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A Contingent, Conditioned Suppression of Eating Following Chronic Benzodiazepine-Induced Hyperphagia

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HUNT, T., C. X. POULOS AND H. CAPPELL. *A contingent, conditioned suppression of eating following chronic benzodiazepine-induced hyperphagia.* PHARMACOL BIOCHEM BEHAV **35**(2) 373–378, 1990.—While the hyperphagic effect of chlordiazepoxide (CDP) has been reported by some to be enhanced with chronic drug treatment, the processes underlying this phenomenon are not well understood. In the present study, it was predicted that following chronic exposure to CDP-induced hyperphagia, animals given a placebo in place of their usual drug injection might be expected to exhibit evidence of a conditioned, drug-like response. Such a finding would then be consistent with an underlying process of behavioral sensitization. In Experiment 1a, Male Sprague-Dawley rats were randomly assigned to one of two groups receiving intraperitoneal (IP) injections of either 5 mg/kg CDP (Group CDP) or physiological saline (1 ml/kg; Group SAL) administered over 15 drug treatment days. Thirty minutes after each injection, all animals were given 30 min access to sweetened condensed milk. A significant enhancement of CDP-induced hyperphagia was observed over treatment sessions, confirming an earlier report. Unexpectedly, in the Placebo Test, the CDP animals exhibited a *suppression* of milk consumption relative to that of the SAL group. Using the same animals, this finding was successfully replicated in Experiment 1b. In Experiment 2, it was hypothesized that if this conditioned, drug-opposite response were to reflect the involvement of some underlying compensatory, homeostatic mechanism, then it should only be observable under food-contingent conditions of chronic drug treatment. This prediction was confirmed. While animals given chronic CDP treatments (5 and 15 mg/kg) followed by milk presentation (Contingent Group CDP/C) eventually exhibited a suppressed eating response in a Placebo Test, animals with an identical drug history, but with no opportunity to consume milk until 24 hr after each drug treatment (Noncontingent, Group CDP/NC) failed to show such a conditioned response relative to their respective saline control group. The implications of this surprising finding are discussed in relation to present theories of benzodiazepine hyperphagic action.

Benzodiazepine Tolerance Hyperphagia Chlordiazepoxide Conditioning

IT has not yet been clearly determined what adaptive processes may underlie behavioral changes associated with chronic exposure to benzodiazepine-induced hyperphagia. For instance, Cooper and colleagues (5) reported that the increased eating induced by chlordiazepoxide (CDP) persisted and actually was *enhanced* with chronic drug treatment, while in the same animals, an initial anxiolytic (antineophobic) action of the CDP was diminished over the same period. Such findings might be taken to support the hypothesis that the anxiolytic and hyperphagic effects of CDP reflect relatively distinct and independent pharmacological actions. However, the capacity of benzodiazepines to induce hyperphagia has been attributed by other researchers to the well-known anxiolytic action of this drug class [e.g., (1,12)].

Furthermore, it remains unresolved whether some process of tolerance (decreased drug response) and/or of sensitization (increased drug response) is responsible for any adaptive changes associated with the chronic drug exposure. There are several reports that no tolerance develops to benzodiazepine-induced hyperphagia (1,19). However, as pointed out by File (7), it is not clear to what extent this reported lack of tolerance may actually reflect ' . . . two opposite changes . . . cancelling each other.' Elsewhere, there are some data to suggest that what appears to be an increase in hyperphagic benzodiazepine efficacy with repeated drug exposure (6,12) may simply reflect a process of 'unmasking' that comes as a result of the relatively rapid disappearance of initial sedative drug effects [due to tolerance, see (7)]. Even though, in theory, a process of sensitization is most readily implied by the observation of an increase in hyperphagic action across chronic CDP treatment, the involvement of such an underlying process of sensitization remains to be determined.

