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Effects of Cholecystokinin, *d*-Amphetamine and Fenfluramine in Rats Trained to Discriminate 3 from 22 Hr of Food Deprivation[1]

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ABSTRACT

Attempts to assess similarities between the interoceptive stimuli of anorectic drugs and food satiation have generally been limited to human verbal reports. The purpose of the present study was to develop a procedure for assessing similarities between the interoceptive stimuli of food in the gut and various drugs known to alter food intake in rats. Rats (n = 23) were trained in a two-lever, food-reinforced, discrimination paradigm to press one lever when deprived of food for 3 hr and another lever when deprived of food for 22 hr. Criteria for stimulus control over responding were achieved after a mean of 92 (range = 26–175) training sessions. In time course tests, rats were tested when 22, 12, 6 and 3 hr food-deprived. As the number of hours of food deprivation decreased, the percentage of responses that occurred on the 3-hr food deprivation lever increased. In substitution tests, rats that were 22-hr food-deprived consistently responded as if they were 3-hr food deprived after administration of sweetened condensed milk preloads or cholecystokinin, but only occasionally after administration of water preloads, LiCl, *d*-amphetamine or fenfluramine. These results demonstrate that the presence of food in the gut can function as a discriminative stimulus to control lever choice in rats. Furthermore, they suggest that the discriminative stimulus effects of cholecystokinin, but not *d*-amphetamine or fenfluramine, are similar to those of food in the gut, and support the hypothesis that cholecystokinin plays a role in the regulation of food intake.

When animals eat, physiological changes occur that may be discriminable to the animal and can alter behavior. Although the behavioral changes can be observed experimentally, they may be indistinguishable from behavioral changes that occur for reasons other than food ingestion. For instance, decreases in food intake may occur when an animal becomes sated, or when an animal is ill. Likewise, animals may sleep after ingesting food, or when given a sedative. Because behaviors that occur in the presence of internal stimuli associated with food ingestion are often indistinguishable from behaviors occurring in the presence of internal stimuli not associated with food ingestion, it would be useful to train animals to respond differentially to the discriminable internal stimuli (interoceptive stimuli) associated with food deprivation and satiation. In this way, similarities between the interoceptive stimuli associated with food ingestion and those associated with a putative satiety agent could be assessed.

For many years only human subjects were used to study interoceptive stimuli because humans can verbally report their internal states. It has been known for some time, however, that internal stimuli can function as cues in animals, as well. In 1928 Bykov and his co-workers (1957) conditioned salivation in dogs by pairing feeding or no feeding with the interoceptive stimuli of different temperatures of water infused into the stomach. Other investigators have also demonstrated that a variety of responses can be conditioned using internal stimuli in classical conditioning paradigms (Balagura, 1968; Collins and Tatum, 1925; Davidson, 1987; Reiss, 1958). Paralleling these classical conditioning studies are a number of operant conditioning studies demonstrating differential control of responding based on a variety of interoceptive stimuli including food and water deprivation (Hull, 1933; Jenkins and Hanratty, 1949; Kendler, 1946; Leeper, 1935), mechanical stimulation (Slucki *et al.*, 1965) and drugs (Schuster and Balster, 1977; Schuster and Brady, 1971; Schuster and Johanson, 1988; Thompson and Pickens, 1971). One purpose of the present study was to establish the internal state associated with food ingestion as a discriminative stimulus in rats.

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ABBREVIATIONS: AMPH, *d*-amphetamine; CCK, cholecystokinin; FEN, *dl*-fenfluramine; SAT, 3-hr food-deprived; DEP, 22-hr food-deprived; STC, sessions to criteria; FR, fixed ratio; i.g., intragastric; i.p., intraperitoneal; DZ, diazepam; RO, RO 16–6028; CS, conditioned stimulus; UCS, unconditioned stimulus.

A second purpose was to compare the internal state associated with food ingestion to that produced by a putative satiety agent (CCK) and two anorectic drugs (FEN and AMPH). CCK is a hormone released by the small intestine in response to food ingestion (Ivy and Oldberg, 1928), and has been proposed to function as an endogenous satiety agent (Gibbs *et al.*, 1973). Research regarding similarities between the interoceptive stimuli associated with food ingestion and the interoceptive stimuli associated with CCK administration has been limited, and conflicting results have been reported (Davidson *et al.*, 1988; Smith and Gibbs, 1987; Stacher, 1979). Subjective ratings by human subjects after CCK administration were similar to those expected after eating in some studies, but not in others (Stacher, 1979; see also Smith and Gibbs, 1987 for review). In a recent report using classical conditioning with rats, Davidson *et al.* (1988) suggested that the interoceptive stimuli associated with an i.p. injection of CCK were not similar to those associated with recent food ingestion. FEN and AMPH, two drugs traditionally used as prototypic anorectics, were used in the present investigation in addition to CCK. These drugs are thought to reduce food intake *via* different mechanisms from CCK and from each other (Fuxe *et al.*, 1975; Garattini *et al.*, 1975; Mennini *et al.*, 1981; Offermeier and Preez, 1978). Animal studies comparing the interoceptive stimuli associated with injections of AMPH or FEN to those of food ingestion have not been done. Data collected from human subjective reports, however, suggest that although both AMPH and FEN reduce hunger (Chait *et al.*, 1985; Patel *et al.*, 1963; Silverstone, 1986) these drugs differ from each other, and probably differ from food intake, in other discriminable effects (Chait *et al.*, 1985, 1986).

