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Chlordiazepoxide-Induced Conditioned Place and Taste Aversion Learning in Rats

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PARKER, L. A., C. L. LIMEBEER AND G. R. SIMPSON. *Chlordiazepoxide-induced conditioned place and taste aversion learning in rats*. PHARMACOL BIOCHEM BEHAV **59**(1) 33–37, 1998.—The hedonic properties of chlordiazepoxide (CDP) were examined using the place conditioning and the taste conditioning paradigms. Following four conditioning trials, CDP (5–20 mg/kg) produced a conditioned place aversion in an "unbiased" paradigm in which the chamber paired with CDP was counterbalanced among two equally preferred chambers. In a "biased" place-conditioning paradigm, CDP (5 and 20 mg/kg) prevented the dissipation of the natural aversion to the nonpreferred chamber. Finally, although CDP unconditionally potentiated sucrose consumption, it produced a sucrose aversion in the taste reactivity test and sucrose avoidance in the taste avoidance test when the taste conditionally preceded injections of CDP. The pattern of findings suggest that, when novel to rats, CDP is hedonically aversive. © 1998 Elsevier Science Inc.

Chlordiazepoxide Anxiolytics Benzodiazepines Place preference Place aversion Taste avoidance Taste reactivity Drug reward Palatability Conditioning

MANY drugs that animals self-administer or that produce a conditioned place preference also produce conditioned taste avoidance at equivalent dosages (5). It is often assumed that the suppressed consumption of a flavor previously paired with a psychoactive drug is due to the development of an association between some aversive stimulus property of the drug and the taste of the flavored solution; therefore, the phenomenon has been called "conditioned taste aversion learning" [e.g., (13)]. However, we (21,22,24,25) and others (27) have argued that the term is not entirely accurate. Although flavors paired with the emetic agent, lithium, are actively rejected by rats in the taste reactivity (TR) test [a direct measure of palatability (17)], flavors paired with rewarding drugs (such as amphetamine, cocaine, and morphine) are not actively rejected [e.g., (21,22, 24, 25)], even though they are avoided in the typical consumption test. This suggests that conditioned taste avoidance produced by rewarding drugs differs in nature from the conditioned taste avoidance produced by emetic drugs.

Like most psychoactive drugs, the anxiolytic drug, chlordiazepoxide (CDP) produces conditioned taste avoidance (5); however, it is not known whether this avoidance is mediated by a conditioned taste aversion in the TR test. Although CDP is abused by humans (1,16), the evidence that CDP is reinforcing to rats is equivocal. Rats have been reported to self-administer CDP (10), but CDP has also been reported to interfere with intravenous cocaine self-administration in rats (15), suggesting that it interferes with the rewarding properties of cocaine. Additionally, CDP has been reported to unconditionally enhance the palatability of sweet solutions (3,4, 7,18,23); however, it is not clear that this effect is related to its hedonic properties (3).

Another animal model of drug reward, the place-conditioning paradigm, evaluates the hedonic properties of drugs in rats that are tested drug free. The unconditioned sedative effects of benzodiazepines, therefore, should not interfere with the display of conditioned reward. In the only report of a CDP-induced place preference, the author (12) writes, "Whilst conditioned place preference was clear for lorazepam and diazepam, chlordiazepoxide produced only weak effects, whether given acutely or chronically." The hedonic properties of CDP are, therefore, not well established. Reports of human abuse also suggest that CDP is less rewarding than other benzodiazepines (1,16).

Because there is relatively little information about the hedonic properties of CDP, the following experiments examined the rewarding/aversive properties of CDP using the taste reactivity and place-preference paradigms. In the place-preference paradigm, we examined the hedonic properties of CDP using

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both the "unbiased" and the "biased" place-conditioning paradigms. In the "unbiased" paradigm, the side paired with the drug is counterbalanced between two chambers that are equally preferred when assessed by group means. In the "biased" paradigm, the rats are pretested for their initial side preferences and the drug is consistently paired with the nonpreferred chamber. The previous demonstration of CDP-induced place-preference learning employed the latter paradigm (12); however, it has been suggested (6,32) that the display of a place preference in the "biased" paradigm may reflect the ability of the drug to reduce the aversive properties to the initially nonpreferred chamber, rather than the rewarding properties of the drug. With such procedures, it is conceivable that the increased preference for the least preferred chamber may be the result of the anxiolytic properties of the benzodiazepines reducing the anxiety-arousing properties of the nonpreferred chamber rather than their rewarding properties.

