INTRODUCTION

Much research has been directed toward the nature and causes of food satiety. Various theories have emphasized oral cues, gastric distention, blood glucose levels, intestinal hormones, conditioning, or combinations of these factors and others.

There is a growing literature that suggests that cholecystokinin (CCK), a gastrointestinal hormone, is a mediator of short-term satiety. CCK is secreted by cells in the mucosa of the upper small intestine. Among its effects in the digestive system are the following: (1) the stimulation of gastric juice secretion, (2) a contraction of the gall-bladder, (3) an enhancement of the motility of the small intestine, and (4) a stimulation of pancreatic juice secretion (Johnson, 1974). According to Johnson (1974), the release of CCK is primarily stimulated by the presence in the duodenum of fatty acids, amino acids, and calcium and hydrogen ions. An immunoreactive CCK content has been found in the mouse cortex (Straus and Yalow, 1979) and an effect of CCK has been shown in the hypothalamus by Schanzer, Jacobson, and Dafny (1978).

Gibbs, Young, and Smith (1973) have demonstrated that CCK can suppress feeding in the rat. A reduction in meal size as a result of CCK infusion in rhesus monkeys has been shown by Gibbs, Falasco, and McHugh (1976). Using human subjects, Kissileff et al. (1979) have demonstrated a CCK-related reduction in food intake, although Greenway and Bray (1977) failed to demonstrate this same effect. In a more
recent paper, Stacher, Bauer, and Steinringer (1979) found a self-reported reduction of hunger when human subjects were given CCK along with appetite stimulation (smells and sounds associated with meal preparation).

These and other studies have led to the theory that CCK is a mediator of short-term satiety. According to this theory, stimulation of the duodenum by certain food products causes the mucosa cells in the intestine to secrete CCK, which then travels in the blood to the brain (probably hypothalamus) to suppress food intake and elicit the entire behavioral sequence usually accompanying satiety in rats (grooming, inactivity, etc.).

Other lines of research, however, have shown that other factors are able to terminate feeding. Studies by Jordan (1969) and Walike, Jordan, and Stellar (1969) suggest that accurate food regulation is managed by gastric and oral cues working synergistically, whereas Davis and Collins (1978) have reported that distention of the small intestine can inhibit food intake.

Conditioning theories take many forms, but generally suggest that an organism learns when to start and stop eating. Using rats, Booth and Davis (1973) have shown that oral cues can be associated with their post-ingestional consequences such that in subsequent meals, intake is regulated on the basis of these oral cues. A paper by Revusky (1968) has shown that associations can be made between orosensory cues and post-ingestional consequences even if separated by several hours. Stunkard (1975) states that this long-term conditioning is the mechanism
by which an animal regulates food intake. Booth (1977) speculates that conditioning might be the only automatic short-term satiety mechanism available to mammals. In a model proposed by Hawkins (1977), CCK release or nutrient repletion are unconditioned stimuli for satiety, while orosensory cues or gastric distention are the conditioned stimuli that become associated with the unconditioned stimulus.

The suggestion that CCK causes satiety is not without controversy. A primary charge is that CCK inhibits feeding not by a natural satiety mechanism, but by creating illness or a food aversion. Deutsch and Hardy (1977) created a conditioned aversion to a novel flavor by following its taste with injections of CCK. They presume that the aversion is due to sickness or nausea caused by the CCK. Holt et al. (1974) could not produce a taste aversion with injections of CCK and conclude that CCK's inhibition of feeding is not due to illness. A report by Deutsch and Gonzalez (1978), however, suggests that the taste aversion paradigm is not sensitive enough to detect a very mild aversion. In a review of CCK and its status as a satiety hormone, Mueller and Hsiao (1978) conclude that aversion is not the cause of the suppressive effect of CCK on food intake. They base this conclusion on the lack of toxic effects of CCK and the many unsuccessful attempts to produce a conditioned taste aversion with CCK.

