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Individual Differences in Reactivity to the Rewarding/Aversive Properties of Drugs: Assessment by Taste and Place Conditioning

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TURENNE, S. D., C. MILES, L. A. PARKER AND S. SIEGEL. *Individual differences in reactivity to the rewarding/aversive properties of drugs: Assessment by taste and place conditioning.* PHARMACOL BIOCHEM BEHAV **53**(3) 511–516, 1996.—The ability of individual differences in the strength of conditioned taste avoidance (CTA) to predict strength of place conditioning produced by the same drug was assessed. In Phase 1, rats were assigned to High CTA and Low CTA groups on the basis of their intake of saccharin solution previously paired with morphine, amphetamine, lithium, or fenfluramine. In Phase 2, the rats received place conditioning training with the same drug used during Phase 1. The rats that displayed the strongest amphetamine-induced CTA also displayed the strongest amphetamine-induced place preference, suggesting that a common mechanism mediates both effects. On the other hand, the strength of the CTA was unrelated to the strength of the place preference or place aversion produced by morphine, lithium, or fenfluramine.

Amphetamine Morphine Lithium Fenfluramine Place conditioning Place preference
Taste avoidance Taste aversion Individual differences Drug reward Aversion

FOR the past 20 years, investigators have explored the nature of the paradoxical rewarding/aversive properties of psychoactive agents that tend to be abused by humans. Drugs such as amphetamine and morphine are self-administered, establish a preference for a place with which they are paired, but also paradoxically produce avoidance of a taste with which they are paired (5). Although there have been numerous reviews of the massive literature documenting this phenomenon, there has been little success explaining it.

Considerable evidence suggests that the conditioned taste avoidance (CTA) produced by rewarding drugs tends to be more variable within a group (5,12,14) than that produced by an emetic drug, such as lithium chloride. If rewarding drugs produce a CTA in some rats, but not in others, then it is likely that individual differences exist in sensitivity to the aversive properties of drugs. Indeed, individual differences in sensitivity to the rewarding properties of drugs have been documented in rats. Piazza and colleagues (10) reported that individual differences in reactivity to novelty and in reactivity to the locomotor activating properties of amphetamine predict the ability of low doses of amphetamine to reinforce lever pressing in rats. This difference in sensitivity to amphetamine reward may, in part, account for differences in vulnerability to drug addiction (10). Because individual differences in sensitivity to amphetamine reward have been documented, in the present investigation, we determined whether sensitivity to the rewarding and aversive properties of amphetamine were related within a given animal.

Although the ability of a given drug injection to produce both rewarding and aversive properties has been established (11,15,19), to our knowledge, only one investigation has assessed the strength of the relationship between these two properties of a given drug. Switzman et al. (18) demonstrated that rats that ran faster down a runway for an injection of morphine in the goal box also ate less food that was accessible in the goal box, suggesting that the rats most sensitive to the aversive properties of morphine were also most sensitive to its rewarding properties.

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If a common mechanism mediates both the rewarding and aversive properties of a given psychoactive agent, then individual differences in the strength of a CTA should predict the strength of place conditioning. The experiments that follow examined the ability of the strength of a CTA to predict the strength of place conditioning produced by the same agent in the same animals. The drugs employed were morphine and amphetamine, which paradoxically produce CTA and conditioned place preference (5), and lithium and fenfluramine, which consistently produce CTA and conditioned place avoidance (3,8).

GENERAL METHODS

Subjects

Male Sprague-Dawley (Charles River, Quebec) rats weighing 300–324 g at the time of arrival in the lab served as subjects. The rats in each experiment were experimentally naive. They were maintained on a 12 h light/dark cycle with lights on at 0800 h. All experimental procedures were conducted during the light phase of the cycle. Rats were housed in isolation in stainless steel mesh cages. Food and water were available ad lib, except as indicated. The rats were allowed 1 week to habituate to the laboratory conditions during which they were handled on each of the first 4 days.

Drugs

Morphine sulfate (NIDA; Research Triangle Park, NC), amphetamine sulfate (NIDA), and fenfluramine HCl (A.H. Robbins) were dissolved in saline solution. Lithium Chloride (LiCl) was dissolved in distilled water at a 0.15 M concentration.