In the present experiment rats were trained in a two-lever, food-reinforced, discrimination paradigm to press one lever when deprived of food for 3 hours and another lever when deprived of food for 22 hours. A two-lever operant paradigm was used based on the extensive literature supporting the utility of this procedure in assessing the discriminative stimulus properties of drugs (Schuster and Balster, 1977). After establishing the discrimination, drugs known to reduce food intake (CCK, AMPH and FEN) were tested for their ability to engender responding similar to that of recent food ingestion. If a food-deprived rat responded as if food-sated after an injection of CCK, AMPH or FEN, it would suggest that the interoceptive stimulus associated with an injection of any of these drugs was similar to the interoceptive stimulus of recent food ingestion.

Methods

Animals and apparatus. Twenty-six male Sprague-Dawley rats (Holtzman Co., Madison, WI) were used. Rats were maintained at 80 ± 5% of their initial free-feeding body weights (220–330 g) and were housed individually in stainless-steel cages in a room maintained on a 12-hr (7:00 A.M.-7:00 P.M.) light-dark cycle. Water was available continuously in the home cage. In addition to the 45-mg food pellets (P. J. Noyes Co., Lancaster, NH) delivered during the experimental sessions, Teklad 4% Mouse and Rat Diet (Winfield, IA) was provided, as needed, to maintain body weights at the appropriate level. Four identical operant chambers for rats (R. Gerbrands Co., Arlington, MA) were used. On one wall of each chamber were mounted two response levers with a food receptacle between them. A house light was mounted on the outside of each chamber. Extraneous noise was minimized by enclosing the chambers in wooden cabinets with a ventilation fan mounted on the outside of each cabinet. Stimulus events were controlled and lever presses recorded by an AIM-65 microcomputer (Dynatem Corp., Irvine, CA) connected to a custom designed input/output interface (ERH Electronics, Delton, MI) located in an adjacent room.

Procedure

Training. The rats were assigned randomly to one of the four experimental chambers. In two chambers, the right lever was the 3-hr deprivation-appropriate lever (satiated or SAT condition) and the left lever was the 22-hr deprivation-appropriate lever (deprived or DEP condition). In the other two chambers, the opposite assignments were made. All rats were trained to discriminate 2 hr of access to food given 3 hr before the session (SAT) from food ingestion occurring approximately 22 hr before the session (DEP). On SAT days the rats were weighed, a preweighed quantity of Teklad 4% Mouse and Rat Diet (usually 16–20 g) was placed into the home cages, and the rats were returned to the home cages and allowed to eat for 2 hr with water freely available. At the end of that 2-hr period the rats were again weighed, remaining food, if any, was removed from the home cages and weighed, and the rats were then returned to the home cages for 3 hr. At the end of the 3-hr period, the rats were placed into the test chamber. After a 10- to 15-min period of darkness (depending upon the drug pretreatment time), the house light was illuminated and food was available for every nth response (FRn) on the condition-appropriate lever. Responses on the inappropriate lever were counted and caused the response requirement on the appropriate lever to reset. Sessions lasted for 10 min after which rats were returned to the home cage. Sessions were conducted once a day 6 days a week. Rats were given additional food, if needed to maintain body weight, after sessions ended and approximately 22 hr before the next day's session. Handling on DEP days was exactly the same except that after the initial handling and weighing, no food was placed into the home cage. A typical 2-day sequence for 3 hr of food deprivation (SAT) on Day 1 and 22 hr of food deprivation (DEP) on Day 2 is outlined in table 1. The SAT-DEP sequence was varied pseudorandomly to avoid any learning based on sequence patterns, and to assure equal opportunity for responding on each lever throughout the week. One weekly sequence, for example, consisted of Mon.-DEP, Tues.-SAT, Wed.-SAT, Thurs.-DEP, Fri.-DEP and Sat.-SAT.

Initial training consisted of 10-min sessions conducted once a day, 6 days a week and followed a single alternation sequence (*i.e.*, SAT, DEP, SAT, DEP, SAT, DEP, etc.). Once rats were reliably pressing the condition-appropriate lever under a FR1 requirement, sessions were conducted using a pseudorandom alternation sequence such as that described above (*i.e.*, DEP, SAT, SAT, DEP, DEP, SAT). If a rat developed a lever preference, additional training was provided on the nonpreferred lever. In addition, levers were cleaned with 70% ethanol before each session, and different rats were exposed to different alternation sequences. This was done so that odor cues from one rat's lever pressing would not provide cues for the next rat's performance (Extance and Goudie, 1981). During the training period, the response requirement on each lever was increased gradually to FR20 on the condition-appropriate lever. Training continued until the following criteria for stimulus control over responding were achieved. First, at least 80% of the responses before the delivery of the first food pellet occurred on the appropriate lever. Second, 90% of the responses that occurred throughout the session were on the appropriate lever. Testing began when both of these criteria were met during at least seven of eight consecutive sessions.