Although Johnson (1974) states that CCK may enhance intestinal motility, Deutsch, Theil, and Greenberg (1978) found that CCK decreased duodenal motility, as opposed to the large, regular fluctuations seen in normal satiety. They conclude that this effect is due to the
aversive nature of exogenous CCK. Conclusive answers to the aversion question must await a more detailed and systematic study of the doses necessary for aversion and suppression of feeding, along with a more exact knowledge of the quantities of endogenously released CCK.

Mineka and Snowden (1978) demonstrated an initial inhibition of food intake in rats when injected with CCK, but after repeated injections, the response was inconsistent. They also found some evidence of habituation to CCK.

In light of the questions raised by the above studies regarding the role of CCK as a satiety hormone, it is obvious that the story is far from complete and that more study is needed on the parameters of the CCK effect. Nevertheless, the evidence is compelling that CCK plays a role, although as yet an unclear role, in food intake.

Young et al. (1974) found that sham-fed rats do not satiate. They implanted gastric fistulas into rats and allowed them to sham-feed on a liquid diet. With the fistulas open, the rats sham-fed continuously for periods up to 7.5 hours. They interpret this finding as evidence that taste and oropharyngeal stimulation alone are not enough to elicit satiety. A later paper, however, suggests that pre-gastric food-contingent stimulation is sufficient for the termination of a meal. Kraly, Carty, and Smith (1978) found that sham-feeding rats would terminate a meal, although the meal size was larger and the inter-meal interval shorter than in a normal feeding situation. Because of these differences, they conclude that pre-gastric stimuli alone are not sufficient for normal satiety. Kraly and Smith (1978) found that stimulation
from gastric and pre-gastric sites was enough for normal satiety and that the contact of food with the intestines was not necessary; they do not, however, rule out an interaction of stimuli from gastric, pre-gastric, and intestinal sites.

Kraly et al. (1978) also found that when rats were sham-fed, meal size was larger and inter-meal interval was shorter than that found in normal-feeding rats. However, when sham-fed rats were also given an injection of CCK (30 U/kg), meal size and inter-meal interval became normal. They interpret their results to mean that pre-absorptive stimuli alone (pre-gastric plus CCK) are sufficient for normal-appearing satiety. Antin, Gibbs, and Smith (1978) found that rats sham-fed less after injections of CCK than after injections of NaCl. They also found a direct relationship between the duration of sham-feeding before CCK injection and the satiating effect of CCK. They interpret this relationship as evidence for pre-gastric stimulation and CCK acting synergistically.

There exist, then, several studies in which the effects of pre-gastric stimulation alone are studied (Kraly, Carty, and Smith, 1978; Young et al., 1974), and several in which the effects of pre-gastric stimulation and CCK together have been studied (Kraly et al., 1978; Antin et al., 1978; Gibbs and Smith, 1977). Studies involving intact animals and CCK injections (Gibbs et al., 1973; Gibbs et al., 1976) are similar to the latter group (sham-feeding plus CCK) in that the animal has the benefit of pre-gastric stimulation and CCK (endogenous and exogenous). There has not been any systematic study of CCK in the absence of
pre-gastric stimulation. Although there have been numerous studies in which the stomach or intestine was pre-loaded with food (that is, placed in the body by means other than normal ingestion), the tests for the effects of these pre-loads have usually been a measure of subsequent food intake (Ehman, Albert, and Jamieson, 1971; Walike et al., 1969). The subsequent food intake necessarily provides some type of pre-gastric stimulation to the animal which may interact with gastric or intestinal factors, even though the usual sequence of these factors is reversed.

In the studies that follow, an attempt is made to study the effects of CCK in the absence of any other satiety cues or interactions. In an operant conditioning paradigm, the number of responses (barpresses) for food varies with the motivational level (i.e., hunger level) of the animal. A food-deprived animal will bar-press more than a satiated animal. Similarly, the number of responses to extinction varies with the hunger level of the animal. A hungry animal will take longer (or bar-press more) until extinction than a satiated one. This idea makes intuitive sense and is supported by an early experiment by Perin (1942). Perin found that the number of responses required for extinction had a positive relationship to both the number of previous reinforcements and the number of hours of food deprivation. Using a large number of previous reinforcements maximizes the effect of hunger level on the number of responses required for extinction. Responses to extinction, therefore, offer an index of hunger (or satiety) that is free from the interaction effects that may develop during a feeding test of hunger; in this sense, it is a "purer" test of the hunger or
satiation of the animal. Hull (1943) regards the number of responses to extinction as a reflection of the animal's level of drive. By injecting rats with CCK and testing them in an extinction situation, the effects of CCK on the rats' hunger can be directly assessed without contamination by any food-related cues.
EXPERIMENT 1

