LSD Produces Place Preference and Flavor Avoidance but Does Not Produce Flavor Aversion in Rats

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The hedonic properties of lysergic acid diethylamide (LSD) were assessed using the place conditioning, taste reactivity, and taste avoidance tests. LSD produced a conditioned place preference, but only at the highest dose tested (0.2 mg/kg). A single preexposure to the conditioning chamber (latent inhibition) prevented the establishment of a place preference. When paired with sucrose, doses of 0.05 to 0.2 mg/kg of LSD produced taste avoidance, but no dose of LSD produced an aversion to the taste as assessed by the taste reactivity test. These results suggest that LSD, like other rewarding drugs, produces taste avoidance by a mechanism other than that produced by emetic drugs.

Many drugs that are self-administered or that produce a preference for a distinctive location also produce conditioned taste avoidance at equivalent dosages (for a review, Hunt & Amit, 1987). In fact, after a history of amphetamine injections before placement in a distinctive chamber in which a flavored solution is also available, rats display an avoidance of the flavored solution but a preference for the distinctive chamber (Reicher & Holman, 1977). Most drugs that humans tend to abuse produce this paradox: flavor avoidance but place preference.

Although the hedonic properties of most known psychoactive agents have been assessed in the taste and place conditioning paradigms, there are few published reports of the rewarding and aversive properties of lysergic acid diethylamide (LSD). It is generally reported that LSD is not self-administered by animals (e.g., McKim, 1986); however, this conclusion appears to be based on summarized reports presented in secondary sources (Griffiths, Bigelow, & Henningfield, 1980; Johanson & Balster, 1978). In a review of ongoing research in various laboratories, Johanson and Balster (1978) reported that LSD is not self-administered on the basis of unpublished findings from the laboratory of F. Hoffmeister; however, to this author's knowledge the data that formed the basis for this conclusion did not subsequently appear in the published literature. Additionally, in another review article, Griffiths et al. (1980) reported that LSD and other classic hallucinogens are not self-administered by animals, but they did not cite published evidence for this conclusion. In fact, the only published evidence that LSD may possess aversive properties of which the author is aware is a report that rhesus monkeys learn to press a lever that turns off a cue previously paired with LSD (Hoffmeister, 1975).

The goal of the present study was to assess the rewarding and aversive properties of LSD in both place conditioning and taste conditioning paradigms. Experiments 1 and 2 evaluated the ability of LSD to produce either conditioned place preference or conditioned place aversion. Experiment 3 determined whether LSD would become associated with a flavored solution using both the taste reactivity (TR) (e.g., Grill & Norgren, 1978) and the taste avoidance (e.g., Garcia & Koelling, 1966) paradigms.

Experiment 1

Experiment 1 determined whether LSD is capable of producing either a place preference or a place aversion. The doses selected were those that produce detectable stimulus properties in drug-discrimination experiments (Glennon, 1992).

Method

Subjects. The subjects were 85 male Sprague-Dawley rats weighing between 241 and 340 g on the first conditioning trial. They were purchased from Charles River Laboratories, St. Constant, Quebec. The rats were maintained on ad-lib food and water throughout the experiment and were housed singly in stainless steel hanging cages (Hoeltge, Inc., Cincinnati, OH) in a room on a 12-hr light-dark cycle. Apparatus. The place conditioning apparatus, previously described (Parker & Rennie, 1992), included two chambers separated during conditioning trials by a wooden divider. The wooden walls of each chamber (35 x 25 x 30 cm) 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 (5 cm) located 5 cm apart. When assessed for their preference for each of these cues after three pairings with intraperitoneally injected saline solution, rats displayed equal preference for the two floors (n = 8; mean duration on sandpaper side = 438 s ± 35 SEM; mean duration on mesh floor = 462 s ± 35 SEM).

During testing, the divider between the chambers was removed, allowing the rats to explore both chambers. The activity of the rats during testing was monitored by a video-tracking apparatus (Video-plex-V, Columbus Instruments, Columbus, OH) from a video camera...
mounted to the ceiling. This provided a measure of the amount of time that the rats spent in each chamber.