General Procedure

Phase 1: Conditioned taste avoidance. Conditioning and testing was conducted in the home cage. One week after their arrival in the laboratory, the rats were placed on a water access schedule of 20 min per day for each of 5 days. Twenty-four hours later, they were given access to a graduated tube containing 0.1% saccharin solution for 20 min, immediately followed by an intraperitoneal (IP) injection of the appropriate solution. On the intervening days between conditioning trials, the rats received 20 min per day of water. Three days after the final conditioning trial, the rats were given the CTA test; they were presented with saccharin solution for 20 min and the amount consumed was measured. On the basis of test trial consumption, the rats were divided by a median split into high CTA and low CTA groups.

Phase 2: Place conditioning. The conditioning apparatus consisted of two wooden chambers (35 × 25 × 30 cm) painted flat black and separated by a black wooden divider. The floor of one chamber was covered with 1 cm strips of black sandpaper located 5 cm apart and the floor of the other chamber was covered with black corrugated plastic. In preliminary testing, these floors were found to be equally preferable (by group means); however, in some subsequent experiments, rats displayed a greater baseline preference for the sandpaper floor than the plastic floor.

Four days following the CTA test, the Phase 1 High-CTA and Low-CTA groups received place conditioning training. A Pavlovian differential conditioning procedure was used to establish a conditioned place preference with rats in the High-CTA and rats in the Low-CTA groups assigned to one of two subgroups, matched for strength of CTA. On alternate days, rats in the SAND+ subgroup were injected with the drug prior to placement in the chamber with the sandpaper floor (conditioned stimulus, CS+ trial) and with saline prior to placement in the chamber with the plastic floor (CS− trial). In contrast, rats in the SAND− subgroup were injected with saline prior to placement in the chamber with the sandpaper floor (CS− trial) and were injected with the drug prior to placement in the chamber with the plastic floor (CS+ trial). The advantages of this design have been extensively discussed by Cunningham (2). With this design, the baseline preference for the two floors need not be equivalent, because the difference in preference for one floor (sandpaper) is compared between a group that had that floor paired with the drug (CS+) and a group that had that floor paired with saline (CS−).

Each cycle of training trials consisted of a drug-chamber pairing and a saline-chamber pairing separated by 24 h. On each trial, the rats were injected with the appropriate solution 5 min prior to placement in a chamber for 30 min. Half of the rats in each group received the drug on the first trial and half received the drug on the second trial of each cycle.

During the place preference tests, conducted 48 h after the final training trial of a cycle, the divider between the chambers was removed and an overhead camera monitored the amount of time that the rat spent in each chamber during the 15-min test. The signal from the videocamera was analyzed by a videotracking apparatus (Videomex V, Columbus Instruments) and sent to an IBM computer for later analysis.

EXPERIMENT 1: MORPHINE

Specific Procedures

During Phase 1, the rats received either 2 (n = 23) or 4 (n = 16) CTA training trials, during which saccharin was paired with 15 mg/kg of morphine. Because morphine has been shown to be less effective in producing a CTA than the agents to be assessed in Experiment 2 (5,9,12,16), the number of Phase 1 training trials was greater in Experiment 1 (two or four trials) than in Experiment 2 (one trial) in an attempt to equate strength of CTA across the drugs employed. Although the factor of number of training trials was included in the analysis of the data collected in Experiment 1, it was consistently nonsignificant; therefore, the two groups are pooled in further discussion. The CTA test occurred 3 days later. On the basis of the rats' consumption of saccharin solution during the test trials, they were assigned (half from the group given two training trials and half from the group given four training trials) to High (n = 20) and Low (n = 19) CTA groups.

During the Phase 2 place conditioning training, rats from each of the Phase 1 High-CTA and Low-CTA groups were assigned to Group SAND+ (n = 10) and Group SAND− (n = 9–10). The rats received one cycle of training trials during which they were injected IP with either 15 mg/kg of morphine or saline (1.5 ml/kg) prior to a test trial (Test 1). They received an additional three cycles of training trials prior to another test trial (Test 2).