METHOD

Subjects

Male Sprague–Dawley rats, obtained from Charles River Labs, St. Constant, Quebec, weighing 250–300 g at the beginning of the experiments served as subjects. For the place-conditioning experiments, the rats were housed in pairs in plastic cages with woodchip bedding and for the taste conditioning experiments, they were housed individually in stainless steel cages. The room was maintained on a 12 L:12 D schedule. Throughout the experiment, the rats were maintained on ad lib food and water. They were handled daily over a 1 week adaptation period prior to the initiation of experimental procedures.

Drug

The chlordiazepoxide, obtained from Hoffman–LaRoche, was prepared in saline solution at a concentration of 10 mg/ml. The drug was always administered intraperitoneally.

"Unbiased" Place Conditioning

The place-conditioning apparatus, previously described (26), included two wooden chambers separated during conditioning trials by a wooden divider. The walls of each chamber were painted flat black. The conditioning cues consisted of the textural floors in the chambers: one floor was covered with wire mesh (0.625 cm), and the other floor was covered with sandpaper strips (3 cm) located 2.5 cm apart. In an initial test of the relative preference for these cues after each floor was paired on four occasions with a saline injection, the amount of time spent in the sandpaper (415 s) and the mesh (485 s) floors that did not significantly differ.

Thirty-six rats received a total of four differential conditioning trial cycles with 2–3 days intervening between cycles. Each cycle consisted of one trial in which rats were injected with 5 mg/kg ($n = 12$), 10 mg/kg ($n = 12$) or 20 mg/kg ($n = 12$) of chlordiazepoxide 5 min prior to placement in the chamber with either the sandpaper on mesh floor and another trial on which they were injected with physiological saline solution prior to placement in the opposite chamber for 30 min. The trials within each cycle were separated by 24 h and the order of drug trial and the chamber paired with CDP were counterbalanced. The group that had CDP paired with the sandpaper floor (and saline paired with the mesh floor) are designated as Sand+ and the group that had saline paired with the sandpaper floor (and CDP paired with the mesh floor) are designated as Sand−.

The place-preference test occurred 72 h after the final conditioning trial. On the test, the barriers between the chambers were removed allowing the rats to explore both chambers and the amount of time that the rats spent in each chamber was automatically recorded over a 15-min test trial. The activity of the rats during testing was monitored by a video-tracking apparatus (Videomex-V, Columbus Instruments, Columbus, OH) from a video camera mounted to the ceiling. The number of seconds that Group Sand+ and Group Sand− spent in the sandpaper chamber were compared. A conditioned place preference would be evident if Group Sand+ spent more time in the sandpaper chamber than Group Sand− [e.g., (9,26)].

"Biased" Place Conditioning

Twenty-four rats were treated in a manner similar to that of "unbiased" place-conditioning experiment except as specified. The apparatus was identical except that one chamber had a mesh floor and the other had a rubber mat floor. Because most rats preferred the grid floor to the rubber mat floor, this configuration produced an apparatus that would readily reveal a biased preference.

During the preconditioning phase, the rats were allowed to explore both chambers for 15 min on each of three pretest trials and the time spent in each chamber was recorded. The number of seconds spent in the least preferred chamber on the third pretest served as the pretest score. The least preferred chamber was the chamber with the plastic floor for all but two rats.

The rats received four conditioning trial cycles in a similar manner as that of the previous experiment, except that the chamber paired with chlordiazepoxide [0 mg/kg (saline, $n = 8$), 5 mg/kg ($n = 8$) or 20 mg/kg ($n = 8$)] was the nonpreferred chamber during the third pretest trial. The order of the drug trial was counterbalanced. A single place-preference test occurred 48 h after the final conditioning trial. The number of seconds spent in the nonpreferred chamber during the pretest and the test trial were compared for each group.

Taste Conditioning: Taste Reactivity and Taste Avoidance

Twenty-six rats were surgically implanted with intraoral cannulae. The surgical procedure has been previously described (20). Briefly, all rats were given an IP injection of atropine (0.25 mg/kg), 5 min prior to receiving an IP injection of a mixture of ketamine (100 mg/kg) and rompun (3 mg/kg). Once the rats were anesthetized, a 15-ga thin-walled stainless steel needle was inserted in the midneck region and brought subcutaneously (SC) around the ear and out on the inside of the rat's cheek behind the first molar. Then, PE 90 (i.d., 0.86 mm; o.d. 1.27 mm) intramedic tubing was inserted through the shaft of the needle and the needle was removed. The tubing was held in place with a rubber washer on the inside of the cheek and a 20-ga adapter in the back of the neck. The rats were allowed 1 week to recover from surgery before the adaptation and conditioning trials began.