Experiment 1 is a basic experiment designed to demonstrate that CCK does indeed reduce food intake in the operant chamber under conditions similar to those to be used in the extinction procedures.

Method

Sixteen male Sprague-Dawley rats weighing 325-400 grams at the beginning of the experiment were individually housed in stainless-steel cages (24.5 x 18 x 18 cm.) with wire-mesh floors. All rats were maintained on a 12:12 hr light-dark schedule with ad lib access to tap water throughout the experiment. The rats were left in plexiglass Skinner boxes (23.5 x 20 x 19 cm.) overnight for one night, where they learned, without shaping, to bar-press for 45mg food pellets (Noyes Lab pellets) on a continuous schedule of reinforcement. Because of the limited number of available Skinner boxes, the experiment was run in two separate groups of eight rats each. In each group of eight, four rats were left in the boxes overnight for one night, and the other four were left in the next night. After the entire group learned to bar-press on a continuous schedule of reinforcement, they were again left in the Skinner boxes overnight where the reinforcement schedule was fixed at 5:1. If a rat failed to respond, additional training in the form of shaping or additional time in the box was given until the experimenter judged that the rat was adequately responding.
After all rats learned the bar-press response, they were returned to their home cages with ad lib food (Wayne laboratory animal diet) and water. On the afternoon of the same day, all except 15 g of lab chow was removed from the cages. Water remained ad lib. Beginning at approximately 1:00 p.m. of the following day (baseline 1), half of the rats were placed in the Skinner box where they bar-pressed for food on a fixed reinforcement ratio of 5:1 for one hour. Water was ad lib during this period. A cumulative recorder recorded the bar-pressing activity for each rat. After the hour elapsed, the rats were then returned to their home cages and given 15 g of lab chow. The other half of the rats were then placed in the Skinner boxes and similarly recorded for one hour. They were also returned to their home cages after the hour and given 15 g of lab chow. An identical procedure was followed for the next three days, yielding a total of four baseline days in which the rats bar-pressed for food for one hour each day. During these four days, the only food the rats received was the food they bar-pressed for and the 15 g that was placed in their cages after the bar-pressing.

On day 5, prior to being placed in the Skinner boxes, rats were injected with either CCK Octapeptide (1.5 µg/kg dissolved in distilled water) or physiological saline (in an equivalent volume). Five minutes after injection, the rats were placed in the Skinner boxes, where again they bar-pressed for food pellets on a fixed ratio of 5:1.

**Results**

The numbers of pellets consumed during each hour trial on baseline days 2, 3, and 4 were averaged for each rat to yield a baseline
amount for each rat. The mean baseline amount was 155.04 pellets for the NaCl group and 144.95 pellets for the CCK group. During the one-hour test period (day 5), the number of pellets consumed was recorded at 15-minute intervals. The cumulative number of pellets consumed at each measurement for each rat was expressed as a percentage of the total mean baseline consumption for that rat. Each rat's food intake, then, is expressed in terms of four cumulative percentages. The means of these cumulative percentage scores are represented in Table 1.

Table 1. Baseline data and cumulative mean percentages of baseline (+ S.E.M.) for NaCl and CCK groups in experiment 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Base (# Pellets)</th>
<th>Minutes after Beginning of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>NaCl</td>
<td>155.04</td>
<td>40.25</td>
</tr>
<tr>
<td></td>
<td>(+25.51)</td>
<td>(+5.47)</td>
</tr>
<tr>
<td>CCK</td>
<td>144.95</td>
<td>40.50</td>
</tr>
<tr>
<td></td>
<td>(+23.58)</td>
<td>(+7.14)</td>
</tr>
</tbody>
</table>

\[ t < 1 \quad 1.52 \quad 2.09* \quad 2.09* \]

*p < 0.05
The means for the two groups at each measurement (taken at 15, 30, 45, and 60 minutes after placement in the Skinner boxes) were analyzed using a one-tailed t-test for independent groups. CCK and NaCl groups differed significantly ($t = 2.09$, $df = 14$, $p < .05$) at the 45- and 60-minute measurements. Figure 1 illustrates the changes in cumulative percentages over time for the two groups.