In the present investigation, it was proposed that this determination may be made through application of specific predictions

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derived from a Pavlovian conditioning model of tolerance and sensitization acquisition [see (14, 16, 17)]. Perhaps the best known example of drug sensitization is to be found in the case of chronic exposure to psychomotor stimulants such as cocaine [e.g., (8,13)]. Administration of a placebo injection in place of the expected cocaine drug administration results in elicitation of conditioned, 'drug-like' stimulatory behavior (8,13). Accordingly, it was hypothesized that the observation of an increase in the hyperphagic action of CDP over repeated drug exposure reflects a process of sensitization. If so, then if the animals chronically treated with CDP (always given prior to presentation of food) subsequently are given a placebo test, they should exhibit a 'drug-like' conditioned, hyperphagic response [see (8)]. Alternatively, if an increased CDP hyperphagic effect reflects simply a loss of initial sedative effects (unmasking) due to drug tolerance, then no such observation of a hyperphagic response following a placebo test would be anticipated.

EXPERIMENT 1a

A moderate dose of 5 mg/kg CDP was used as this dose is previously reported to show sensitization-like, hyperphagic effects with chronic exposure [see Cooper, (3)]. Also, pilot data indicated minimal sedative effects at this dose. Extended familiarization with the test food (sweetened condensed milk) was provided for all animals prior to initiation of drug treatment. To be certain that all animals were optimally food-satiated at time of CDP exposure, each subject was given a supplemental food pellet prior to drug injection. Animals were given repeated drug treatments with test food presentation following each CDP injection. When a statistically reliable increase in CDP-induced hyperphagia had developed, a placebo test was conducted.

METHOD

Subjects

Twenty-four male Sprague-Dawley rats (Charles River, St. Constant, Quebec) were individually housed in stainless steel cages and maintained on a 12:12 hr light:dark cycle. The animals weighed 375–425 g at the start of the experiment. Tap water was available ad lib throughout the experiment. Each animal was maintained on a basic diet of seven rat chow (Purina) pellets (28–35 g) daily. An additional pellet was given just prior to each drug treatment.

Procedure

All animals were presented with sweetened condensed milk (Borden's, mixed in a 1:2 milk:tap water ratio) for a 30-min period each day for 6 days arbitrarily distributed over an initial 9-day baseline phase. On each day, the milk was presented in a graduated Richter tube attached to each animal's home cage. Subsequently, animals were randomly assigned to one of three experimental groups. One group of rats (Group Ad Lib, n = 8) was given ad lib access to lab chow and their body weights were monitored over the remainder of the experiment. These animals did not receive further milk presentations or drug treatments. These data on ad lib body weight gain permitted an evaluation of the level of food satiation by comparison with the two drug treatment groups. On each drug treatment day, the remaining 16 animals were weighed and given a supplemental food pellet (4–5 g) in the home cage for a 30–40 min preinjection period. Each rat was then given an intraperitoneal (IP) injection of either 5 mg/kg CDP (Group CDP, n = 8) or physiological saline (Group SAL, n = 8) administered in a volume of 1 ml/kg. At this point, all lab chow was removed from each animal's home cage. Following a 30-min postinjection period each subject was given access to sweetened condensed milk for a 30-min period. As in all previous baseline milk presentations, access to lab chow was only restored

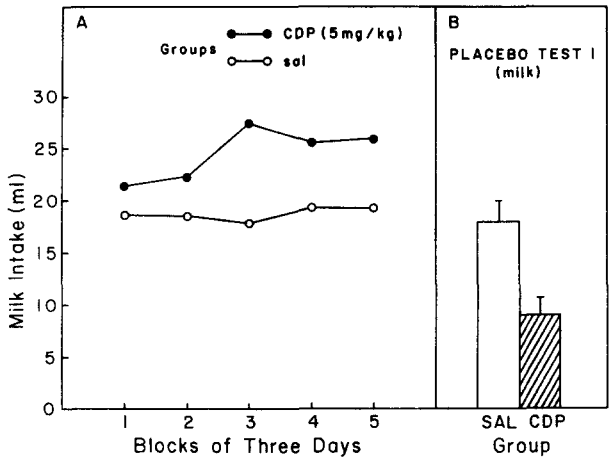

FIG. 1. (A) Mean levels of milk intake (ml) for CDP (5 mg/kg) and SAL Groups calculated from consecutive three-day blocks of drug treatment data averaged for each subject. (B) Mean (±SEM) milk intake (ml) observed on Placebo Test 1 for SAL (empty bar) and CDP (striped bar) treatment groups.