Testing. Test sessions were conducted every 3rd day as long as the criteria for stimulus control were met in the intervening training sessions. In addition, the 2 days immediately preceding a test session (one day of each condition) also had to meet criteria for testing to occur. If criteria were not met during the intervening training sessions, the training sequence was reinitiated and, occasionally, higher or lower FR values were instituted, until stimulus control over behavior was again achieved. Test sessions were identical to training sessions except that food was available for completing the FR on either lever. When a pretreatment time was longer than 15 min, the rat was returned to the home cage after the pretreatment and then placed into the experimental

TABLE 1
Daily schedules for SAT and DEP conditions

Day 1 (SAT)				
hr 0	hr 2	hr 5	hr 5.5	hr 6
Weigh rat; present chow	Weigh rat; remove chow	Inject rat; conduct SAT session	Return rat to home cage	Supplement with chow
Day 2 (DEP)				
hr 0	hr 2	hr 5	hr 5.5	hr 6
Weigh rat	Weigh rat	Inject rat; conduct DEP session	Return rat to home cage	Supplement with chow

chamber 10 to 15 min before the start of the session. When the pretreatment time was 15 min or less, the rat was placed into the experimental chamber immediately after being pretreated, and remained there until the session began.

In time course tests, 2 hr of food access was allowed at 3, 6, 12 and 22 hr before the test session. In substitution tests, i.g. preloads and/or drugs were administered before the test session. Sweetened condensed milk (17.6 ml, 4–41 kcal/rat) was administered 1 hr before the session, *via* i.g. intubation, to rats that were 22-hr food-deprived (DEP condition). This quantity was chosen so that the highest caloric preload would approximate the number of calories ingested during the 2-hr access period on SAT days. SAT-appropriate responding after i.g. administration of milk preloads to DEP rats would indicate that postingestive events, rather than preingestive events such as the presence or absence of food in the home cage, governed responding. Tap water preloads were given 10 min before the session *via* i.g. intubation, in volumes of 3.0 to 17.6 ml, to assess the importance of volume in mediating the discrimination.

In addition to the milk and water preloads, CCK, AMPH and FEN were also tested. CCK (0.3–17.6 μg/kg) was given i.p. either 10 or 15 min before the session. AMPH (0.03–3.2 mg/kg) and FEN (0.3–5.6 mg/kg) were given 15 min before the session, i.p. In DEP rats, SAT-appropriate responding after pretreatment with any of these agents would suggest that the interoceptive stimuli associated with injections of these compounds were similar to the interoceptive stimuli associated with the recent ingestion of food.

LiCl (10–75 mg/kg) was given 15 min before the session, i.p. Lithium has been reported to reduce food intake in rats (Ervin and Teeter, 1986; Kulkosky *et. al.*, 1981) but is thought to do so by invoking mechanisms not normally involved in the regulation of food intake. DEP-appropriate responding in DEP rats after pretreatment with LiCl would indicate that the interoceptive stimulus produced by LiCl was not the same as that of ingesting food. DZ (0.3–3 mg/kg, 15 min before the session, i.p.), a benzodiazepine that has been reported to increase food intake in rats (Wise and Dawson, 1974), was tested as well as RO (0.03–3.2 mg/kg, 20 min before the session, i.p.), a benzodiazepine partial agonist that increases feeding in rats and does not decrease locomotor activity (Cooper *et al.*, 1987; Yerbury and Cooper, 1987). These two drugs were used to assess the effects of drugs that increase feeding. In SAT rats, DEP-appropriate responding after administration of either benzodiazepine would indicate that the discriminative stimulus effects of these drugs were similar to those of food deprivation.

Data analysis. Test session data for each rat include the percentage of the total responses that occurred on the SAT-appropriate lever and the rate of responding on both levers. Most tests were conducted twice, preceded once by a DEP training session and once by a SAT training session and the mean of both tests was calculated. If no food pellets were delivered during a test session, the data for that session were not included in the percentage of SAT-appropriate response calculations but were included in the response rate calculations. The mean number of training sessions required to meet the criteria for stimulus control over responding (sessions to criteria) were counted from the first day of lever press shaping and were included as a measure of the discriminability of the deprivation conditions. The mean number of sessions required to complete the first 10 tests was calculated as a measure of discriminative stability.

Drugs. The drug solutions used were as follows: AMPH sulfate (National Institute on Drug Abuse, Rockville, MD); FEN hydrochloride (A. H. Robins Co., Richmond, VA); RO (Hoffmann La Roche, Nutley, NJ); DZ (Hoffmann La Roche); and LiCl (Mallinckrodt Chemical Works, St. Louis, MO). All of these drugs except DZ and RO were dissolved in 0.9% saline and doses are expressed as the salt. DZ was mixed in a 1:1 stock solution of emulphor (GAF Corporation, New York, NY) and alcohol and then diluted with saline as needed. RO was suspended in sterile water to which Tween 80 (2 drops in 10 ml) was added. Doses of both DZ and RO are expressed in terms of the base. CCK was obtained from Sigma Chemical Co. (St. Louis, MO), Behring Diagnostics (San Diego, CA) and Peninsula Laboratories (Belmont, CA) as the sulfated COOH-terminal octapeptide ([Tyr-SO_3H^{27}]-CCK fragment 26–33 amide) in powdered form. It was mixed with physiological saline at room temperature and then stored below freezing in aliquots which were thawed immediately before injecting. Injections of all drugs were generally 1.0 ml/kg and the concentration was varied appropriately. LiCl was generally given in a volume of 10 ml/kg to reduce discomfort due to high concentrations at smaller volumes.