**Discussion**

As shown in Figure 1, injections of CCK significantly decreased operant responding for food. The results are consistent with those of Hsiao, Wang, and Schallert (1979) and Maddison (1977) which report a significant CCK-related decrease in operant responding for food. Glick, Thomas, and Mayer (1971) failed to find a significant CCK-related reduction in bar-pressing.

Since the difference between the NaCl and CCK groups was not significant at the 30-minute measurement but was significant at the 45-minute measurement, the effect of CCK must have begun to take place in the interval from 30 to 45 minutes after the beginning of the trial. This time course is in agreement with Maddison's (1977) finding that the effect of CCK on operant responding is maximal 30 minutes after injection.
Figure 1. Bar-pressing expressed as a cumulative mean percentage of baseline for experiments 1, 2, and 3.--(*denotes significant difference from control, p < .05)
EXPERIMENT 2

Having confirmed that CCK reduces operant responding for food, the author next wanted to study the effects of CCK on extinction. If CCK is a natural satiety signal, it is possible that exogenously administered CCK actually reduces the hunger of the animal. It has been demonstrated that a hungry animal will respond more times until extinction than a less hungry animal (Perin, 1942). Therefore, a rat that has been injected with CCK should be less hungry than its saline control and should extinguish quicker or with fewer responses. Experiment 2 is designed to test this effect. If CCK reduces hunger at some central location (equivalent to hunger reduced by food intake), the CCK-treated rats should extinguish with fewer responses. However, if satiety is the result of a synergy between orosensory cues and CCK, as suggested by Antin et al. (1978) and Gibbs and Smith (1978), the CCK alone will not be effective in reducing the number of responses to extinction. According to a synergy model, this lack of effect would be due to a lack of pre-gastric cues.

**Method**

Sixteen male Sprague-Dawley rats weighing between 280-405 grams were treated and trained in a manner identical with that in Experiment 1. Also, four days of baseline data were collected in a manner identical with Experiment 1. On day 5, however, no food reinforcement was given to any of the rats, although they did receive injections of CCK
Octapeptide (1.5 µg/kg) or NaCl (in an equivalent volume) exactly as in Experiment 1. Since no food reinforcement was given, day 5 was an extinction trial. An equipment malfunction necessitated eliminating the results from one rat in the NaCl group, so the results from one randomly selected rat in the CCK group were also thrown out to preserve equal group sizes.

Results

As in Experiment 1, baseline bar-pressing amounts were averaged for each rat, and the cumulative amount of bar-pressing after each 15 minutes of the test period was expressed as a percentage of that rat's total average baseline amount. Again, the baseline score is the mean number of food pellets each rat consumed on baseline days 2, 3, and 4. The mean baseline amount was 158.77 pellets for the NaCl group and 169.07 pellets for the CCK group. Since the reinforcement schedule (during baseline) was a fixed-ratio of 5:1, the number of pellets consumed is actually one-fifth of the number of bar-presses. To keep the percentages on the same scale as those in Experiment 1, the number of bar-presses during the test period (extinction) was also divided by 5.