to the animals 4 hr after completion of the milk presentation. Fifteen drug treatment and milk presentation sessions were conducted given over a 31-day period. A minimum of at least 24 hr elapsed between each of these drug treatment sessions. Three days following the last of these sessions, a Placebo Test (TEST 1) was conducted. On this test day, an injection and food presentation procedure identical to that just described for a drug treatment session was followed, with the one exception being that each rat in the CDP group received an injection of physiological saline in place of its usual injection of drug.

RESULTS AND DISCUSSION

One animal in the CDP group died during the initial drug treatment sessions and the data for this subject were, therefore, removed from further analysis. The mean body weight over the chronic drug treatment phase was 2.56 g/day for the Ad Lib group (n = 8), 2.84 g/day for the SAL group (n = 8), and 3.3 g/day for the CDP group (n = 7). Thus, there was no significant deleterious effect on overall body weight gain as a result of any disruption in food availability introduced by the experimental procedure.

Mean (±SEM) baseline levels of milk consumption measured on the last baseline day were 14.0 ml (±1.5) and 15.9 ml (±1.9) respectively for the CDP and SAL groups. The daily milk intake data (ml) collected for each subject over the fifteen drug treatment sessions were transformed into three-day block averages and mean group intake (±SEM) calculated accordingly (see Fig. 1A).

A two-way (split-plot) ANOVA with repeated measures revealed a significant increase in the hyperphagic effect of CDP over Days [Drug × Day interaction, $F(4,52) = 3.73$, $p<0.01$], in addition to significant main effects of Drug, $F(1,13) = 6.85$, $p<0.02$, and of Days, $F(4,52) = 3.68$, $p<0.01$. Post hoc Tukey tests, $Q(2,22) = 5.25$, $p<0.05$, revealed that a significant between-group difference was attained by Block 3 (Sessions 6–9) with the CDP group consuming significantly more milk than the SAL group. This difference was maintained over Blocks 4 and 5 (see Fig. 1A). Such a pattern of increasing hyperphagia over repeated drug trials confirms a previous report of enhanced CDP-induced hyperphagia in food-satiated rats (5).

In contrast, a two-tailed *t*-test performed on the Placebo Test data (see Fig. 1B) indicated that the CDP group consumed significantly *less* milk than the SAL group following a saline placebo injection, $t(13) = 2.92$, $p<0.05$. This unexpected result is

TABLE 1

MEAN MILK INTAKE (ml) OVER EIGHT SUPPLEMENTAL DRUG TREATMENT SESSIONS CONDUCTED BETWEEN PLACEBO TESTS 2-4

Drug Session	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Group CDP	24.3	24.6	23.7	24.6	24.9	23.7	22.1	23.0
Group SAL	17.9	18.9	15.3	15.6	17.3	17.0	16.8	16.4

particularly intriguing. If a process of behavioral sensitization was responsible for the observed enhanced CDP hyperphagic effect, then based on previous experimentation, a drug-like, hyperphagic response should be expected in animals given a placebo injection in place of the expected drug administration (8,13). In fact, what was observed in these animals was a *drug-opposite* suppression of eating. Given the unexpected nature of this finding, a further assessment was conducted as described below.

EXPERIMENT 1b

In order to more firmly establish the reliability of this phenomenon, a second Placebo Test was conducted using the animals from Experiment 1a. In addition, the specificity of this conditioned eating suppression response was probed by conducting additional saline placebo tests incorporating test presentations of familiar food substances other than milk.

METHOD

Subjects

The subjects were the animals from groups CDP and SAL of Experiment 1a. The housing and general maintenance conditions remained unchanged. As before, animals were kept on a basic diet of 7 lab chow pellets daily (in addition to the preinjection single-pellet supplement).

Procedure

Supplemental drug treatment sessions. In between each of the Placebo Tests (1–4), two supplemental drug treatment sessions (identical in procedure to previously described drug treatments) were always conducted.

