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Chronic Cadmium Exposure Attenuates Conditioned Place Preference Produced by Cocaine and Other Drugs

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MILLER, D. K., K. M. PALME, S. A. NAJVAR, S. D. CAUDILL AND J. R. NATION. *Chronic cadmium exposure attenuates conditioned place preference produced by cocaine and other drugs.* PHARMACOL BIOCHEM BEHAV **64**(1) 15–20, 1999.—Adult male rats were exposed ad lib for 40 days to 100 ppm dietary cadmium chloride (group cadmium) or an identical diet with no added cadmium (group control). Conditioned place preference (CPP) was conducted in a two-chamber apparatus in which all drugs were paired with the least-preferred side as determined by a pretest. In Experiment 1, animals received 0, 2.5, or 5 mg/kg cocaine HCl (IP) for 4 days and vehicle only for 4 days. Control animals showed a place preference for the drug side at 2.5 and 5 mg/kg, while the cadmium-exposed animals showed a preference at 5 mg/kg only. In Experiment 2, animals received 0, 5, or 10 mg/kg of the D_1/D_2 dopamine receptor agonist apomorphine HCl (SC) for 4 days and vehicle only for 4 days. Control animals showed a place preference at 5 and 10 mg/kg, while metal-exposed animals showed a preference at 10 mg/kg only. To determine the possible effects of alterations of learning mechanisms by cadmium, a conditioned place aversion (CPA) procedure was employed for Experiment 3. Animals received 0, 10, or 40 mg/kg lithium chloride (IP) for 4 days or vehicle only for 4 days. Control animals showed a significant place aversion at 40 mg/kg, while cadmium-exposed animals did not. These findings are discussed within a framework of possible metal-induced disturbance of neurochemical function and/or associative processing. © 1999 Elsevier Science Inc.

Cadmium exposure Conditioned place preference Cocaine

THE deleterious effects of tobacco smoking on health have been publicized widely. The traditional focus has been on carcinogenic, cardiovascular, or respiratory problems associated with long-term tobacco exposure. But, another important risk associated with smoking is increased exposure to cadmium, a heavy metal that selectively accrues in tobacco leaves (29). Cigarette smoking has been shown to elevate the body burden of cadmium to a level twice that of nonsmokers (19,28, 29). As smoking behaviors often occur long term, the effects of chronic exposure to cadmium are significant, as the metal is efficiently retained and accumulates in the body with age (10). Due to the higher body burdens of cadmium in smokers, and a correlation between tobacco use and other drug taking (21), it is important to examine the potential interactions of this heavy metal with drugs of abuse.

Using an animal model, chronic cadmium exposure has been shown to produce a subsensitivity to the locomotor activating properties of both acute and repeated administration of cocaine (13). Consistent with this pattern of metal-related antagonism of the effects of cocaine, in a drug discrimination procedure cadmium-exposed animals required more training sessions to attain reliable discrimination of a cocaine cue from vehicle only, and did not develop tolerance to the discriminative stimulus when large-dose injections were administered in the home cage (15). Finally, with high doses of cocaine, cadmium-exposed animals demonstrated increased rates of drug self-administration compared to control animals, and the cocaine dose that produced maximum responding was greater for the metal-exposed animals (14).

It has been demonstrated that the differences in cocaine sensitivity expressed through behavioral measures are not a result of metal-induced decreases in levels of cocaine in the blood and brain (16). Accordingly, it must be considered that cadmium has an action on the neural substrates of drug re-

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ward. With regard to dopamine, cadmium has been shown to decrease stimulated release of the transmitter in the striatum (17) and nucleus accumbens (7). This antagonism of dopaminergic pathways was also demonstrated through a drug-discrimination procedure in which cocaine served as the discriminative stimulus. Nonmetal-exposed animals generalized the nonselective D_1/D_2 dopamine receptor agonist apomorphine, the selective D_2 agonist quinpirole, and the selective D_1 agonist SKF-82958 to cocaine, while metal-exposed animals did not (15). Cadmium also acts as a nonspecific calcium channel antagonist, and through this action has been shown to block *N*-methyl-D-aspartate (NMDA)-induced dopamine release in the striatum (3).