As shown in Figure 1, the activity of the NaCl and CCK groups is quite similar. Cumulative mean percentage scores for both groups at each measurement are given in Table 2. A one-tailed t-test was performed on these mean scores at each of the four measurements. No significant differences were found between the NaCl and CCK groups at any time during the test period.
Table 2. Baseline data and cumulative mean percentages of baseline (+ S.E.M.) for NaCl and CCK groups in experiment 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Base (# Pellets)</th>
<th>Minutes After Beginning of Trial</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>NaCl</td>
<td>158.77 (+11.88)</td>
<td>23.21 (+4.37)</td>
</tr>
<tr>
<td>CCK</td>
<td>169.07 (+17.84)</td>
<td>25.18 (+2.90)</td>
</tr>
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Discussion

As Figure 1 illustrates, there does not appear to be any significant effect of CCK on extinction, either on the total number of responses or on the distribution of these responses over time. This lack of effect supports the view that satiety is more the result of a synergy between the oral cues derived from eating food and the release of CCK from the intestines. The lack of effect of CCK alone is not surprising when one considers the history of feeding in the animal. Throughout its entire lifetime, a food-stimulated release of CCK is preceded by the tasting, chewing, and swallowing of food. Therefore, presentation of CCK to the animal in the absence of these oral cues represents a novel experience; perhaps it is an experience that the
animal does not "recognize." It is possible that satiety is the result of a learned association between orosensory cues and elevated CCK levels. CCK may produce a state change in the animal which has to be tested with some food before the state is "recognized" as one of satiety. This association would be acquired and strengthened throughout the lifetime of the animal as it learns to adjust its food intake to its nutritional needs.

On the other hand, the interaction between orosensory cues and CCK may be a physiological one. One of many possibilities is that with time, CCK may alter the sensitivity of taste receptors. Another possibility is that CCK alters the animal's perception of taste. A much more sophisticated study would be required to ascertain the physiological basis for the interaction.
EXPERIMENT 3

This experiment was designed to determine whether oral cues and CCK can interact to reduce food-seeking behavior in an extinction situation. Results from Experiment 2 suggest that CCK alone does not have an effect on extinction. This lack of effect was hypothesized to be due to a lack of orosensory stimulation, with which CCK might interact. In this experiment, a few reinforcements of food were given to the rats prior to the onset of the extinction condition. It was reasoned that giving a large number of food reinforcements would confound the experiment because the rats would satiate to some extent before the extinction trial began. A smaller number of pellets, however, would give the rats a small taste of the food without substantially lowering their hunger level. It was hypothesized that this small amount of food, or "priming," would allow the rat to test its "state change" (caused by the CCK) and therefore cause the rat to extinguish quicker. If satiety is the result of an interaction between CCK and orosensory cues, this small amount of food might be adequate to allow the interaction to be manifested as a reduction in the number of trials to extinction.

Method

Sixteen male Sprague-Dawley rats weighing 335-480 grams were treated and trained to bar-press in a manner identical to that in Experiment 1. Similarly, four days of baseline data were collected to
yield an average baseline level of bar-pressing for each rat. On day 5, the rats were given injections of CCK Octapeptide (1.5 μg/kg) or NaCl (in an equivalent volume) exactly as in Experiment 1. Five minutes after injection, the rats were placed in the Skinner boxes, where each rat was rewarded with food pellets on a 5:1 fixed ratio until it had received 10 pellets. After a rat received 10 pellets, all subsequent bar-presses were unreinforced; thus, this trial became an extinction trial after 50 bar-presses. In later discussions, this 10-pellet reinforcement preceding extinction is referred to as "priming."

**Results**

As in Experiment 1, bar-pressing amounts for days 2, 3, and 4 were averaged for each rat. The mean baseline amount was 157.79 pellets for the NaCl group and 139.33 pellets for the CCK group. Cumulative bar-pressing activity after each 15-minute period of day 5 (priming plus extinction procedure) was then expressed as a percentage of each rat's total mean baseline amount. Again, as in Experiment 2, the number of bar-presses during the test period was divided by 5 to keep the results on the same scale as Experiment 1.