Placebo Test 2 (pellets). This was conducted 48 hr following the second supplemental drug session. Just as in Experiment 1a, all procedural details were identical to those observed on the drug treatment days except that animals in the CDP group received injections of physiological saline in place of their usual drug injections. However, instead of milk, each animal was given lab pellets to eat following the placebo injection. Each rat in both the SAL and CDP groups was given a 30-min presentation of a weighed amount of their regular lab chow pellets, presented in a petri dish placed inside each animal's home cage. Aluminum foil trays were placed under each cage to collect any spillage.

Placebo Test 3 (milk). Three days following the second supplemental drug treatment, both the CDP and SAL groups were weighed, injected with saline and presented with milk exactly as in Test 1 (Experiment 1a).

Placebo Test 4 (wet mash). Following two further supplemental drug sessions (conducted at 3-day intervals following completion of Test 3), a final placebo test was performed using a procedure identical to the previous such tests except that wet mash food was presented in place of milk. This wet mash was prepared from the regular lab chow (2:5 water:powdered Purina lab chow). All animals had been habituated to this food during five separate daily 30-min presentations.

Two days after Test 4, a single drug treatment session was conducted in order to confirm that CDP pretreatment would effectively induce increased eating of the wet mash food.

RESULTS AND DISCUSSION

The magnitude of CDP-induced hyperphagia was maintained over the eight supplemental drug treatment sessions conducted during Experiment 1b (see Table 1).

These findings indicate that the magnitude of the enhanced CDP-induced hyperphagia observed in Experiment 1a does not change significantly following a further eight drug exposures. With chronic CDP exposure (up to twenty-three exposures), the capacity of the drug to induce increased eating would appear to grow to reach an asymptotic level.

The data for the Placebo Tests 2, 3 and 4 are presented in Fig. 2. Analysis of the group intake data on each test day using two-tailed *t*-tests ($p<0.01$) revealed a significant between-group difference in food consumption on Test 3, when milk was used as the test food substance, $t(13)=5.30$, $p<0.01$. This finding, therefore, constitutes a successful replication of the conditioned suppression of eating observed in Experiment 1a and serves to help increase confidence in the apparent robustness of the basic phenomenon.

Between-group differences on Test 2, $t(13)=1.03$, $p>0.05$, and Test 4, $t(13)<1$, $p>0.05$, failed to reach levels of statistical significance. However, an overall (across tests) ANOVA (split plot with repeated measures) performed on the Placebo Tests data revealed significant main effects of Drug, $F(1,13)=6.65$, $p<0.05$, and of Test, $F(2,26)=20.81$, $p<0.01$, but no significant Drug ×

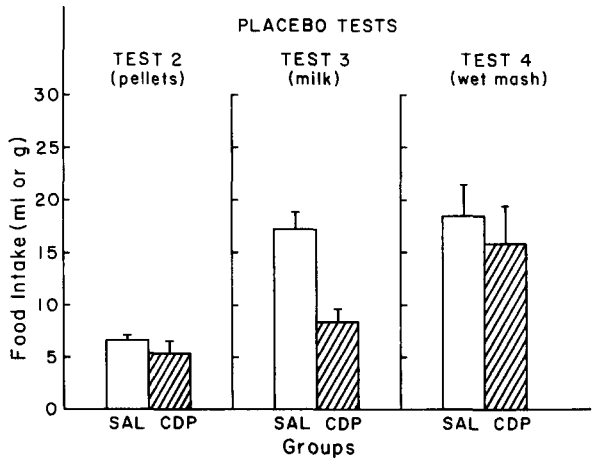

FIG. 2. Mean (±SEM) intake levels for SAL (empty bar) and CDP (striped bar) treatment groups measuring consumption of food pellets (g) on Placebo Test 2, consumption of milk (ml) on Placebo Test 3, and consumption of wet mash (g) on Placebo Test 4.