Regardless of the neural loci associated with cadmium/cocaine interactions, the established behavioral pattern of results produced by cadmium exposure has implications on the abuse potential of the drug. Drug-related stimuli have been demonstrated to be important in control of the behavioral and subjective properties of drugs in animals and humans (20). An appropriate procedure to study the stimulus factors that underlie drug use is conditioned place preference (CPP). In this model, a drug is administered to the animal immediately before placement in an environment with unique contextual stimuli (e.g., olfactory, visual, tactile). Following several pairings of the drug and the unique context, and separate pairings of a distinctively different context and no-drug (vehicle), the animal is tested for preference by being allowed free-choice access to the drug-paired and the vehicle-paired contexts. CPP is then defined by some measure of preference for one context over another. In this regard, cocaine (1) and other dopaminergic agonists, such as apomorphine (18), have been shown to produce a robust CPP in animals that have not been exposed to cadmium. With regard to metal exposure, cadmium has been demonstrated to produce an attenuation in the conditioned reinforcing properties of morphine administered centrally and through the periphery (12).

The CPP procedure has been demonstrated to be sensitive not just to the stimulus effects of drug use, but also to the neural mechanisms of cocaine reinforcement. The D_1 dopamine receptor antagonist SCH 23390 and the noncompetitive NMDA antagonist MK-801, each administered with cocaine during conditioning, have been shown to block the acquisition of cocaine CPP (4). With regard to opiates, coadministration of the mu-opioid antagonist naltrexone (25) or the delta-opioid antagonist naltrindole (24) antagonizes the acquisition of cocaine-induced CPP. Calcium channel blockers (isradipine and nifedipine) have been demonstrated to antagonize the expression of cocaine place preference (1). Because cadmium presence disrupts neurochemical processes related to dopaminergic (7,15,17), NMDA (11), and opiate function (26), and because the metal is an established calcium channel blocker (3), cadmium could alter the development or expression of cocaine CPP or CPP produced by related drugs. Accordingly, the present report presents findings from a series of investigations on the effects of chronic cadmium exposure on the conditioned reinforcing properties of the dopaminergic agonists cocaine (Experiment 1) and apomorphine (Experiment 2).

It must also be considered that an attenuation in cocaine or apomorphine CPP in metal-exposed animals could derive from challenges to associative or cognitive processing, rather than neural mechanisms of drug reinforcement. CPP is a learned phenomena in which the contextual cues of the environment acquire secondary reinforcing properties via classical conditioning (2). Blockade of glutamate neurotransmission by MK-801 impairs attention to exteroceptive stimuli (6), and compromises of NMDA activity by MK-801 retard behavioral plasticity and limit associative formation in a learning context (5). Because cadmium acts as an NMDA antagonist (11), it is reasonable to assert that any effects of the metal on CPP are due to alterations in learning and conditioning mechanisms rather than drug action exclusively. With regard to smoking as an exposure vector for cadmium in humans, heavy smokers of tobacco have been shown to perform less well than light or nonsmokers on several learning tasks (23). To address issues related to the actions of cadmium on mechanisms of learning, Experiment 3 will employ a conditioned place aversion (CPA) procedure in which an aversive stimulus (lithium chloride, LiCl) is paired with one distinct context and vehicle only is paired with another.

METHOD

Apparatus

Place conditioning and testing were conducted in seven 20 × 60 × 20-cm wooden shuttle boxes with wooden tilt floors. At each end of a box was a microswitch interfaced with an IBM compatible computer. A BASIC computer program was written to continuously record the number of times and duration the switch was activated through a tilt of the floor by a rat.

Half the box had white walls with a smooth white floor, and the other had black walls with a black sandpaper floor. For conditioning sessions, the boxes were divided into two equal-sized compartments by removable partitions. On test sessions the partitions were removed and a 20 × 10 × 5-cm wooden platform was installed 2 cm above the floor to divide the two compartments but allow free access by rats. Pilot research indicated that subjects showed a strong preference for the black side. Accordingly, in the experiments reported here, a 40-watt light was positioned 50 cm above the black side of each apparatus. These seven lamps provided the only illumination in the room. Following each conditioning and test session the apparatus was cleaned with a mild soap solution. The apparatus was located in a sound-resistant room with a 40-dB white noise generator operating continuously.

Drugs

Cocaine HCl (provided gratis by the Research Technology Branch of NIDA), apomorphine HCl (Sigma Co.; St. Louis, MO), and LiCl (Sigma Co.) were dissolved in a 0.9% w/v saline vehicle, and the dosages are expressed as the salt. Cocaine and lithium chloride were administered IP and apomorphine was administered SC. All injections were given at a volume of 1 ml/kg.