Results

Twenty three of 26 rats achieved the criteria for stimulus control over responding after a mean of 92 (range = 26–175) training sessions. The three rats that failed to meet the criteria for stimulus control were discarded after a mean of 122 (range = 80–175) sessions. Of the 23 rats that met criteria, 14 rats completed the first 10 tests after an average of 119 (range = 49–190) sessions. The nine rats that did not complete 10 tests either failed to maintain performance or died in the course of the study.

In time course test sessions, 3 hr of food deprivation occasioned 99.9 ± 0.1% (S.E.M.) SAT-lever responses whereas 22 hr of food deprivation resulted in 1.6 ± 2.3% (S.E.M.) SAT-lever responses (fig. 1). For deprivation levels between 3 and 22 hr, the percentage of SAT-lever responses was between that obtained for the training conditions for the group. Individual animals generally responded either on the SAT lever or on the DEP lever throughout a session. Thus, intermediate levels of responding for the group represent the average of the individual means. Group response rate was unaffected by length of deprivation.

Four of five DEP rats responded on the SAT lever after sweetened condensed milk preloads were administered i.g., 1 hr before the session (fig. 2). The percentage of SAT-lever responses was directly related to the caloric density of the preload in three of the rats (rats 19, 10 and 3). Two of these rats (rats 10 and 3) emitted SAT-lever responses after receiving 41 kcal on one determination, but lever pressing was suppressed completely during the second determination. In rat 2, the preload containing the lowest number of kilocalories occasioned SAT-lever responding whereas a sham infusion occasioned DEP-lever responding. Rat 21 rarely emitted SAT-lever responses

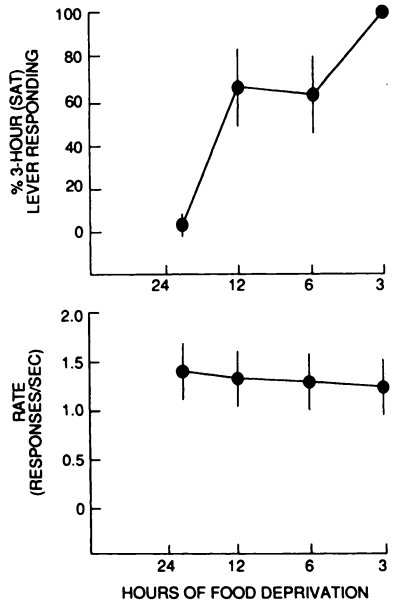

Fig. 1. Effects of various levels of food deprivation in rats trained to discriminate 3 from 22 hr of food deprivation. Upper panel: percentage of responses during test sessions that occurred on the SAT-appropriate lever as a function of number of hours since the last meal. Lower panel: response rate during test sessions as a function of number of hours since the last meal. Each point represents the mean and vertical lines represent ± S.E.M. (n = 10 to 16 rats per point).

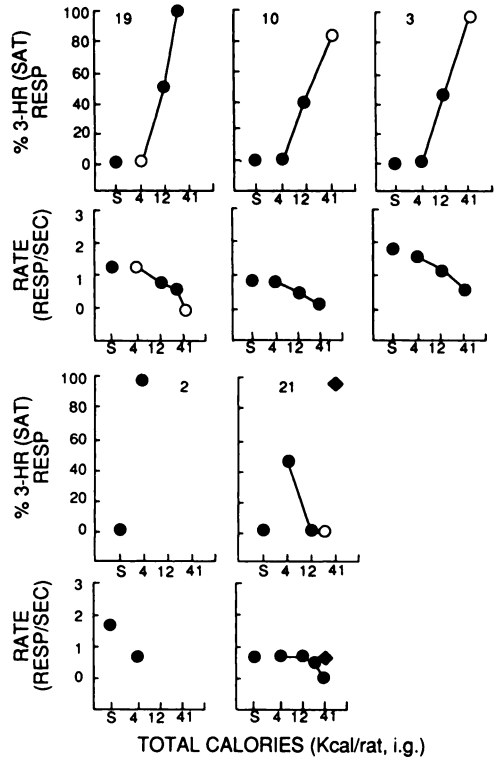

Fig. 2. Effects of sweetened condensed milk preloads given i.g. before the session to DEP rats trained to discriminate 3 from 22 hr of food deprivation. %3-HR (SAT) RESP = percentage of responses during test sessions that occurred on the SAT-appropriate lever as a function of number of calories in the preload. RATE = response rate during test session as a function of calories. S = sham intubation (tube was inserted but nothing was infused). Volume was held constant at 17.6 ml for all preloads. ● and ◆, double determinations. ○, single determinations. ●, milk preloads given 1 hr before the session; ◆, (rat 21) represents milk preloads given 2 hr before the session.

with any preload tested at the 1-hr pretreatment time. When 41 kcal were administered to this rat 2 hr before the session, however, 100% SAT-lever responding occurred on two separate determinations (◆, fig. 2). Thus, all five rats responded on the SAT lever after i.g. administration of milk. Response rate decreased directly as a function of caloric density at the 1-hr pretreatment time in all rats. In contrast, tap water preloads administered to DEP rats, i.g., 10 min before the session did not consistently engender SAT-lever responding (fig. 3). In four of the six rats, water preloads engendered predominantly DEP-lever responding. Response rate was not systematically affected.