Drugs. The LSD, obtained from the National Institute on Drug Abuse (NIDA; Research Triangle, NC), was prepared in saline solution at a concentration of 0.05 mg/ml. The doses used were 0.025, 0.05, 0.1, and 0.2 mg/kg.

Procedure. The rats arrived in the laboratory 1 week before the initiation of experimental manipulations and were handled on each of 5 days before the first conditioning trial. The rats received a total of three differential conditioning trial cycles; the first conditioning day of each cycle consisted of a CS- trial and the second conditioning day of a cycle (24 hr later) consisted of a CS+ trial (CS = conditioned stimulus); 2 days intervened between cycles of trials. In the CS+ trial, the rats were injected intraperitoneally with saline 5 min before placement in the chamber with the sandpaper or mesh floor for 30 min. In the CS+ trial, rats were injected intraperitoneally with the appropriate dose of LSD (0.025 mg/kg [n = 22], 0.05 mg/kg [n = 22], 0.1 mg/kg [n = 21], or 0.2 mg/kg [n = 20]) 5 min before placement in the chamber opposite of that paired with saline on the previous day. For each group, the volume of saline injected on Day 1 was equivalent to the volume of LSD injected on Day 2 of each cycle. Immediately after each rat’s trial, the apparatus was cleaned.

On the test trial (2 days after the final CS+ trial), the rats were placed at the intersection between the two chambers with the divider removed and were allowed to explore both chambers for 15 min. The amount of time spent in each chamber was automatically recorded by the video-tracking apparatus.

Results

Figure 1 presents the mean number of seconds spent on the LSD-paired minus the saline-paired floor for each group in Experiment 1. A 2 x 4 between-groups analysis of variance (ANOVA) with floor paired with LSD (mesh or sandpaper) and dose of LSD (0.025, 0.05, 0.1, or 0.2 mg/kg) revealed only a significant dose effect, \( F(3, 81) = 3.0, p < .05 \). By subsequent Newman-Keuls comparison tests, 0.2 mg/kg of LSD produced a greater preference for the LSD-paired chamber than did any other dose condition \((ps < .05)\).

Discussion

LSD produced a conditioned place preference at a dose of 0.2 mg/kg. Within a class of drugs that are typically classified as hallucinogenic drugs, methylenedioxymethamphetamine has also been reported to produce a conditioned place preference (Schoechter, 1991), but tetrahydrocannabinol (THC; Parker & Gillics, 1995) produces a conditioned place aversion.

Experiment 2

The procedure used to establish a conditioned place preference varies among laboratories. Some investigators (e.g., Spyraki, Kazanijian, & Varonos, 1985) use a pretest baseline measure and compare the time in the drug-paired chamber during a posttest with the time in that chamber before conditioning. Other investigators (Carr, Fibiger, & Phillips, 1989; Cunningham, 1993), however, argue that such pretest measures may reduce the associability of the chamber CS cues. CS preexposure effects (or latent inhibition) are widely reported in other conditioning preparations (e.g., Lubow & Moore, 1959). Experiment 2 specifically assessed the ability of a single pretest to modify the strength of a conditioned place preference produced by 0.2 mg/kg of LSD.

Method

Thirty-two male Sprague-Dawley rats weighing between 224 and 281 g on the first conditioning trial served as subjects. They were treated identically as in Experiment 1 except as indicated.

The rats were randomly assigned to two groups: Group Pretest \((n = 16)\) and Group No Pretest \((n = 16)\). Twenty-four hours before the first conditioning trial, the 16 rats in Group Pretest were placed in the place conditioning apparatus with the barrier between the chambers removed and allowed to explore both chambers for 15 min. When assessed by a paired \(t\) test, the mean time spent in the mesh chamber \((452\) s) did not significantly differ from that spent in the sandpaper chamber \((448\) s).

Beginning 24 hours after pretesting, the rats in both groups received three conditioning trial cycles followed by a place preference test in an identical manner as in Experiment 1. The dose of LSD administered to all rats was 0.2 mg/kg ip.