Experiment 1: Cocaine CPP

Subjects. The subjects used in this study were 34 male Sprague–Dawley rats (Holtzman Co., Madison, WI) that were approximately 50 days old at the time of their arrival at the laboratory. Body weights ranged from 175 to 199 g. Fifteen animals received ad lib access to a purified rodent diet (AIN-93G). The remaining 19 animals received ad lib access to an identical diet, except that it contained 100 ppm added cadmium chloride. Both were specially prepared by Dyets, Inc. (Bethlehem, PA). Continuous access to tap water was available in the home cages.

Throughout the experiment, animals were double housed in hanging polycarbonate cages. Each cage contained two animals from the same exposure group (cadmium or control diet). The cages were located in a temperature and humidity

controlled animal colony with a 12-h light/dark cycle (lights on at 0600 h). Food consumption and body weights were recorded weekly throughout the experiment. Individual animal food consumption was measured by halving the total consumed by the cage pair. Behavioral training and testing sessions were conducted at 1000 h.

The animal holding and testing facility is approved by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International), and all animal maintenance and research was conducted in accordance with the guidelines provided by the University Laboratory Animal Care Committee (ULACC). The health of the animals was monitored throughout the duration of the project by the campus veterinarian.

Procedures. Following 40 days of preexposure to their appropriate control or cadmium diets, the animals began CPP conditioning and testing. On day 1 of the study, animals were transferred from the colony to the testing room for 40 min to habituate to transportation and the sound and illumination of the room. They were not placed in the CPP apparatus. Initial biases for the white or black chamber (pretest) were determined on day 2, as noninjected control and cadmium-exposed animals were given free access to either chamber for 15 min. On days 3–10, different groups of control or cadmium-exposed animals received one of three injections of cocaine (0, 2.5, or 5 mg/kg) on four of the conditioning days, and four vehicle (saline) injections on the remaining four conditioning days. All injections were given at a volume of 1 ml/kg. In all cases, the animal was confined to the side least preferred (defined as the side in which the animal spent the least amount of time on the day 2 pretest), 5 min after receiving a cocaine injection. The animal was confined to the most-preferred chamber (defined as the side in which the animal spent the most amount of time on the day 2 pretest), 5 min following a vehicle injection. The period of confinement for each conditioning trial was 30 min. Cocaine and vehicle were presented on alternating days (8 total), and the injection received first was counterbalanced for type of injection (saline, cocaine) and exposure regimen (control, cadmium). Animals were run in squads of five, counterbalancing by dose and group assignment. A posttest was conducted on day 11 following the same procedure as the day 2 pretest.

Twenty-four hours after the posttest, animals were rendered unconscious with 60 mg/kg sodium pentobarbital (IP), decapitated, and approximately 0.5–1.0 ml of trunk blood was collected.

Experiment 2: Apomorphine CPP

Subjects. The subjects used in Experiment 2 were 51 male Sprague–Dawley rats (Holtzman Co., Madison, WI) that were approximately 50 days old at the time of their arrival at the laboratory. Body weights ranged from 175 to 199 g. Twenty-five animals received ad lib access to a purified rodent diet (AIN-93G). The remaining 26 animals received ad lib access to an identical diet, except that it contained 100 ppm added cadmium chloride. All other aspects of animal maintenance were as described in Experiment 1.

Procedures. The conditioning and testing procedures for Experiment 2 were precisely as described for Experiment 1, with the exception that separate groups of animals received one of three apomorphine doses (0, 5, and 10 mg/kg) on the drug side of the chamber during the training period (days 3–10). All injections were given immediately prior to placement in the chamber and the duration of confinement was 30 min. All other aspects of the study, including posttest procedures on day 11, were as described for Experiment 1.

Experiment 3: LiCl CPA

Subjects. The subjects used in Experiment 3 were 66 Sprague–Dawley rats (Holtzman Co., Madison, WI) that were approximately 50 days old at the time of their arrival at the laboratory. Body weights ranged form 175 to 199 g. Thirty-two animals received ad lib access to a purified rodent diet (AIN-93G). The remaining 34 animals received ad lib access to an identical diet, except that it contained 100 ppm added cadmium chloride. All other aspects of animal maintenance were as described in Experiment 1.