Results

During the Phase 1 test, the mean amount of saccharin consumed by the High CTA group after two trials was 11.0 ml and after 4 trials was 9.6 ml, and by the Low CTA group after two trials was 17.0 ml and after four trials was 16.0 ml. The number of training trials did not modify the strength of the CTA in either the High or the Low CTA group.

Figure 1 presents the mean number of seconds that the rats in Group SAND+ and SAND− spent in the chamber with the sandpaper floor during Test 1 (after one training cycle)

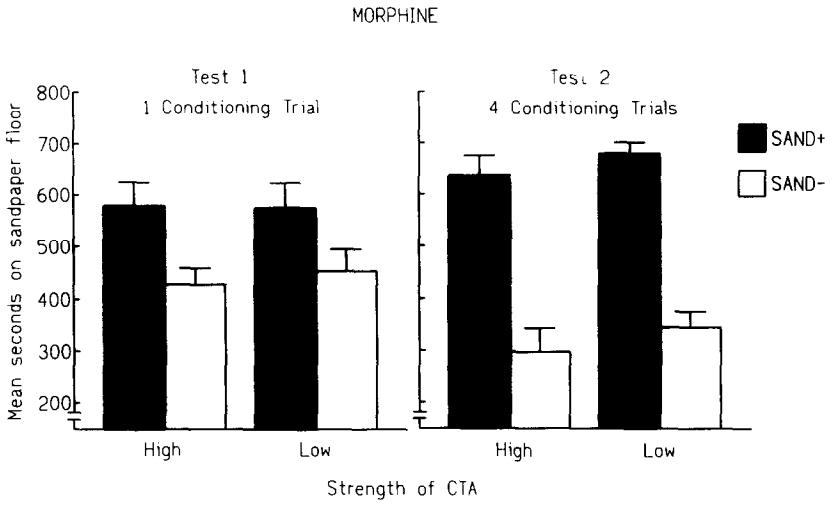

FIG. 1. Mean (+SEM) seconds on sandpaper floor following one and four place conditioning trials with morphine during Experiment 1 for Groups Sand+ and Sand− divided on the basis of the strength of their Phase 1 CTA.

and Test 2 (after four training cycles). The High CTA and Low CTA groups are depicted along the abscissa of the figure. As is apparent, the rats in Group SAND+ displayed a greater preference for the sandpaper floor than did the rats in Group SAND− and the strength of this preference was not modulated by the strength of CTA.

The data was analyzed as a 2 × 2 × 2 × 2 mixed factors analysis of variance (ANOVA) with the between groups factors of Strength of Phase 1 CTA (High, Low), Conditioning Group (SAND+, SAND−), Number of CTA training trials (two, four) and the within-groups factor of Test Trial (Test 1, Test 2). The analysis revealed only a significant main effect of Conditioning Group, $F(1, 31) = 50.5$; $p < 0.001$, with Group SAND+ spending more time on the sandpaper floor than Group SAND−. Additionally, there was a significant Conditioning Group × Test Trial interaction, $F(1, 31) = 22.1$; $p < 0.001$; the strength of the conditioned place preference was greater after four trials than after one trial.

EXPERIMENT 2: AMPHETAMINE, LITHIUM, AND FENFLURAMINE

Specific Procedures

During Phase 1 CTA training, the 63 experimentally naive rats received a single conditioning trial with one of d-amphetamine sulfate (3 mg/kg [$n = 15$], 5 mg/kg [$n = 16$]), 50 mg/kg (1.2 mEq/kg) lithium chloride ($n = 16$) or 3 mg/kg fenfluramine ($n = 16$). Three days after the training trial the rats were tested for a saccharin CTA with a 20 min single bottle test.

During the Phase 2 place conditioning training, the High CTA and Low CTA groups were assigned to SAND+ or SAND− subgroups. The rats received a total of eight training cycles, and were given place preference tests 48 h after each of Cycles 2, 4, and 8.

Results

Amphetamine. During the Phase 1 CTA test, the mean amount of saccharin solution consumed by the High CTA group conditioned with 3 mg/kg of amphetamine was 6.8 ml and with 5 mg/kg of amphetamine was 6.0 ml, and by the Low CTA group conditioned with 3 mg/kg of amphetamine was 13.8 ml and with 5 mg/kg of amphetamine was 13.0 ml. The dose of amphetamine did not modify intake in either the High or the Low CTA group.