Doses of 3.2 and/or 5.6 μg/kg of CCK engendered SAT-lever responding in seven of eight DEP rats (fig. 4). Generally, CCK produced dose-dependent increases in SAT-lever responding. Response rate was decreased in a dose-dependent fashion by CCK and fell below that seen on SAT training days in three of the rats. Rats 3 and 2 both responded on the SAT lever, when the pretreatment time was reduced from 15 to 10 min. The 10-min pretreatment time was subsequently used for the remainder of the study (rats 48, 43, 22 and 41).

FEN engendered SAT-lever responding in two of the four rats tested with a 15-min pretreatment time (fig. 5, rats 16 and 4). In these two rats, FEN engendered SAT-lever responding during one determination, but behavior was suppressed completely during the second determination (○, rats 16 and 4, fig. 5). A 30-min pretreatment time was later used in rat 3 and a dose-related increase in SAT responding resulted. However, when this pretreatment time was used in rat 19, effects were unsystematic. Thus, the FEN results were not as consistent as the CCK results. AMPH produced exclusively DEP-lever responding in three of the four DEP rats tested up to doses that suppressed response rate (fig. 6). In the fourth rat (rat 3), 1.0 mg/kg of AMPH produced SAT-lever responding on one determination, but not on the second.

LiCl rarely engendered responding on the SAT lever in the four DEP rats tested, up to doses that decreased response rate (75 mg/kg), and in no instance did responding resemble that seen after 3 hr of food deprivation (the SAT condition) (table 2). Neither benzodiazepine (RO and DZ) engendered DEP-lever responding in SAT rats (table 2). DZ was tested in two rats and had no effect on responding at the lower doses (0.3 or 0.56 mg/kg), whereas the higher doses (1 and 3 mg/kg) suppressed responding. RO was tested in three rats and did not engender DEP-lever responding. Response rate was unaffected by RO in two of the rats (rats 7 and 21), but the third rat's response rate was decreased at all three doses tested.

Discussion

The present experiment demonstrates that recent food ingestion can function as a discriminative stimulus in rats in a two-lever, food-reinforced, discrimination paradigm. These results confirm and extend previous studies showing differential control of behavior based on recency of food ingestion in the rat (Davidson, 1987; Jenkins and Hanratty, 1949). Several factors suggest that the discriminability of the stimulus in the present study was relatively low. Overton *et al.* (1986) have suggested that STC be used as an index of the discriminability of an interoceptive discriminative stimulus. The present discrimination took a mean of 92 sessions to train (from initial magazine training to meeting the criteria for stimulus control over re-

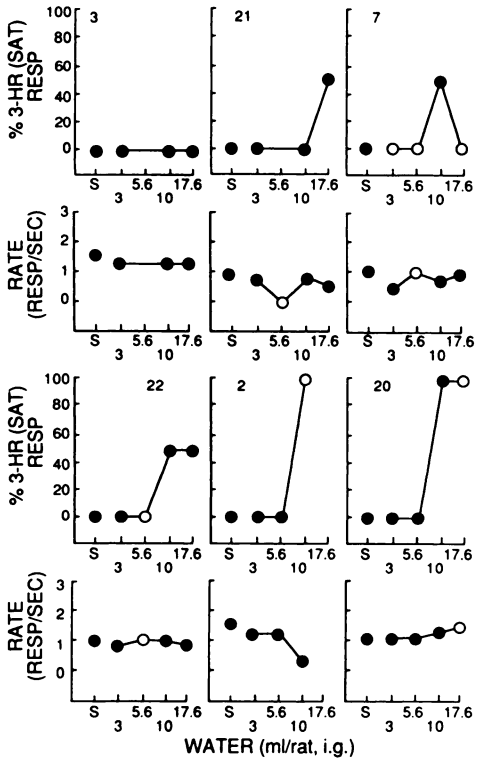

Fig. 3. Effects of tap water preloads given i.g. 10 min before the session to DEP rats trained to discriminate 3 from 22 hr of food deprivation. % 3-HR (SAT) RESP = percentage of responses during test sessions that occurred on the SAT-appropriate lever as a function of number of milliliters in the preload. RATE = response rate during test session as a function of number of milliliters in the preload. S = sham intubation (tube was inserted but nothing was infused). ●, double determinations. ○, single determinations.

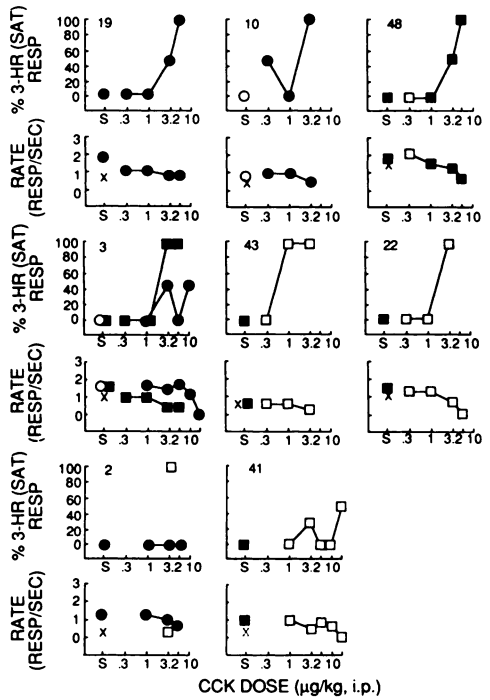

Fig. 4. Effects of CCK given i.p. before the session to rats trained to discriminate 3 from 22 hr of food deprivation. % 3-HR (SAT) RESP = percentage of responses during test sessions that occurred on the SAT-appropriate lever as a function of dose. RATE = response rate during test sessions as a function of dose. S = saline. ● and ■, the mean of two determinations. ○ and □, single determinations. ○ and ●, results obtained using a 15-min pretreatment time; □ and ■, results obtained using a 10-min pretreatment time. ×, mean response rate on SAT training days.