Results

Figure 2 presents the mean time on the LSD-paired floor minus the saline-paired floor for Groups Pretest and No Pretest. An independent groups \(t\) test revealed that Group No Pretest spent significantly more time on the LSD-paired floor than did Group Pretest, \(t(30) = 2.4, p < .025\), two-tailed.

Discussion

When the chamber CS cues were novel during conditioning, a dose of 0.2 mg/kg of LSD produced a conditioned place preference as in Experiment 1. However, a single 15-min pretest prevented the chamber cues from becoming associated with LSD. Although place preferences can be detected after pretests (e.g., Spyraki et al., 1985), the present results suggest that strength of the association may be attenuated as a result of the prior exposure to the conditioning cues. Because a single
pretest is sufficient to eliminate an LSD-induced conditioned place preference, the strength of a place preference produced by LSD appears to be weak relative to other rewarding drugs.

Experiment 3

LSD is one of the rare psychoactive agents that has not been assessed for its ability to produce conditioned taste avoidance. Therefore, Experiment 3 examined whether LSD would produce taste aversion, as measured by the taste reactivity (TR) test, and taste avoidance, as measured by a two-bottle consumption test. Parker (1995) has argued that, although rewarding drugs produce taste avoidance, they do not necessarily produce an aversion to that taste.

Although taste avoidance is measured by a standard consumption test, taste aversion is measured by the TR test, devised by Grill and Norgren (1978), in which rats are intraorally infused with a flavored solution and their orofacial reactions to the fluid are videotaped. The TR test directly measures the palatability of a taste. When assessed by the TR test, rats react to a lithium-paired taste as if it is aversive; that is, they display reactions of chin rubbing, gaping and paw treading, which are typically elicited by unconditionally aversive quinine solution. On the other hand, rats do not display this aversive TR pattern during an intraoral infusion of a flavored solution previously paired with a rewarding drug, such as amphetamine (e.g., Parker, 1982). This difference is not the result of the rats forming a stronger flavor-drug association when lithium serves as the unconditioned stimulus, because even when the doses of lithium and amphetamine are adjusted to produce a weaker taste avoidance with lithium than with amphetamine, only the lithium-paired flavor produces the aversive reactions in the TR test (Zalaquett & Parker, 1989).

We have previously reported that, when paired with a taste, rewarding drugs do not produce aversive taste reactions in the TR test (e.g., Parker, 1995). This suggests that the taste avoidance produced by rewarding drugs is motivated by a different mechanism than that produced by emetic drugs, such as lithium, that do produce aversive reactions in the TR test.

Because LSD produces a conditioned place preference, it was expected to be ineffective in conditioning aversive reactions in the TR test, even at doses that produce taste avoidance.

Method

Subjects. The subjects were 56 male Sprague–Dawley rats weighing 299 to 353 g on the first conditioning trial. They were maintained in an identical manner to those of Experiment 1.

Surgery. The rats were implanted with intraoral cannulas as described by Parker (1980). They were administered a preanesthetic intraperitoneal injection of atropine sulfate (0.5 mg/kg). Ten minutes later, they were injected intraperitoneally with a mixture of ketamine (100 mg/kg) and xylazine (3 mg/kg). Once anesthetized, a 15-gauge stainless steel needle was inserted through the rat's skin in the midneck region, was brought subcutaneously behind its ear along the inside of the cheek, and exited through the soft part of its cheek behind the first molar. The skin around each of the punctured sites was swabbed with iodine. With the needle in place, a 10-cm length of polyethylene (PE-90) tubing was inserted through the barrel. The needle was then removed, and the tubing was secured at the neck by a 20-gauge intramedic adapter and in the mouth by a 5-mm plastic washer.

Procedure. One week after the rats recovered from surgery, the TR adaptation trials began. The rats received three adaptation trials, each separated by 24 hr, which served to habituate them to the apparatus and procedures. On each adaptation trial, a rat was transported into the room that contained the glass TR test chamber (22.5 × 26 × 20 cm). The room was illuminated by two 25-W lightbulbs that were located 30 cm from either side of the cage. Each rat was placed individually into the test chamber, and a 30-cm infusion hose was then connected to the cannula through the ceiling of the chamber. A syringe was connected to the hose and placed into the holder of the infusion pump (model 22, Harvard Apparatus, South Natick, MA). After 60 s, the pump delivered water through the tube into the rat's mouth at the rate of 1 ml/min for 2 min. The rat was then returned to its home cage.