Figure 2 presents the mean number of seconds that the rats in Groups SAND+ and SAND− spent on the sandpaper floor on each of the three test trials. As can be seen in Fig. 2, the High CTA group displayed a greater amphetamine-induced place preference than the Low CTA group.

The data were analyzed by a 2 × 2 × 2 × 3 mixed factors ANOVA with the between groups factors of Strength of CTA (High, Low), Conditioning Group (CS+, CS−), and Dose of Amphetamine (3, 5 mg/kg) and the within groups factor of Test Trial (Test 1, Test 2, Test 3). The analysis revealed a significant effect of Conditioning Group, $F(1, 23) = 17.0$, $p < 0.01$; rats in group SAND+ displayed a greater preference for the sandpaper floor than rats in group SAND−. Furthermore, the Strength of CTA × Conditioning Group interaction was significant, $F(1, 23) = 5.8$, $p < 0.025$. Subsequent Newman-Keuls tests revealed that pooled across test trials, Group SAND+ displayed a greater preference for the sandpaper chamber than Group SAND− only in the High CTA subgroup ($p < 0.01$), not in the Low CTA subgroup. No other effects were significant.

Lithium. During Phase 1 testing, the High CTA group drank a mean of 5.3 ml and the Low CTA group drank a mean of 9.8 ml of saccharin solution.

Figure 3 presents the mean number of seconds that the rats in Groups SAND+ and SAND− spent on the sandpaper floor during each test for the rats that were conditioned with lithium. Although Fig. 3 suggests that the high CTA group displayed a greater conditioned place aversion than the low CTA group, the strength of CTA × Conditioning Group interaction was not significant in this experiment. A 2 × 2 × 3 mixed factor ANOVA revealed only a significant main effect of Conditioning Group, $F(1, 12) = 36.7$; $p < 0.01$, with Group SAND+ displaying a lower sandpaper preference than

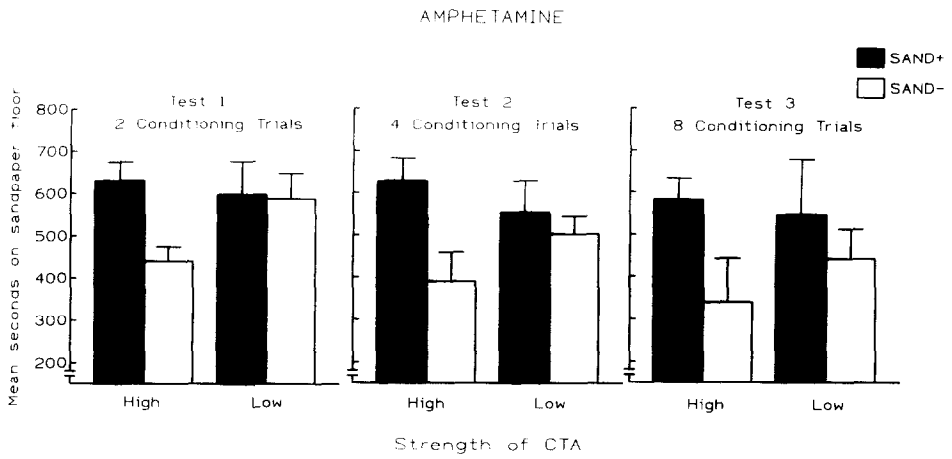

FIG. 2. Mean (+SEM) seconds on sandpaper floor following two, four, or eight place conditioning trials with amphetamine (pooled across 3 and 5 mg/kg) for Groups SAND+ and SAND− divided on the basis of the strength of their Phase 1 CTA.

Group SAND−; however, the strength of CTA did not interact with this factor. No other effects were significant.

Fenfluramine. Group High CTA drank a mean of 4.8 ml and Group Low CTA drank a mean of 11.0 ml of saccharin solution during the Phase 1 consumption test.