sponding). The present results compare favorably to some drug discrimination studies using similar training procedures and STC measures, but not to others (Kamien *et al.* 1987; Woolverton and Cervo, 1986). Although comparisons between studies are difficult because of differences in training procedures and in the methods used to count STC, the present results suggest low discriminability. Discriminations based on the interoceptive discriminative stimuli of hunger and thirst have been reported previously to be difficult to train, depending upon the training conditions used. Discriminative control of behavior based on different levels of food deprivation has been reported to take as long as 119 days (approximately 550 trials, Bailey, 1955; see Boles, 1975; Capaldi and Davidson, 1979; Webb, 1955, for reviews). Thus, obtaining such a discrimination within 92 sessions, as was done in the present study, seems reasonable.

Milk preloads, but not water preloads, engendered responding appropriate to recent food ingestion in the present study. This suggests that the ability to discriminate between 3 and 22 hr of food deprivation is the consequence of an interoceptive state produced by the presence of food itself in the gastrointestinal tract rather than simply volume, the occurrence of an event (*i.e.*, presence or absence of food in the home cage each day), or the passage of time. This finding confirms and extends a recent report by Davidson (1987) in which different levels of food deprivation (CS) were paired with shock (UCS) in a classical conditioning paradigm. Davidson (1987) administered a single milk preload, i.g., 1 hr before the session and found conditioned responding indicative of recent food ingestion. Our results extend this finding to an operant rather than a classical conditioning paradigm. Additionally, the results obtained after administration of several different caloric loads, rather than just one as in the Davidson (1987) study, as well as the results obtained with water preloads, suggest that the discriminative stimulus was based on postingestive stimuli associated with food in the gut.

Although the discrimination appears to be mediated by postingestive food-related cues, some other accounts of the data need to be considered. One possibility is that differential responding was governed by an exteroceptive, preingestional event rather than an interoceptive cue related to food intake. Two exteroceptive events that might govern behavior in the present study were the presence or absence of food in the home cage each day and the amount of time elapsed since food was last consumed. In the present study, if the event itself (*i.e.*, the presence or absence of food in the home cage each day) and/or the amount of time that had passed since the event occurred were the stimuli governing behavior, then i.g. administration of milk preloads, and i.p. administration of CCK, should not have engendered SAT responding in DEP rats. Because, in the present study, milk preloads and CCK did produce SAT responding, time and/or external preingestional events can be ruled out as the relevant stimuli. Additionally, although rats are able to discriminate the occurrence of an event in their environment as well as the passage of time (Terrace, 1966; Stubbs, 1979) the amount of time involved in these studies usually is seconds or minutes. Very few studies have been

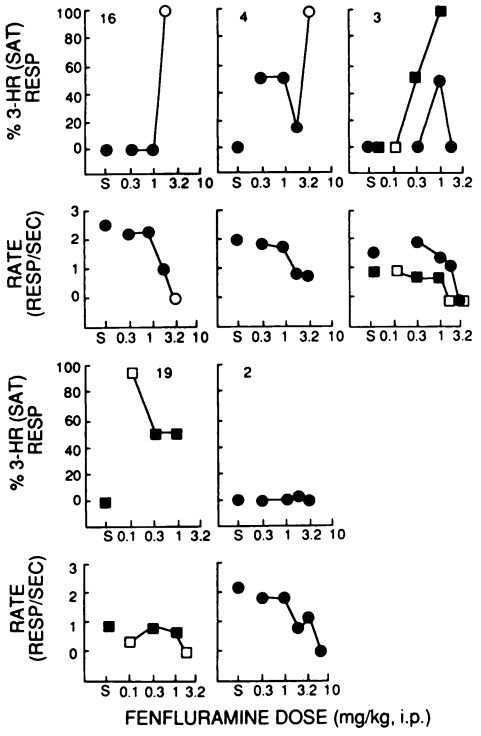

Fig. 5. Effects of FEN given i.p. to DEP rats trained to discriminate 3 from 22 hr of food deprivation. %3-HR (SAT) RESP = percentage of responses during test sessions that occurred on the SAT-appropriate lever as a function of dose. RATE = response rate during test session as a function of dose. S = saline. ● and ■, double determinations. ○ and □, single determinations. ○ and ●, data obtained when FEN was given 15 min before the session; □ and ■, data obtained when FEN was given 30 min before the session.