Test interaction, $F(2,26) = 2.78$, $p > 0.05$. As indicated by the failure to observe a statistically reliable Drug × Test interaction, the conditioned suppression of eating in chronically CDP-treated animals following a placebo injection tends to generalize across different foods. Clearly, the issue of the transferability of this conditioned effect to other food requires more systematic investigation in the future.

Also, the CDP was found to induce overeating of the wet mash food in a manner comparable to that seen with milk. Intake of the wet mash observed over the last two habituation presentations of this quite different food indicated equivalent levels of intake for the two experimental groups (11.6 and 11.1 g for the CDP Group, and 10.5 and 10.5 g for the SAL Group). The results of a subsequent drug treatment test revealed a significant CDP-induced increase in wet mash consumption, $t(13) = 2.10$, $p < 0.05$, one-tail.

What would seem apparent is that the suppression of milk intake observed in the CDP group (but not the SAL group) following a placebo injection of physiological saline cannot be accounted for by any simple physiological drug-withdrawal or drug carry-over effect, as on both Test 1 (Experiment 1a) and Test 3 (Experiment 1b), the previous CDP treatment occurred three days earlier. In fact, on both of these occasions, the CDP animals actually *gained* weight (average increases of 4 and 6 g respectively) over the three days prior to each test. A more parsimonious explanation is that the observed suppression of milk intake reflects some form of conditioned response. This idea is explored in the following experiment.

EXPERIMENT 2

In the case of the acquisition of tolerance to amphetamine-induced anorexia, it has been well documented that this form of behavioral adaptation is *response-contingent* (2, 15, 20). It was found that interaction with a food stimulus during drug exposure facilitated the acquisition of drug tolerance. Animals given an identical history of chronic amphetamine exposure without being allowed to interact with food while undergoing drug treatment failed to develop tolerance to the drug's anorexic effects.

Benzodiazepine-induced overeating might represent a disruption of the organism's homeostatic regulatory systems in much the same manner as amphetamine-induced anorexia, although the direction of this disruption would be opposite. This interpretation is consistent with a homeostatic regulatory hypothesis proposed to explain the development of tolerance to amphetamine anorexia (15). According to this theory, only under conditions in which animals are exposed to food while under the pharmacological effect of CDP should the suppression of eating be observed following administration of a saline challenge test. Animals given an identical history of CDP exposure, but not presented with the test food during the time of the drug's action should not exhibit any conditioned response when given a saline challenge. This prediction was evaluated in the experiment presented below.

METHOD

Subjects

Sixty male Sprague-Dawley rats were individually housed and maintained under the same conditions as in Experiment 1. The animals weighed 325–375 g at the start of the experiment.

Procedure

Sweetened condensed milk was used as the test food. Ten days of baseline intake (30-min daily sessions) data were collected prior to assignment of all animals to one of four experimental groups ($n = 15$ per group). Animals in the four independent groups were matched on the basis of the intake data for the last baseline day. A 2×2 design (Food Contingency × Drug) was used. Two groups of rats received chronic CDP injections followed by milk either 30 min after (Contingent drug exposure: Group CDP/C) or 24 hr after a drug injection (Noncontingent drug exposure: Group CDP/NC). Similarly, saline-treated rats received milk either 30 min (Group SAL/C) or 24 hr after (Group SAL/NC) saline injection. As in Experiment 1, all lab chow was removed from the animals in all four groups at time of injection and food availability was only restored 4 hours later.

Phase 1. Twelve drug treatment sessions were conducted over a thirty-day period. On each session, IP injections of CDP (5 mg/kg) or saline (1 ml/kg) were followed 30 min later by milk presentation to the two Contingent groups (CDP/C and SAL/C). Noncontingent groups (CDP/NC and SAL/NC) received a 30-min milk presentation 24 hr after drug or saline exposure. Milk intake for all four groups was recorded (to nearest ml). Over these first twelve drug treatment sessions, no supplemental lab chow pellet was given to the animals during the approximately 30–40 min preinjection period, as was done in Experiment 1.

Forty-eight hr after the last drug treatment session, a Placebo Test (Test 1) was conducted. Procedures followed here were identical to those described in Experiment 1, with the exception of the omission of a supplemental food presentation prior to injection. On this test day, all groups received injections of saline. Thirty minutes later, all four treatment groups were given a 30-min milk presentation.