Figure 4 presents the mean number of seconds that Groups SAND+ and SAND− spent on the sandpaper floor during each test for the groups trained with fenfluramine. As indicated in the figure, Group SAND+ displayed a sandpaper place aversion only after multiple conditioning trials, but the strength of CTA did not modulate the strength of that place aversion. The 2 × 2 × 3 mixed factor ANOVA revealed a significant main effect of Conditioning Group, $F(1, 12) = 6.31$, $p < 0.05$, and a Conditioning Group × Test Trial interaction, $F(2, 24) = 9.6$, $p < 0.001$. On Test Trial 3, but not Trials 1 or 2, a 2 × 2 ANOVA revealed a significant effect of Conditioning Group, $F(1, 12) = 25.1$, $p < 0.01$, with Group SAND+ displaying a lower sandpaper preference than Group SAND−.

GENERAL DISCUSSION

Individual differences in the strength of an amphetamine-induced CTA predicted the subsequent strength of an amphetamine-induced place preference; the greater the CTA, the greater the place preference. This finding suggests that a common property mediates the strength of both the aversive and rewarding properties of the psychostimulant. Considerable evidence suggests that amphetamine-induced taste avoidance and place preference may be mediated by the same neurochemical system. Interference with the mesolimbic dopamine system attenuates both taste avoidance and place preference produced by amphetamine (4,6,7,13,17). Pretreatment with the dopamine antagonist, pimozide, as well as intraventricular injections of 6-hydroxydopamine (6-OHDA), attenuate amphetamine-induced CTAs (4,13), and the dopamine blocker, haloperidol, disrupts amphetamine-induced place preferences (6,7,17). Because a common system appears to mediate the taste avoidance and place preference produced by amphet-

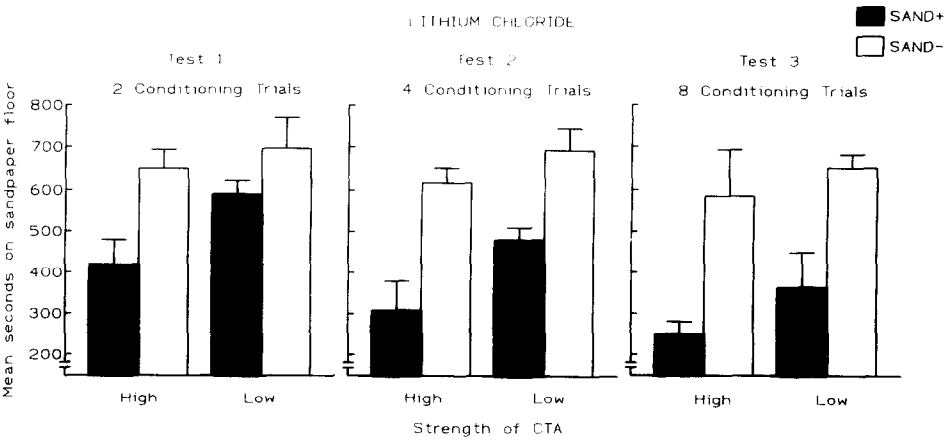

FIG. 3. Mean (+SEM) seconds on the sandpaper floor following two, four, or eight place conditioning trials with lithium for groups SAND+ and SAND− divided on the basis of the strength of their Phase 1 CTA.

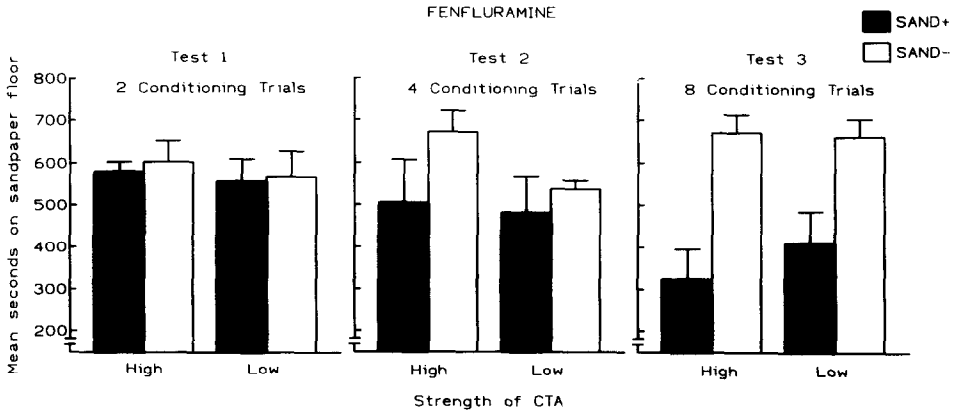

FIG. 4. Mean (+SEM) seconds on the sandpaper floor following tow, four, or eight place conditioning trials with fenfluramine for Groups SAND+ and SAND− divided on the basis of the strength of their Phase 1 CTA.

amine, individual differences in sensitivity of this system to the effects of amphetamine may determine the strength of the both the rewarding and aversive properties of amphetamine.