Twenty-four hours after the final adaptation trial, the rats received the first conditioning trial. The conditioning trials were conducted in a manner identical to the adaptation trials except that the rats were infused with 0.5 M sucrose solution (17% [wt/vol]) instead of water. During the 2-min intraoral infusion, the rats' orofacial and somatic reactions were videotaped. Immediately after the TR conditioning trial, the rats were injected intraperitoneally with 0.0 (n = 14), 0.025 (n = 8), 0.05 (n = 8), 0.1 (n = 9), or 0.2 (n = 10) mg/kg of LSD or 25 mg/kg of lithium chloride (LiCl; n = 7). The LSD was prepared at a concentration of 0.05 mg/ml dissolved in saline as in Experiment 1. The LiCl was prepared in a 0.15-M solution with distilled water.

The rats received a total of three conditioning trials followed by a final TR test trial, during which they did not receive an injection after the infusion. The conditioning trials were separated by 2 to 3 days; the final TR test trial occurred 2 days after the third conditioning trial.

Two days after the final TR test trial, the rats were tested for sucrose taste avoidance. The water bottles were removed from their cages and replaced with two graduated tubes for 2 hr; one tube contained 0.5 M sucrose solution and the other tube contained water. The amounts consumed were measured and converted to sucrose preference ratios using the following equation: the amount of sucrose consumed/the amount of sucrose + the amount of water consumed. The taste avoidance test was conducted while the rats were not water deprived to ensure that they were in the same deprivation state that they experienced during the TR conditioning trials.

Behavioral measures. The 2-min TR videotapes were scored in real time by an observer blind to experimental conditions on a computer using the event recorder program, "The Observer" (Noldus, Inc.
Wagenigen, The Netherlands). The frequency of each aversive behavior 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 pushing (sequential extension of one forelimb forward against the floor while the other forelimb is being retracted) were combined to produce a composite aversive reaction score. The mean duration (in seconds) that the rats spent displaying the ingestive reactions of tongue protrusions (extensions of the tongue either to the side or to the front of the mouth), mouth movements (movement of the lower mandible without opening the mouth), and paw licking (licking the solution from front paws) was also measured and combined for each rat to produce a composite ingestive reaction score.

**Results**

Figure 3 presents the mean frequency of aversive reactions displayed during the 2-min TR test by each group in Experiment 3. A $6 \times 4$ mixed-factor ANOVA with drug condition (saline, 0.025 LSD, 0.05 LSD, 0.1 LSD, 0.2 LSD, and LiCl) and conditioning-testing trial (1–4) for the aversive TR scores revealed a significant drug effect, $F(5, 50) = 8.4, p < .01$, trials effect, $F(3, 150) = 13.7, p < .01$, and Drug $\times$ Trials interaction, $F(15, 150) = 2.9, p < .01$. Separate between-groups single-factor ANOVAs for each conditioning-testing trial revealed a significant drug effect on Trials 2 to 4, $F(5, 50) = 3.8, ps < .01$. Newman–Keuls tests for each of these trials revealed that Group LiCl displayed more aversive reactions than any other group ($ps < .05$), and no other groups significantly differed from one another.

Although the mean frequency of aversive reactions displayed by the rats trained with various doses of LSD did not differ significantly from that of the rats trained with saline, the scores show a nonsignificant gradual increase across trials. This increase was the result of a display of aversive reactions by 1 to 2 rats in each of groups 0.05 LSD, 0.1 LSD, and 0.2 LSD on each of Trials 3 and 4. On the other hand, on each of these trials 5 to 7 rats in Group LiCl displayed aversive reactions. This pattern suggests that individual differences may exist in the ability of LSD to produce taste aversion, but even when each LSD group mean score was compared with the saline group mean score on the same trial by less conservative individual $t$ tests, no significant differences were found.