Procedures. The conditioning and testing procedures for Experiment 3 were precisely as described for Experiment 1, with two exceptions. First, separate groups of animals received one of three LiCl doses (0, 10, and 40 mg/kg, IP) on the drug side of the chamber during the training period (days 3–10). The injections were given 5 min prior to placement in the chamber and the duration of confinement was 45 min. Second, each animal was confined to the side most preferred (defined as the side in which the animal spent the most amount of time on the day 2 pretest) 5 min after receiving a LiCl injection. The animal was confined to the least-preferred chamber (defined as the side in which the animal spent the least amount of time on the day 2 pretest) 5 min following a vehicle injection. All other aspects of the study, including posttest procedures on day 11, were as described for Experiment 1.

Cadmium Residues in Blood

Following collection of blood samples, cadmium residues in blood were measured via atomic absorption spectrophotometry (16).

Statistical Analysis

Conditioning scores were defined by the change in time (measured in seconds) in the drug-paired chamber from the pretest to posttest (time on posttest minus time on pretest). A CPP or CPA occurred when the mean group conditioning score was significantly greater than the vehicle-only (0 mg/kg) group. Comparisons were made within exposure groups (control or cadmium). For example, cadmium–cocaine dose groups were compared to the cadmium–vehicle group. Additional comparisons of group differences were made at each dose in an effort to more explicitly detail points of separation between control and cadmium-exposed animals.

For each experiment, a group $\times$ dose factorial analysis of variance (ANOVA) test was employed, and simple effects analyses and Newman–Keuls post hoc tests were used when appropriate to determine significant differences ($p < 0.05$).

RESULTS

Body Weights and Food Consumption

For each of the three experiments, there were no significant group differences or interaction effects with respect to body weights or food consumption. Body weights did increase systematically by week for all animals, and at the start of behavioral testing, body weights ranged from 397–488 g. Average cadmium exposure was approximately 10.0 mg/kg/day for animals receiving the adulterated diet.

Experiment 1: cocaine CPP. Control and cadmium-exposed animals spent more time in the black chamber on the day 2

pretest. There were no significant differences, $t(32) = 0.46$, $p > 0.05$, between cadmium-exposed (mean = 303.2 s, SEM = ±65.3 s) and control (mean = 293.4 s, SEM = ±57.1 s) animals with respect to the amount of time spent in the least-preferred side of the apparatus.

With respect to the results from the ANOVA conducted on the conditioning scores from day 11 testing (see Fig. 1), a significant main effect of dose was found, $F(2,33) = 12.06$, $p < 0.001$, and post hoc tests indicated that across groups all animals that received the 5 mg/kg dose (mean = 203.8 s, SEM = ±26.9 s) had greater conditioning scores than all animals that received the vehicle-only dose (mean = 7.5 s, SEM = ±30.9 s). A significant main effect of group was also found, $F(1,33) = 7.30$, $p < 0.05$, as across doses the control-diet exposure group (mean = 141.8 s, SEM = ±24.1 s) showed greater overall conditioning scores than the cadmium-diet group (mean = 54.9 s, SEM = ±21.4 s).

Based on a simple main effect analysis and post hoc tests, the control animals showed a significant place preference at 2.5 and 5 mg/kg, $F(2, 14) = 9.04$, $p < 0.01$. Within the cadmium exposure group, a significant place preference was found only at the 5-mg/kg dose, as indicated by the simple main effect analysis, $F(2, 18) = 4.67$, $p < 0.05$, and post hoc tests (see Fig. 1). An additional comparison of group separation at the 2.5-mg/kg dose indicated a marginally significant difference between control and cadmium-exposed animals, $t(11) = 2.17$, $p = 0.053$. These differences in the doses that produced place preference between groups indicate disturbance in the pattern of cocaine CPP performance among cadmium-exposed animals.

Although previous investigators have demonstrated an attenuation in the locomotor-increasing properties of cocaine in cadmium-exposed animals (13), no significant differences were noted between exposure groups at any doses in the number of times an animal entered the drug or saline-paired chamber (all Fs < 1). This pattern of results was also present in Experiments 2 and 3.

For Experiment 1, animals receiving the diet containing 100 ppm added cadmium chloride (mean = 9.06 μg/dl, SEM = ±0.42 μg/dl) had significantly greater blood cadmium levels than control animals (mean < 1.0 μg/dl) receiving the unadulterated diet ($p < 0.001$).