Phase 2. Three days after Placebo Test 1, drug treatment sessions were resumed as before (5 mg/kg CDP), with both Contingent and Noncontingent conditions being maintained. The provision of a food supplement during the preinjection period was reintroduced into the procedure. An additional twelve drug treatment sessions were conducted in Phase 2 over a 36-day period. Placebo Test 2 was performed two days after the last drug treatment.

Phase 3. The same procedure as in Phase 2 was followed in this final phase, except that the dose of CDP was increased to 15 mg/kg. Placebo Test 3 was conducted two days following the last drug session.

RESULTS

Baseline mean (±SEM) milk intake data (ml) for the four treatment groups were: CDP/C, 16.8 ± 1.1; CDP/NC, 16.7 ± 1.1; SAL/C, 17.1 ± 1.2; SAL/NC, 16.9 ± 1.2. Following completion of Placebo Test 1, two animals in the SAL/C and three rats in the SAL/NC fell ill or died. Thus, for all data analysis after Test 1, the group sizes were: CDP/C, $n = 15$; CDP/NC, $n = 15$, SAL/C, $n = 13$; and SAL/NC, $n = 12$.

Three-way, split-plot ANOVAs (with repeated measures) were performed for each drug treatment phase. As in Experiment 1, the data were expressed in blocks of three days prior to statistical analysis. Separate two-way (Drug × Contingency) ANOVAs were conducted for each of the three Placebo Tests.

Phase 1

As expected, the CDP/C animals exhibited a significant increase in eating relative to the three other groups. Over the first three-day block, the mean intake level of the CDP/C group was 26.4 ml compared to an intake of 19.3 ml for the CDP/NC animals, 19.1 ml for the SAL/C, and 19.7 ml for the SAL/NC groups. This level of hyperphagia was maintained unchanged over the three remaining three-day blocks.

Statistical analysis revealed significant main effects of Drug, $F(1,56)=11.5$, $p<0.01$, and of Contingency, $F(1,56)=16.6$, $p<0.01$, with a significant Drug × Contingency interaction, $F(1,56)=12.65$, $p<0.01$. Post hoc Tukey tests confirmed that the milk intake of the CDP/C Group was significantly greater than that observed in the three remaining Groups, $Q(4,56)=4.91$, $p<0.01$. The absence of any significant effect of Days underscores the observation that there was no substantial enhancement of the CDP/C hyperphagia.

On Placebo Test 1, no significant between-group differences were observed either in terms of a Drug × Contingency interaction, $F(1,56)<1$, $p>0.05$, or main effects of Drug, $F(1,56)=1.87$, $p>0.05$, or of Contingency, $F(1,56)=2.89$, $p>0.05$.

Phase 2

A similar pattern of CDP-induced hyperphagia was observed here as in Phase 1. Significant main effects of Drug, $F(1,51)=20.9$, $p<0.01$, and of Contingency, $F(1,51)=18.5$, $p<0.01$, and a Drug × Contingency interaction, $F(1,51)=15.5$, $p<0.01$, were found. Post hoc Tukey tests again revealed that the CDP/C group consumed significantly more milk than the other three groups, $Q(4,51)=5.44$, $p<0.01$. While there was a significant main effect of Days, $F(3,153)=11.6$, this would not appear to be attributable to any increasing trend in level of intake for the CDP/C group over Days. The mean intakes (ml) data for this group across Days were: 28.4, 26.5, 29.6 and 29.9.

The results of Placebo Test 2 revealed only a significant main effect of Contingency, $F(1,51)=4.3$, $p<0.01$, with the two Contingent groups together consuming less milk overall than the two Noncontingent groups. The data for the Contingent (CDP and SAL) groups were 17.4 and 18.8 ml, and for the Noncontingent groups (CDP and SAL) were 21.2 and 21.2 ml. It is unclear as to why the SAL/C animals decreased their milk intake on this day.