Figure 4 presents the mean number of seconds that each group spent displaying ingestive reactions during the 2-min TR test. The $6 \times 4$ mixed-factors ANOVA of the ingestive TR scores revealed a significant Drug $\times$ Trials interaction, $F(3, 150) = 3.7, p < .01$. Individual single-factor between-groups ANOVAs on each trial revealed a significant drug effect on Trial 4 only ($F = 4.2, p < .01$); when assessed by Newman–Keuls tests, on Trial 4 only, all of the drug-conditioned groups displayed fewer ingestive reactions than did the saline-conditioned group ($ps < .05$), but no other groups significantly differed from one another.

**Discussion**

At doses ranging from 0.05 to 0.2 mg/kg, LSD produced taste avoidance that did not differ in strength from that produced by 25 mg/kg of LiCl. Even though the results of the taste avoidance test suggest that sucrose-lithium and sucrose-LSD (0.05–0.2 mg/kg) associations are similar in strength, the results of the TR test suggest that they are dissimilar in nature. When paired with lithium, sucrose elicited more aversive reactions than when paired with saline or any dose of LSD. On the other hand, when paired with LSD, sucrose did not elicit aversive reactions that differ significantly from sucrose paired with saline (although the mean frequency of aversive reactions elicited by LSD displays a nonsignificant gradual increase across trials).

These results are consistent with the pattern of reactions elicited by flavors paired with other rewarding drugs (e.g., Parker, 1995); that is, rewarding drugs produce taste avoidance and produce suppression of ingestive TR reactions but
Like LSD and other rewarding drugs, THC produces aversive reactions (McLendon, 1974). Additionally, unconditioned appetitive stimuli (e.g., Harris, Waters, & McEwen, 1969) produce place conditioning, THC does produce conditioned place aversions rather than conditioned place preferences. Because the TR test directly assesses taste reactions, the taste avoidance produced by this drug, therefore, does not appear to be the result of the taste of the LSD-paired sucrose acquiring aversive properties.

**General Discussion**

At high doses, LSD appears to be rewarding to rats. A dose of 0.2 mg/kg of LSD produced a conditioned place preference, taste avoidance, and suppression of ingestive reactions in the TR test. Other drugs of abuse, including amphetamine, cocaine, and morphine (e.g., Parker, 1993, 1995), also produce place preference, taste avoidance, and suppression of ingestive taste reactions. On the other hand, LSD, like other rewarding drugs, did not produce conditioned aversive taste reactions in the TR test that are elicited by flavors paired with emetic agents. This pattern of results suggests that, although both rewarding drugs and emetic drugs, such as LiCl, are similarly capable of producing taste avoidance, the taste avoidance produced by these two classes of agents is motivated by different mechanisms. Because the TR test directly assesses palatability (e.g., Berrios & Berridge, 1983; Berridge & Norgren, 1978), taste avoidance produced by lithium appears to be motivated by a conditioned distaste for the sucrose solution, but taste avoidance produced by LSD (at equivalent strengths) is not motivated by a distaste for the solution.

In animal models of drug discrimination, stimulus generalization occurs between the “classic hallucinogens” of LSD, mescaline, dimethyltryptamine, and 2,5-dimethoxy-4-methylamphetamine (e.g., Glennon, 1992); however, generalization does not occur between LSD and THC. Although the “classic hallucinogens” have not been assessed for their ability to produce place conditioning, THC does produce conditioned place aversions rather than conditioned place preferences (Parker & Gillies, 1995) and is not readily self-administered (e.g., Harris, Waters, & McLendon, 1974). Additionally, unlike LSD and other rewarding drugs, THC produces aversive reactions in the TR test similar to emetic agents, such as LiCl (Parker & Gillies, 1995). Future research might determine whether other drugs that cross-generalize with LSD are also rewarding to rats.

It is surprising that the rewarding properties of LSD have not been more extensively assessed in other paradigms, such as drug self-administration and brain stimulation–reward threshold paradigms. Clearly, further investigation of the rewarding properties of LSD and other hallucinogenic agents is needed.

### References


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