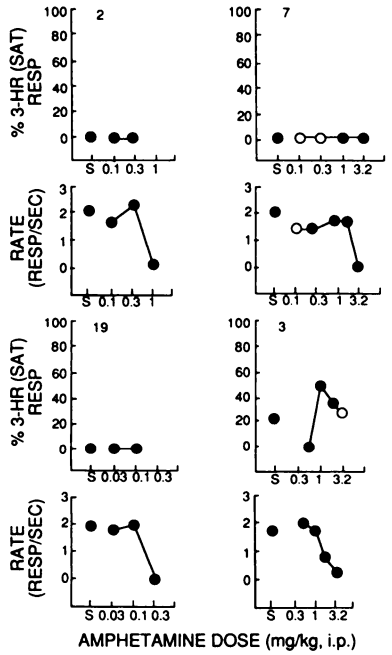

Fig. 6. Effects of AMPH given i.p. 15 min before the session to DEP rats trained to discriminate 3 from 22 hr of food deprivation. %3-HR (SAT) RESP = percentage of responses during test sessions that occurred on the SAT-appropriate lever as a function of dose. RATE = response rate during test sessions as a function of dose. S = saline. ●, double determinations. ○, single determinations.

reported in which the passage of hours was the critical stimulus. In one study that did examine this, negative results were reported (Bailey, 1955). Thus, it is unlikely that an exteroceptive, preingestional event, or the passage of time, controlled responding in the present study.

Volume, a characteristic of food unrelated to the nutritive, chemical, osmotic and/or caloric content, might also account for the responding observed. It has been known for some time that noncaloric substances administered to the gut will reduce food intake (Balagura and Coscina, 1969; Janowitz and Grossman, 1949) and may contribute to the mediation of satiety (Balagura and Coscina, 1969; Moran and McHugh, 1982). If the discriminative stimulus in the present study was based on volume, then noncaloric preloads should have produced SAT-lever responding in DEP rats. This did not occur in the majority of rats tested with water preloads or at the lowest milk preload, which also provided a volume control at the 1-hr pretreatment time. Volume was varied with the water preloads, and they were given 10 min before the session to minimize the amount of absorption that took place before testing occurred. Because volume was held constant for the caloric preloads and the pretreatment time and size of the 10 and 17.6 ml water preloads were similar to those shown previously to produce distention as well as to have behavioral effects on feeding (Balagura and Coscina, 1969), further preloads and pretreatment times were not examined. These results demonstrate that for most of the rats, volume alone did not control responding. Further studies are needed to clarify the role of nutritive, chemical and/or osmotic factors in the discrimination.

Another concern in the present study was that the interoceptive stimulus produced by allowing rats to eat a large quantity of food 3 hr before the session would be one of nimiety (". . . the clearly adverse state resulting from consumption [of food] in gross excess of optimal capacity.", Kulkosky, 1985) rather than satiety. Inasmuch as food preloads have been reported to produce conditioned taste aversions in rats (see Deutsch, 1978 for review), and milk preloads occasioned responding comparable to recent food ingestion in the present study, the question remained as to whether or not the rats were basing their discrimination on the presence or absence of some aversive state rather than something closer to satiety. An argument against nimiety is that the rats were responding for food during experimental sessions. Presumably, if the animals were ill after being prefed, responding for food would not have occurred during the experimental sessions. Additionally, the 3-hr delay after prefeeding and 1-hr delay after milk preloads made it even less likely that nimiety was functioning as the relevant discriminative stimulus.

CCK administered i.p., 10 min before the session, consistently occasioned responding like that seen after 3-hr of food deprivation in rats that had been deprived of food for 22 hr. Additionally, the doses that occasioned SAT responding are within the range reported to reduce food intake in 24-hr food deprived rats (Schallert *et al.*, 1982). The present results differ from a recent report by Davidson *et al.* (1988) in which 2.0 μg/kg of CCK did not elicit conditioned responding similar to that elicited by recent food ingestion when food deprivation (UCS) and shock (CS) were paired. In the present study, doses of CCK higher than 2.0 μg/kg engendered SAT-lever responding, whereas doses lower than 2.0 μg/kg did not. The Davidson *et al.* (1988) results might differ from the present results because Davidson *et al.* (1988) used a classical conditioning paradigm

TABLE 2

Effects of LiCl, DZ and RO in rats trained to discriminate SAT from DEP of food deprivation

Numbers represent the mean of two determinations unless otherwise noted. Doses are expressed as milligrams per kilogram.

LiCl						DZ			RO		
% SAT-lever responding in DEP rats						% DEP-lever responding in SAT rats			% DEP-lever responding SAT rats		
Rat	No. 2	No. 7	No. 10	No. 19	No. 21	Rat	No. 3	No. 10	Rat	No. 3	No. 7
Dose						Dose			Dose		
Saline	0.0	0.0	0.0	0.0	0.0	Vehicle	0.1	0.0	Vehicle	0.0[a]	0.7
10.0	0.0	6.9	0.0	0.0		0.30		0.4	0.03	41.9[a]	
17.6	0.0[a]			0.0	0.0[a]	0.56	0.1	2.6	0.10		1.0[a]
32.0	0.0	0.4	0.0	0.1	40.0[a]	1.00	0.2		1.00	0.0[a]	3.0[a]
56.0				71.5		3.00	1.1		3.20		0.1[a]
75.0	0.0	6.0[b]	50.0	49.8							
RATE (responses/sec)						RATE (responses/sec)			RATE (responses/sec)		
Rat	No. 2	No. 7	No. 10	No. 19	No. 21	Rat	No. 3	No. 10	Rat	No. 3	No. 7
Dose						Dose			Dose		
Saline	0.8	1.3	0.2	0.9	0.9	Vehicle	1.1	0.4	Vehicle	0.4[a]	0.3
10.0	0.8	0.8	0.2	1.1		0.30		0.3	0.03	0.1[a]	
17.6	1.2[a]			1.1	0.9[a]	0.56	1.0	0.2	0.10	0.0[a]	0.4[a]
32.0	0.8	0.9	0.2	0.9	1.0[a]	1.00	0.7	0.0	1.00	0.0[a]	0.4[a]
56.0				0.2		3.00	0.6	0.0	3.20		0.6[a]
75.0	0.7	0.6[b]	0.2	0.8							

[a] These doses were tested once.