Phase 3

Statistical analysis of the data collected over drug treatment sessions revealed a significant three-way Drug × Contingency × Days interaction, $F(3,153)=3.1$, $p<0.05$. Significant Drug × Days, $F(3,153)=6.9$, $p<0.01$, and Drug × Contingency, $F(1,51)=23.8$, $p<0.01$, interactions were also observed. Main effects of Drug, $F(1,51)=33.3$, $p<0.01$, of Contingency, $F(1,51)=32.7$, $p<0.01$, and of Days, $F(3,153)=4.9$, $p<0.01$, were all statistically reliable. Post hoc Tukey tests, $Q(4,90)=5.68$, $p<0.01$, indicated once more that the CDP/C group persisted in consuming significantly more milk than all three other groups. Of particular importance is the observation, confirmed by post hoc Tukey tests, $Q(4,153)=3.08$, $p<0.01$, that while the amount of milk intake for the CDP/NC group remained unchanged over Days, that of the CDP/C group increased from Block 1 to Block 2, and from Block 2 to Block 3. From Block 3 to Block 4, the milk intake of this CDP/C group decreased back down to a level equivalent to that seen on Block 2. Milk consumption for the SAL/C, $Q(4,153)=2.72$, $p<0.05$, and SAL/NC, $Q(4,153)=2.85$, $p<0.05$, Groups also remained unchanging over the three-day blocks (see Fig. 3A).

Results of the Placebo Test 3 (see Fig. 3B) indicated a significant Drug × Contingency interaction, $F(1,51)=4.8$, $p<0.05$. Post hoc Tukey tests, $Q(2,51)=4.12$, $p<0.05$, confirmed that the level of milk consumption observed in the CDP/C group following saline injection was significantly lower than that of each of the three other treatment groups.

DISCUSSION

First, the results described above demonstrate that the conditioned, drug-opposite hypophagia observed in Experiment 1 is replicable.

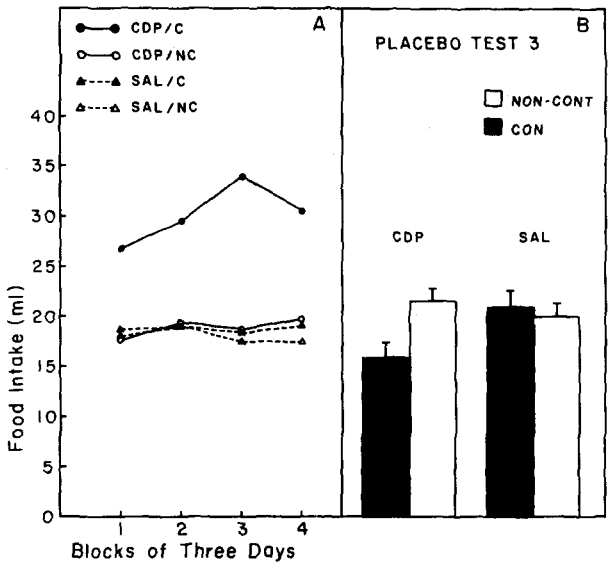

FIG. 3. (A) Three-day block mean levels of milk intake (ml) measured over twelve drug treatment sessions for animals treated with CDP (15 mg/kg) or saline administered with either Contingent (CDP/C and SAL/C) or Noncontingent (CDP/NC and SAL/NC) presentation of milk. (B) Mean (±SEM) milk intake (ml) measured on Placebo Test 3 for CDP and SAL treatment groups previously given Contingent (solid bars) or Noncontingent (empty bars) milk presentations.

Second, these results indicate that chronic exposure to CDP is not sufficient in itself to promote the acquisition of the suppression of eating response. The CDP/NC group, given a history of drug exposure identical to that of the CDP/C group, but not permitted to interact with a food stimulus during their drug treatments, failed to exhibit any conditioned anorexic response. Thus, development of this drug-opposite, anorexic response would appear to be 'response-contingent,' in a manner similar to that seen in the case of learned tolerance to the anorexic effects of chronic amphetamine (15).