Experiment 2: apomorphine CPP. Both control and metal-exposed groups had an overall preference for the black chamber on the day 2 pretest. There were no differences between groups (control mean = 300.8 s, SEM = ±18.5 s; cadmium mean = 282.3 s, SEM = ±22.7 s) on the amount of time spent in the side least-preferred on the pretest, $t(49) = 0.63$, $p > 0.05$.

The ANOVA conducted on the apomorphine conditioning scores (Fig. 2) revealed a significant main effect of dose, $F(2, 45) = 12.67$, $p < 0.001$. Post hoc tests indicated that both control and metal-exposed animals in the 10-mg/kg dose group (mean = 249.0, SEM = ±35.2) had conditioning scores significantly greater than those in the vehicle-only group (mean = 27.0, SEM = ±34.2). A marginal main effect of group was also found, $F(1, 45) = 2.96$, $p = 0.092$.

Based on a simple main effect analysis and post hoc tests, the control animals showed a significant place preference at 5 and 10 mg/kg, $F(2, 24) = 7.29$, $p < 0.01$. Within the cadmium-exposure group, a significant place preference was found only at the 10 mg/kg dose, as indicated by the simple main effect of dose, $F(2, 25) = 6.35$, $p < 0.01$, and post hoc tests (see Fig. 2). These differences in dose required to produce place prefer-

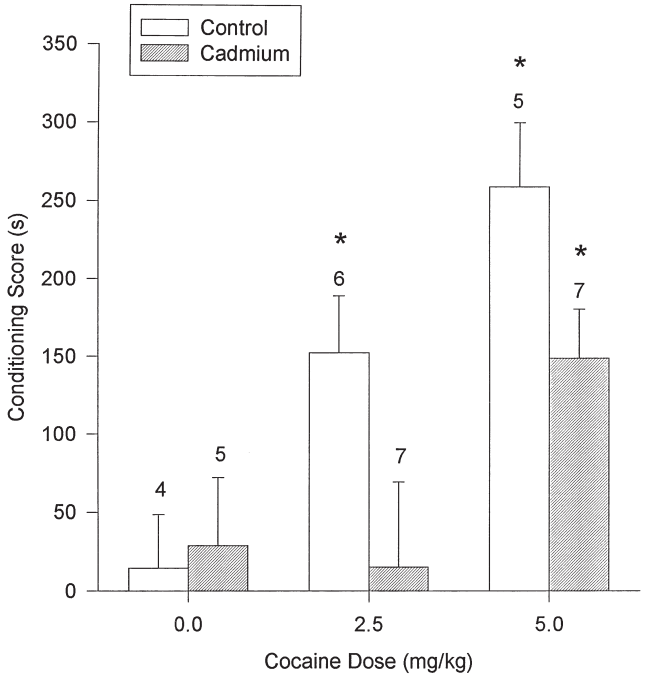

FIG 1. Mean (±SEM) conditioning scores (measured in seconds) or cadmium-exposed and control animals for cocaine CPP. The numbers above the bars indicate group size. Asterisks indicate the dose is significantly different from the same dietary exposure condition (control or cadmium) vehicle-only group ($p < 0.05$).

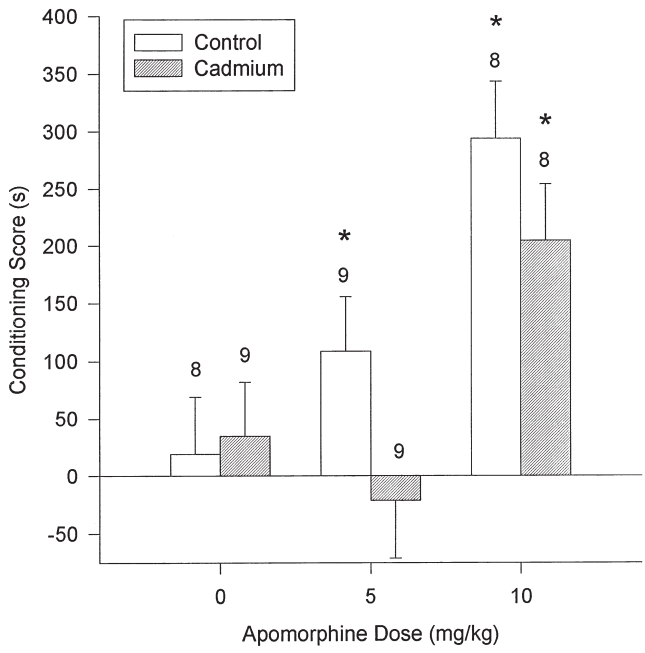

FIG 2. Mean (±SEM) conditioning scores (measured in seconds) or cadmium-exposed and control animals for apomorphine CPP. The numbers above the bars indicate group size. Asterisks indicate the dose is significantly different from the same dietary exposure condition (control or cadmium) vehicle-only group ($p < 0.05$).

ence between exposure groups indicate an antagonism in apomorphine CPP for cadmium-exposed animals.