On each of three adaptation trials (separated by 24 h), the rats received an intraoral infusion of water at the rate of 1 ml/min for a 2-min period in the glass TR test chamber ($25.2 \times 26 \times 20$ cm). On the following day, the rats received the first of five TR conditioning/testing trials that were separated by 72 h. On each trial, the rats were placed in the TR test chamber in which they were infused with a 0.5 M (17%) sucrose solution for a period of 2 min at the rate of 1 ml/min. Their orofacial reactions during the 2-min infusion were videotaped.

Immediately following infusion, the rats were removed from the TR chamber and injected IP with 0.0 mg/kg (saline, $n = 6$), 5 mg/kg ($n = 6$), 10 mg/kg ($n = 8$), or 20 mg/kg ($n = 6$) of chlordiazepoxide. Following the fifth conditioning/testing trial, the rats received no injection. They were returned to their home cage where they were presented with two graduated tubes, one containing 0.5 M sucrose solution and the other containing water for 120 min. The amounts consumed of sucrose and water were measured and converted to sucrose preference ratios (ml sucrose consumed/ml sucrose + ml water consumed).

The videotapes of the TR conditioning/testing trials were later scored by raters blind to the experimental conditions. The behaviors measured included the aversive reactions of chin rubbing (mouth in direct contact with the floor or a wall and projecting the body forward), gaping (large-amplitude, rapid opening of the mandible with concomitant retraction of the corners of the mouth), and paw treading (sequential extensions of one forelimb forward against the floor while the other forelimb is being retracted). These scores were combined to produce a composite aversive reaction category.

Unconditional Effect of CDP on Sucrose Consumption

As a replication of previous reports [e.g., (7,23)], the effect of CDP on sucrose consumption was assessed. Water bottles were removed 2 h prior to a consumption test trial. Rats were injected with 10 mg/kg CDP ($n = 10$) or saline ($n = 9$), 30 min prior to presentation of sucrose solution for 2 h in a graduated tube and the amount consumed was measured.

RESULTS

"Unbiased" Place Conditioning

Surprisingly, CDP produced a conditioned place aversion rather than a conditioned place preference. Figure 1 presents the mean number of seconds that the rats in groups Sand+ and Sand− that were conditioned with various doses of CDP spent in the sandpaper chamber during the place preference test. A 2 by 3 between-groups analysis of variance (ANOVA) revealed only a significant conditioning group effect, $F(1, 30) = 32.8$; $p < 0.01$, and none of the other effects were significant. When pooled across dose conditions, group Sand+ spent less time in the sandpaper chamber than group Sand−.

"Biased" Place Conditioning

Figure 2 presents the mean number of seconds that the rats in the various groups spent in the nonpreferred chamber during the final pretest and the preference test trials using the "biased" place conditioning procedure. A 3 by 2 mixed-factors ANOVA with the between groups factor of dose [0.0 (saline), 5.0 and 20.00 mg/kg of CDP] and the within-groups factor of trial (pretest, test) revealed a significant dose by trial interaction, $F(2, 21) = 5.0$; $p < 0.025$. Subsequent paired t-tests for each dose group revealed a significant difference between the two tests only for group saline, $t(7) = 4.2$; $p < 0.01$. The increased preference for the initially nonpreferred chamber in group saline suggests that the bias in chamber preference dissipated across conditioning trials for the rats experiencing that chamber in a saline state, but did not dissipate across conditioning trials for the rats conditioned with 5 or 20 mg/kg of CDP.

Taste Conditioning: Taste Reactivity and Taste Avoidance

CDP produced conditioned rejection reactions in the taste reactivity test at the highest dose (20 mg/kg) and conditioned taste avoidance at the two highest doses (10 and 20 mg/kg). Figure 3 represents the mean frequency of rejection reactions displayed by the various groups during the taste reactivity conditioning/testing trials. A 4 by 5 mixed-factors ANOVA revealed a significant dose effect, $F(3, 22) = 7.9$; $p < 0.01$, trials effect, $F(4, 88) = 7.6$; $p < 0.01$, and dose by trials interaction, $F(12, 88) = 3.5$; $p < 0.01$. Single-factor ANOVAs for each trial revealed that the groups significantly differed on trials 3–5 Fs $(3, 22) = 5.1$; $p < .05$. By Newman–Keuls pairwise comparison tests, group 20 mg/kg displayed significantly more rejection reactions than groups 0.0 mg/kg or 5 mg/kg on trials 2–5 (ps < 0.05) and more rejection reactions than group 10 mg/kg on trials 3 and 5.