Finally, the pattern of results observed across the three phases of Experiment 2 suggests that methodological changes in schedules of food accessibility (preinjection food supplements), and/or in the CDP dose may be potentially important variables to consider in future investigations of this conditioning phenomenon.

GENERAL DISCUSSION

Consistent with previous studies [see (7)], the present investigation found no direct evidence of tolerance being acquired to the hyperphagic effects of benzodiazepine, CDP. Indeed, the capacity of CDP to induce hyperphagia was found to be enhanced over chronic drug exposure, confirming an earlier report (5). A subsequent attempt to establish whether a process of sensitization may underlie the observed increase in drug efficacy led to an unusual discovery. In theory, an increase in CDP-induced hyperphagia might be attributable to the acquisition of a conditioned, hyperphagic response adding to and thereby enhancing the unconditioned hyperphagic drug effect. If this were to occur, then some evidence of this conditioned, drug-like response would be expected when the usual predrug cues are followed by placebo instead of the usual drug administration [see (8)]. In direct contrast

to such an expectation, what was observed was in fact, evidence of a conditioned, *drug-opposite* response. This effect was shown to be a robust and reliable phenomenon. Moreover, the acquisition of this conditioned response was found to occur only under conditions in which the drug exposure took place contingent with food presentation. Thus, the acquisition of this conditioned, drug-opposite response cannot be attributable simply to chronic CDP exposure alone. The implications of this unexpected finding can be considered from a number of perspectives.

For instance, the apparent increase in hyperphagia has been attributed to some investigators (6,12) to a process of 'unmasking' due to the rapid tolerance to initial sedative effects of benzodiazepines. In this context, the present failure to observe any evidence of drug sensitization is not surprising. In fact, it might be speculated that the observed conditioned suppression of eating could be due to elicitation of a compensatory, excitatory response associated with acquisition of tolerance to CDP's sedative effects. A conditioned, behavioral excitation response opposite to the sedative effects of a benzodiazepine has been reported (11). Such an excitatory response could conceivably disrupt the ability of an animal to perform a consummatory response under placebo conditions, while still not acting to diminish the drug-induced hyperphagia. However, this explanation fails to account for the observation that animals chronically exposed to CDP, but not given concurrent exposure to food (Group CDP/NC), failed to acquire such a conditioned suppression of eating response.

An additional problem for this account of the present data is that the time course of the conditioned excitatory effects (11) might be expected to be relatively short-lived (significantly less than 30 min). It would seem reasonable to assume that any disruptive effect introduced by such conditioned excitation could be overcome by the animal over the course of the 30-min test food presentation.

It would also seem problematic to apply a simple anxiolytic model of benzodiazepine hyperphagia (12) to the present findings. There is some evidence that tolerance may occur to this action of benzodiazepines [see (7)]. Such an account may help to explain the observed conditioned suppression of eating by postulating a conditioned anxiogenic effect serving to disrupt food consumption. However, it would remain difficult to explain the enhancement of CDP hyperphagia seen over repeated drug exposure. Presumably, tolerance to the anxiolytic action of CDP would also be reflected in tolerance to the CDP's hyperphagic effect.

Another possibility is that, rather than reflect a kind of anxiolytic action of benzodiazepines (12), the hyperphagia induced by the CDP reflects some form of enhanced perservative, or impulsive action (9–11). Assuming this were the case, and that such a disinhibitory effect (e.g., frontal lobe mechanism) [see (4)] were susceptible to compensatory regulation, then the development of such a (drug-opposite) *inhibitory* response might be reflected only under placebo conditions, as the benzodiazepine would be expected to serve to pharmacologically disinhibit this potential compensatory response. It would also be necessary to make yet a further assumption that this tolerance to the disinhibitory action of CDP be acquired only under conditions of contingent exposure to food. Perhaps such a compensatory response is elicited due to disruption of self-regulatory mechanisms by the chronic pattern of drug-induced overeating. For such tolerance to develop, it may also be necessary that the organism be in a state of recent satiation. Although this model is quite clearly speculative in nature, further consideration along such lines of inquiry might prove to yield fresh insights into the complex psychopharmacological properties of benzodiazepines.

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