For Experiment 2, animals receiving the diet containing 100 ppm cadmium chloride (mean = 9.65 μg/dl, SEM = ±0.55 μg/dl) had significantly greater blood cadmium levels than control animals (mean < 1.0 μg/dl) receiving the unadulterated diet ($p < 0.001$).

Experiment 3: LiCl CPA. As with Experiments 1 and 2, both groups had an overall preference for the black chamber on the day 2 pretest. Again, there were no differences between groups (control mean = 562.3 s, SEM = ±24.2 s; cadmium mean = 535.0 s, SEM = ±16.4 s) on the amount of time spent in the side most preferred on the pretest, $t(64) = 0.95$, $p > 0.05$.

On the omnibus ANOVA test, a marginally significant main effect of group was found, $F(1, 65) = 3.19$, $p = 0.072$, as control animals (mean = −134.3 s, SEM = ±18.5 s) had overall conditioning scores of a greater magnitude than cadmium-exposed animals (mean = −88.2 s, SEM = ±18.0 s) (see Fig. 3). A significant main effect of LiCl dose was found, $F(2, 65) = 4.18$, $p < 0.05$. Collapsed over control and metal-exposed animals, conditioning scores of a greater magnitude were shown at the 40 mg/kg concentration (mean = −157.8 s, SEM = ±24.2 s) than vehicle only (mean = −68.9 s, SEM = ±19.0 s).

As shown on Fig. 3, based on the simple effects analysis and post hoc tests, control animals showed a significant CPA at 40 mg/kg but not 10 mg/kg, $F(2, 31) = 9.20$, $p < 0.001$. A significant main effect of dose was not found for cadmium-exposed animals, $F(2, 33) = 0.21$, $p = 0.82$. These data indicate that control animals showed a dose-dependent CPA, but cadmium-exposed animals did not at the concentrations of LiCl selected to serve as unconditional stimuli.

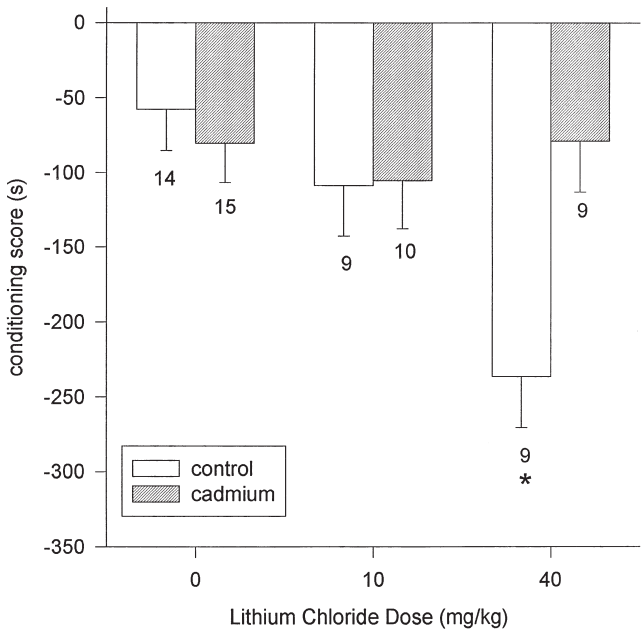

FIG 3. Mean (±SEM) conditioning scores (measured in seconds) or cadmium-exposed control animals for lithium chloride CPA. The numbers above the bars indicate group size. Asterisks indicate the dose is significantly different from the same dietary exposure condition (control or cadmium) vehicle-only group ($p < 0.05$).

For Experiment 3, animals receiving the diet containing 100 ppm cadmium chloride (mean = 9.26 μg/dl, SEM = ±0.56 μg/dl) had significantly greater blood cadmium levels than control animals (mean < 1.0 μg/dl) receiving the unadulterated diet ($p < 0.001$).