The physiological mechanism responsible for individual differences in behavioral reactivity to amphetamine is not specifically addressed by our data. However, one speculative possibility is that individual differences in pharmacokinetics may mediate the effect. For instance, brain amphetamine levels may accumulate more rapidly in the high CTA rats that display a greater amphetamine-induced place preference than in the low CTA rats that display only a weak amphetamine-induced place preference. Whatever the physiological mechanism that underlies the behavioral reaction, it appears that sensitivity to amphetamine varies among the rats selected on the basis of the strength of their CTA.

Switzman et al. (18) similarly reported that rats most sensitive to the rewarding properties of morphine, as assessed by the speed of running to obtain an injection, were also most sensitive to its aversive properties, as assessed by the amount of food eaten in the goal box. They suggested that a common mechanism was responsible for both effects. However, the results of Experiment 1 failed to confirm this suggestion in the taste avoidance and place preference paradigms with morphine. The strength of morphine-induced CTA after two or four training trials did not predict the strength of a morphine-induced place preference after one or four training trials. Unlike amphetamine, it has been reported that the rewarding and aversive properties of morphine are mediated by different anatomical systems; Bechara and van der Kooy (1) reported that peripheral opiate receptors mediate the aversive properties of morphine and central opiate receptors mediate the rewarding properties of morphine. The results of Experiment 1 suggest that the sensitivity of these two systems are independent within a given animal.

It is also possible that the specific procedures employed in Experiment 1 did not effectively select rats that displayed high or low reactivity to the rewarding/aversive properties of morphine. In Experiment 1, rats received either two or four saccharin-morphine training trials, although they received only one training trial with amphetamine, lithium, or fenfluramine in Experiment 2. We varied this parameter to equate the overall mean strength of CTA produced by the various agents, because morphine produces a weaker CTA than the other agents tested (5,9,12,16). However, even with a larger number of training trials, the rats displayed a weaker morphine CTA in Experiment 1 (High CTA groups [Mean = 10.5], Low CTA group [Mean = 16.6]) than an amphetamine CTA in Experiment 2 (High CTA groups [Mean = 6.4], Low CTA groups [Mean = 13.4]). The weaker morphine CTA may account for the failure of the strength of the morphine CTA to predict the strength of morphine place preference. However, the factor of strength of CTA cannot singly be responsible for the difference evidenced in the pattern of results produced by morphine and amphetamine, because the consistently aversive agents of lithium and fenfluramine produced CTAs equivalent to those produced by amphetamine, but the strength of those CTAs did not predict the strength of subsequent place aversions produced by the drugs.

Although individual differences in sensitivity to amphetamine may mediate the relationship between amphetamine-induced CTAs and place preferences, it is also conceivable that individual differences in the rate of learning may be responsible for this relationship. Those rats that displayed stronger taste avoidance and place preference may more readily learn associations than those that displayed weaker taste avoidance and place preference. However, if individual differences in learning efficacy are responsible for the relationship between amphetamine-induced CTAs and place preferences, then such differences should be apparent regardless of the drug employed. Yet, the strength of lithium- and fenfluramine-induced CTAs did not predict the strength of place aversions produced by these two agents and the strength of morphine-induced CTAs did not predict the strength of a place preference produced by this agent. For individual differences in learning to account for our pattern of results, one must speculate that individual differences in learning efficacy interact with drug type.

It is more likely that activation of the mesolimbic dopamine system produces both the rewarding and aversive properties of amphetamine. It remains unclear why flavors selectively become associated with the aversive properties of that state and environmental chambers become selectively associated with the rewarding properties of that state; however, it is clear that the group that displayed the strongest amphetamine CTA also displayed the strongest amphetamine place preference.

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