Figure 4 represents the mean sucrose preference ratios for the various groups during the 2 h two-bottled taste avoidance test. A single-factor ANOVA revealed a significant dose effect, $F(3, 22) = 5.9$; $p < 0.01$. By subsequent Newman-Keuls pairwise comparison tests, groups 10 and 20 mg/kg displayed

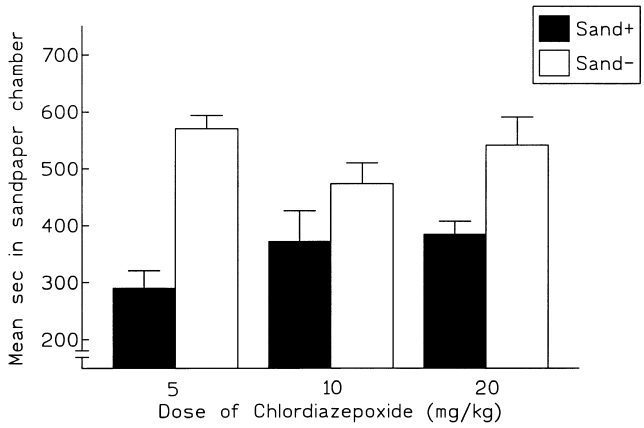

FIG. 1. Mean (± SEM) seconds that the rats in Group Sand+ and Group Sand− conditioned with various doses of CDP (5, 10, 20 mg/kg) spent in the sandpaper chamber using the "unbiased" place conditioning procedure.

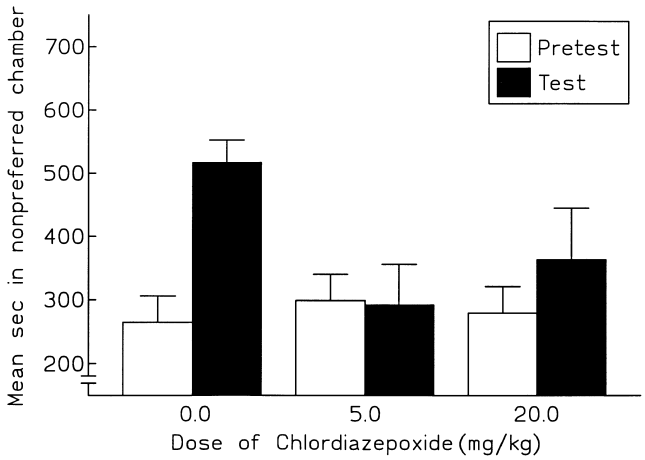

FIG. 2. Mean (± SEM) seconds that the rats in each group spent in their nonpreferred chamber during the third pretest and during the test trial using the "biased" place conditioning procedure.

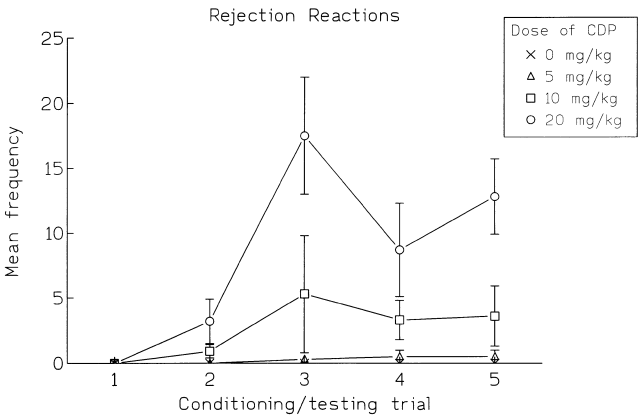

FIG. 3. Mean (± SEM) frequency of rejection reactions displayed by the rats conditioned with the various doses of CDP on each conditioning/testing taste reactivity trial.

lower sucrose preference ratios than did groups 0.0 and 5 mg/kg ($ps < 0.05$).

Unconditional Effect of CDP on Sucrose Consumption

CDP unconditionally enhanced sucrose consumption. The rats pretreated with CDP (mean = 15.8 ml) drank significantly more sucrose solution than the rats pretreated with saline (mean = 1.6 ml), with $t(17) = 3.2$; $p < 0.01$.