As Figure 1 illustrates, there again appears to be no difference in activity between rats receiving CCK and those receiving NaCl. Cumulative mean percentage scores for both groups at each measurement are given in Table 3. A one-tailed t-test was performed on the means at each of the four measurements. No significant differences were found between the NaCl and CCK groups at any time during the test period.
Table 3. Baseline data and cumulative mean percentages of baseline (+ S.E.M.) for NaCl and CCK groups in Experiment 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Base (# Pellets)</th>
<th>Minutes After Beginning of Trial</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>15 30 45 60</td>
<td></td>
</tr>
<tr>
<td>NaCl</td>
<td>157.79 23.87 33.50 38.22 38.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(+15.64) (+2.74) (+3.07) (+3.90) (+4.05)</td>
<td></td>
</tr>
<tr>
<td>CCK</td>
<td>139.33 24.63 32.89 39.75 40.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(+17.81) (+3.67) (+4.27) (+5.39) (+5.41)</td>
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\[ t < 1 < 1 < 1 < 1 \]

**Discussion**

An inspection of the cumulative mean percentages in Table 3 reveals that the CCK and NaCl groups are very similar throughout the entire test period. A comparison of Table 3 to Table 2 (from Experiment 2) shows that the priming procedure used in this experiment made very little, if any, difference in the rate of extinction or the number of bar-presses to extinction. It is possible that the amount of food used for priming (450 mg) did not give enough orosensory stimulation to allow an interaction to manifest itself. By using a larger number of pellets (but still well below the baseline intake), this interaction effect might be demonstrated. However, it is also possible that CCK reduces some aspect of motivation other than that which seems to affect the number of bar-presses to extinction.
GENERAL DISCUSSION

This study has confirmed previous findings that CCK reduces the amount of food that rats will consume in a bar-pressing situation (Hsiao et al., 1979; Maddison, 1977). It also appears that CCK has no effect on the rate or number of responses made under extinction conditions. Furthermore, "priming," or allowing a small amount of oropharyngeal food stimulation, apparently does not potentiate or allow CCK to have an effect on extinction. Since the last two conclusions are based on negative results, they should be considered with caution. Nevertheless, several aspects of the results suggest that CCK does not affect extinction. The very close agreement between the means of the CCK and NaCl groups for all four time periods in Experiment 2 suggests that the two groups are not different. Despite the priming procedure, Experiment 3 is nothing more than a replication of Experiment 2. The close agreement between corresponding means from the two experiments suggests that neither CCK nor priming had much effect. Figure 1 graphically illustrates the similarity between the results of these two experiments. Although it might be argued that the dose of CCK used here (1.5 μg/kg) is not adequate to affect extinction, it is well within the range reported to be effective in reducing food intake (Mueller and Hsiao, 1978). The results of Experiment 2, therefore, are consistent with an interaction model: CCK, in the absence of other food-related
cues, is ineffective in reducing feeding motivation (Antin et al., 1978).

Results from Experiment 3 do not fit easily into an interaction model. The interaction between the priming stimulus and CCK, which was expected to affect extinction, apparently did not take place. As suggested earlier, it is possible that the amount of food used for priming was not enough to allow an interaction. Systematic research with varying amounts of food would be necessary to answer this question. Complex interactions are likely to be found between amount of priming, amount of deprivation, dosage, and extinction measures.

Another possibility is that CCK affects some aspect of motivation other than that reflected by extinction. It may be that an injection of CCK cannot be considered to be equivalent to a reduction in the number of hours of food deprivation. It would be interesting to test the effects on extinction of other factors known to affect hunger or satiety.

The similarity between CCK and NaCl groups in Experiments 2 and 3 also offers some evidence against the suggestion that the CCK effect is due to sickness (Deutsch and Hardy, 1977). While it was not specifically tested, it seems likely that if CCK were making the animals sick, one could expect fewer extinction responses due to a reduction in the animals' activity level. The lack of differences between the groups suggests that sickness was not a factor.

In conclusion, these results suggest that CCK, which is gaining strong support as being important in the induction of satiety,
apparently does not act by simply making the animal less hungry at the outset. The results suggest that CCK and orosensory cues act synergistically to produce a satiating effect that neither stimulus alone is capable of producing. The failure of the priming procedure to induce satiety in this study should be further investigated using varying amounts of food. As Gibbs and Smith (1978, p. 413) editorialized, "it would be surprising if any single physiological signal were sufficient for such a crucial function as satiety. It seems more likely that such a signal would interact with other neural or humoral sequelae of feeding."
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