[b] These doses were tested twice, but behavior was suppressed during one determination.

whereas the present study used an operant conditioning paradigm. However, had Davidson *et al.* (1988) tested higher doses of CCK, conditioned responding like that seen after recent food ingestion might have been seen. The present results suggest that the interoceptive stimuli associated with an i.p. injection of CCK are similar to those of food in the gut, and support the hypothesis that CCK plays a role in the mediation of postprandial satiety (Gibbs *et al.*, 1973). Further work with CCK antagonists as well as agents that stimulate the release of CCK would be useful to clarify whether or not endogenous CCK can function as a discriminative stimulus, and possibly as an interoceptive stimulus in the mediation of postprandial satiety.

In contrast to the CCK results, neither AMPH nor FEN consistently occasioned SAT responding in DEP rats, although FEN occasioned more SAT responding than did AMPH. The doses tested included those reported to reduce food intake in 16- and 20-hr food-deprived rats (Blundell *et al.*, 1976; Kornblith and Hoebel, 1976) as well as those high enough to suppress responding completely in the present paradigm. These results suggest that neither FEN nor AMPH produced interoceptive stimuli similar to those produced by recent food ingestion, but that the discriminative stimulus effects of FEN more closely resembled the discriminative stimulus effects of feeding than did AMPHs. These results are consistent with previous behavioral reports suggesting that FEN more closely resembles food intake than does AMPH (Blundell and Latham, 1980; Blundell *et al.*, 1985; Thurlby *et al.*, 1983), but that neither drug consistently produces behavior like that seen after food ingestion (Blundell and Latham, 1980; Kornblith and Hoebel, 1976). Additionally, the present results are consistent with drug discrimination reports showing differences between the AMPH and FEN discriminative stimuli (de la Garza and Johanson, 1987; McKenna and Ho, 1980; Schechter and Rosecrans, 1973; White and Appel, 1981).

LiCl administered to DEP rats rarely produced SAT-lever responding, and in no instance did responding resemble that seen after recent food ingestion or after caloric preloads. LiCl is a drug traditionally used in animal studies for its presumed ability to induce malaise. It has toxic effects in animals (*e.g.*, diarrhea and death) at appropriate doses (Alexander *et al.* 1982; Ervin and Teeter, 1986; Fregly, 1958; Nachman and Ashe, 1973), produces taste aversions in animals (Nachman and Ashe, 1973) and has been reported to produce nausea when used clinically (Baldessarini, 1985). The doses used in the present study are well within the range used to produce conditioned taste aversions in rats (Nachman and Ashe, 1973) and the pretreatment time and doses correspond to those reported to reduce food intake in rats (Ervin and Teeter, 1986; Kulkosky *et al.*, 1981). Although the induction of malaise by LiCl at these doses could be questioned, clearly the interoceptive cues associated with LiCl are different from those associated with milk preloads or recent food ingestion.

Neither of the benzodiazepines tested in the present study (DZ and RO) produced DEP responding in SAT rats, even though doses of RO were tested that were 30-fold greater than those reported to produce hyperphagia in rats (Yerbury and Cooper, 1987). These results indicate that the interoceptive stimuli associated with injections of RO or DZ are not similar to those associated with 22 hr of food deprivation. However, tolerance to the behavioral effects of DZ was not induced before drug testing was started, hence the rats became unresponsive before doses reported to induce hyperphagia could be administered (Wise and Dawson, 1974). It is possible that if DZ tolerance were developed before testing, responding may have occurred on the DEP lever, although the RO results make this seem unlikely. Another reason that SAT rats given DZ or RO in the present study did not respond on the DEP lever may have been that the rats had recently ingested a large amount of food. In studies reporting hyperphagia after benzodiazepines, the rats were free-fed and thus were probably not near the ceiling of their capacity for food (Wise and Dawson, 1974; Yerbury and Cooper, 1987). Additionally, caloric preloads have

been shown to inhibit DZ-induced eating (Wise and Dawson, 1974), suggesting that the DZ-induced interoceptive state after a caloric load is different from the DZ-induced interoceptive state during free-feeding.

In summary, rats were trained to discriminate 3 from 22 hr of food deprivation. Analysis of this effect indicates that the discrimination was based on a postingestional, food-mediated stimulus. CCK consistently engendered responding similar to that seen after 3-hr of food deprivation in 22-hr food-deprived rats, whereas LiCl, as well as the anorectics AMPH and FEN, did not. These results indicate that the interoceptive stimuli associated with i.p. administration of CCK are similar to those of food in the gut, and support the hypothesis that CCK plays a role in the regulation of food intake. On the other hand, these results suggest that the discriminative stimulus effects of AMPH and FEN are not similar to those of food in the gut and that these drugs reduce food intake by mechanisms other than or in addition to the production of interoceptive stimuli similar to satiety.

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