GENERAL DISCUSSION

Chlordiazepoxide produced a conditioned place aversion in the "unbiased" place conditioning paradigm in which the chamber paired with CDP was counterbalanced among the groups. In the "biased" paradigm, although CDP did not further decrease the rats preference for the initially nonpreferred chamber, it interfered with the dissipation of the natural place aversion that was apparent in saline conditioned rats. The failure to produce a conditioned place preference when CDP was paired with the nonpreferred chamber ("the biased procedure") suggests that not only is CDP nonrewarding, but also it does not reduce the aversive properties of nonpreferred contextual stimuli.

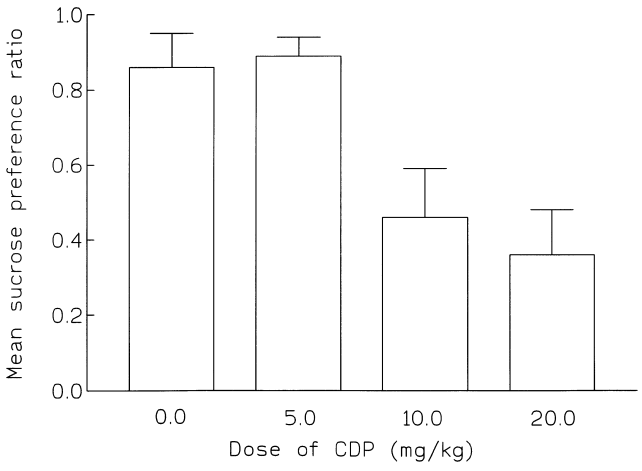

FIG. 4. Mean (± SEM) sucrose preference ratio for the groups conditioned with the various doses of CDP in a 120 min test that immediately followed the final TR test trial. A sucrose preference ratio represents the amount of sucrose consumed divided by the amount of sucrose + water consumed in the 120 min test.

Although CDP did not produce a place preference when novel to rats in the present study, there is evidence that it produces a weak place preference in a "biased" paradigm in rats that are chronically pretreated with the drug (12). Similarly, although alcohol tends to produce a place aversion in rats (8), alcohol-induced place preference learning has been reported in rats with experience with the drug (14,28). Bechara et al. (2) have provided evidence for two separate neural mechanisms of opiate reward in nondependent and dependent rats. It is possible that a similar neural dissociation governs the hedonic properties of CDP and alcohol.

Consistent with the ability of CDP to produce a place aversion (at least in the unbiased paradigm), rather than a place preference, are the findings that it also established conditioned rejection reactions in the TR test. Because the ability of a drug to produce a place preference is negatively related to its ability to produce a taste aversion in the TR test (24), our results suggest that, like lithium, CDP produces a taste aversion by conditionally shifting the palatability of sucrose solution. Future studies will investigate the ability of other benzodiazepines, which have been reported to a place preference [e.g., diazepam; (30,31)] to establish conditioned rejection reactions in the TR test.

The dose of CDP necessary to produce rejection taste reactions and a taste avoidance was 10–20 mg/kg, whereas a dose as low as 5 mg/kg of CDP produced asymptotic place aversion. Therefore, it appears that the place conditioning procedure is more sensitive to detecting the aversive properties of CDP than the taste conditioning procedure. A similar effect was reported by Lett (19) using naloxone and gallamine as the unconditioned stimulus agents. Each of these drugs more effectively produced place avoidance than taste avoidance, although lithium more effectively conditioned taste avoidance than place avoidance. Therefore, it appears that some aversive drug agents become more easily associated with contextual stimuli than with gustatory stimuli.

There is little direct evidence in the literature that CDP is rewarding to animals. However, one might have expected that CDP would be rewarding to rats on the basis of its ability to unconditionally enhance the palatability of sweet solutions in both the taste reactivity test (3,4,18,23), which directly assesses palatability (17) and the more indirect two choice preference tests [e.g., (7)]. In fact, CDP unconditionally increased sucrose intake in the present experiment. Because morphine also unconditionally enhances sucrose palatability at doses that are clearly rewarding to rats (11,29), this effect has been attributed to the rewarding properties of the drug [e.g., (29)]. However, the results presented above indicate that CDP is aversive at similar doses that produce enhancement of palatability, suggesting that the latter effect is not the result of the rewarding properties of the drug.

Human reports of benzodiazepine abuse indicate a greater likelihood of diazepam abuse than CDP abuse (16). Our results suggest that this difference in abuse potential may be the result of aversive properties of CDP that suppress drug intake.

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