DISCUSSION

A CPP for cocaine and apomorphine was demonstrated in animals not exposed to cadmium. An attenuation of cocaine and apomorphine CPP was observed for adult animals exposed to chronic dietary cadmium. A complete antagonism of CPP was not evident, as the cadmium-exposed animals did demonstrate place preference, but greater drug doses were required. A significant CPA with LiCl was evident in control animals, but no CPA was present in metal-exposed animals.

It has been demonstrated that alterations of dopamine (4), opiate (24,25), and NMDA (4) pathways produce an antagonism of the conditioned reinforcing properties of cocaine. Cadmium has action in the central nervous system (CNS) as a dopamine antagonist (7,15,17), inhibits the binding of mu and delta opiate ligands (26), and blocks NMDA (11) and calcium (3) ion channels. It is possible that the attenuation in cocaine CPP by cadmium (Experiment 1) is the result of an antagonistic action by the metal at any or all of these loci.

Beside action on the CNS, cadmium has been demonstrated to have a toxic effect on kidney and liver function (9). Because of this action, it is possible that the attenuation of cocaine CPP is due to alterations in the pharmacokinetics of cocaine, such that CNS levels of the drug are not equal in cadmium and control animals. This explanation is less preferred, as it has been shown that metal-exposure produces no change in the levels of cocaine and a metabolite (benzoylecgonine) in blood or brain (16). Furthermore, cadmium produces an attenuation of CPP with both central and peripheral administration of morphine (12).

The results of Experiment 2 compliment the results of Experiment 1. The attenuation of CPP by cadmium with apomorphine indicates a possible influence by the metal at D_1/D_2 dopamine receptors. Apomorphine produces CPP (18), and the effect appears to be dependent on dopamine pathways (27). Considering behavioral (15), microdialysis (17), and electrophysiology (7) evidence that cadmium acts as a dopamine antagonist, it appears that cadmium could disrupt conditioned reinforcement through a disturbance of CNS dopamine pathways.

It should be recognized that the attenuation observed in Experiments 1 and 2 may be derived from challenges to mechanisms other than pharmacodynamics. Due to the antagonistic action of cadmium at the NMDA receptor (11) and the role of NMDA in perception and learning (5,6), it is reasonable to assert that the attenuation of cocaine and apomorphine CPP could be due to alterations in learning and conditioning mechanisms. The results of Experiment 3 provide insight into the role that conditioning plays in the interaction between cadmium-related changes in drug-induced changes in behavior.

The metal-induced attenuation in both CPP and CPA permits two interpretations regarding the action of cadmium on the CNS and drug-related behavior. First, it is possible that the attenuation in CPP in metal-exposed animals was a function only of an alteration of the neural pathways of learning. Thus, cocaine may have had identical unconditioned (subjective or reinforcing) properties for control and cadmium-exposed animals, but the associative requirements of CPP and differences in learning between exposure groups could have

produced the reported results. A second possibility is that the metal produces an alteration of the aversive properties of lithium. Just as cadmium is proposed to attenuate the unconditioned (13) and reinforcing (14) properties of cocaine, perhaps the metal attenuates the unconditioned or aversive properties of LiCl. It has been demonstrated that opioid and dopaminergic pathways can influence the aversive properties of lithium (8,22), and because cadmium behaves as an antagonist at both sites, possible cadmium/LiCl neural interactions are indicated. Future investigations should examine unconditioned behaviors elicited by exposure to LiCl in metal-exposed animals to further differentiate learned vs. stimulus intensity factors in classical conditioning.

Regardless of mechanism of action by cadmium on cocaine CPP pharmacologic disturbance, these results have implications for the population of human tobacco users. Because there is a correlation between the use of cocaine and the use of tobacco (21), and increased body–cadmium burdens are evident among smokers (19,28,29), the results presented here indicate a possible risk factor. This study suggests a subsensitivity to the behavioral properties of cocaine coincident with cadmium exposure. In an attempt to maintain blood levels of cocaine that produce a set level of arousal or reward, tobacco users may self-administer more cocaine at larger concentrations than nontobacco users. Consistent with this idea, animals exposed to the metal exhibit greater intravascular self-administration of high doses of cocaine relative to controls (14). A particular concern with respect to health risk relates to lethality issues. It is unknown whether cadmium confers protection against the lethal properties of cocaine, such that a parallel attenuation in reinforcement and the lethal dose occurs. The metal may only have an effect on the reward properties of the drug (increased self-administration), and yet have no protective effect on the lethal properties of cocaine. If this occurs, the population of tobacco users who also use cocaine may be at greater risk for an overdose.

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