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Cocaine Preexposure Fails to Sensitize the Acquisition of Cocaine-Induced Taste Aversions

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RILEY, A. L. AND G. R. SIMPSON. *Cocaine preexposure fails to sensitize the acquisition of cocaine-induced taste aversions*. PHARMACOL BIOCHEM BEHAV **63**(2) 193–199, 1999.—In two separate experiments, rats were given either an intraperitoneal (IP) injection of 10 mg/kg cocaine once a day for 10 consecutive days (Experiment 1) or a single IP injection of 40 mg/kg of cocaine (Experiment 2) prior to receiving repeated pairings of a novel saccharin solution with cocaine (32 mg/kg; subcutaneous; SC). Although vehicle-preexposed subjects given saccharin–cocaine pairings readily acquired an aversion to the cocaine-associated saccharin solution, subjects preexposed to cocaine (whether 10 times or only once) displayed a retarded acquisition of the aversion. That is, cocaine preexposure attenuated the acquisition of cocaine-induced taste aversions. There was no difference in the degree of attenuation between the two preexposure conditions. Thus, under conditions that are effective in inducing sensitization within other behavioral preparations there was no evidence of sensitized cocaine-induced taste aversions. The results from the present investigation are similar to reports from this laboratory and others demonstrating that preexposure to cocaine, as with a range of other psychoactive drugs, results in weaker taste aversions. The basis for the attenuating effects of cocaine preexposure was discussed in terms of an adaptation to the aversive effects of cocaine.

Cocaine UCS preexposure Conditioned taste aversion Route of administration Sensitization Rat

ALTHOUGH rats readily avoid consumption of solutions previously paired with one of a number of drugs [(34,74,81) for a bibliography, see (80)], such conditioned taste aversions are significantly attenuated if subjects have received exposure to the drug prior to conditioning [for reviews, see (11,33)]. Initially demonstrated with apomorphine (12), the attenuating effects of drug preexposure on taste aversion learning have now been reported with a wide range of compounds (5,18,22, 29,38,39,46,62,78,90). Most recently, such an effect has been reported with the stimulant cocaine [(77); see also (36)]. In the Riley and Diamond report (77), cocaine (32 mg/kg) was administered either SC or IP once a day (massed) or every fourth day (spaced) for a total of five injections prior to taste aversion conditioning in which consumption of a novel saccharin solution was paired with a SC injection of cocaine (32 mg/kg). Under all but one of these four preexposure conditions (IP/massed), the acquisition of taste aversions was significantly attenuated. This attenuation was evident both in terms of the number of conditioning trials on which cocaine-preexposed subjects drank greater amounts of saccharin than vehicle-preexposed subjects and the number of trials on which the cocaine-preexposed subjects did not differ from nonconditioned controls. Interestingly, under none of the preexposure conditions did cocaine-preexposed subjects drink less saccharin than subjects preexposed to vehicle. That is, there was no evidence that cocaine preexposure sensitized aversions to cocaine.

Although the fact that cocaine preexposure attenuated the acquisition of cocaine-induced taste aversions is consistent with the extensive literature reporting similar attenuating effects on aversion learning by preexposure to other psychoactive drugs (see above), this attenuation contrasts with the results from a variety of behavioral and physiological preparations in which exposure to cocaine has been reported to sensitize subsequent responsivity to cocaine (54,55,60,70–72,84,88,91,95). In the context of the attenuating effects of cocaine preexposure, it is possible that the effects of such preexposure on

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aversion learning are parameter dependent, such that with specific dosing, sequencing, and route parameters adaptation or tolerance to the aversive effects of cocaine may occur, which in turn, weaken or attenuate the acquisition of cocaine-induced taste aversions [see (77)]. Accordingly, it is possible that under yet other parametric conditions, those that more closely match those producing sensitization within other preparations, the acquisition of cocaine-induced taste aversions would be facilitated by cocaine preexposure, i.e., aversions would not be attenuated, but instead sensitized.

To that end, in the present experiments subjects were exposed IP to either a low dose of cocaine (10 mg/kg) once a day for 10 consecutive days or to a single injection of a high dose of cocaine (40 mg/kg) prior to repeated pairings of a novel saccharin solution and cocaine (32 mg/kg, SC). Each of these exposure conditions has been reported to produce sensitization within other behavioral designs (45,67,72,73,85,94), and should provide a test of the ability of cocaine preexposure to sensitize aversion learning. It is important in this context to note that aversions can be sensitized by a variety of behavioral, physiological, and pharmacological manipulations (6,9,23,26,40,56, 61,68). For example, group housing significantly increases aversions induced by naloxone (68). Also, footshock has been reported to significantly potentiate LiCl-induced taste aversions (56). Such potentiation has also been reported when cocaine was used as the aversive agent. For example, ineffective doses of alcohol significantly potentiate aversions induced by cocaine (26). In addition, the pharmacological blockade of receptors mediating corticotropin-releasing factor enhances cocaine-induced aversions (40). The ability to potentiate taste aversion learning has also been reported within the UCS preexposure design [(6,9,61); see also (4,63,65,93) for related discussions on multiple chemical sensitivity and the sensitization to drug toxicity following repeated exposures]. For example, six daily preexposures to the noncompetitive NMDA receptor antagonist, dizolcilpine (MK-801) significantly enhance the acquisition of ethanol-induced taste aversions, even at doses that alone have no suppressive effects on consumption (6). Similar potentiating effects within the UCS preexposure preparation have been demonstrated when exposure to footshock (30 0.5-mA footshocks every other day for two such exposures) was given prior to aversion conditioning with amphetamine (9). Thus, given that the taste aversion preparation can be sensitized, the sensitizing effects of cocaine preexposure on the aversive properties of cocaine might be reflected in the enhanced acquisition of cocaine-induced aversions.

GENERAL METHOD

Subjects

The subjects were 48 experimentally naive, female rats of Long–Evans descent, approximately 120 days of age at the beginning of the experiment. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed at all times.

Apparatus

Subjects were housed in individual stainless steel, wire-mesh cages, on the front of which graduated Nalgene tubes could be placed for the presentation of either water or saccharin. Subjects were maintained on a 12 L:12 D cycle, with lights on at 0800 h and at an ambient temperature of 23°C for the duration of the experiment. Food was available ad lib.

Drugs and Solutions

Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) was prepared as a 10 mg/ml solution in distilled water. Doses of cocaine refer to weight of the free base. Saccharin (0.1% sodium saccharin, Sigma Chemical Co., St. Louis, MO) was prepared as a 1 g/l solution in tap water.

Procedure

Phase I. Habituation: following 23-h water deprivation, subjects were given 20-min access to water. This procedure was repeated daily until all subjects were approaching and drinking from the tube within 2 s of its presentation (between 12–15 days).

Phase II. Preexposure: on day 1 of this phase, subjects were given 20-min access to water during their scheduled fluid-access period. Immediately following this exposure, subjects were matched on water consumption and were assigned to a preexposure condition. Approximately 5 h later, subjects received either an IP injection of cocaine or of equivolume distilled water. Cocaine was given either once a day for 10 consecutive days (Experiment 1) or once (Experiment 2). The dose of cocaine was 10 mg/kg for Experiment 1 and 40 mg/kg for Experiment 2. All subjects received two water-recovery days following cocaine preexposure during which they were given 20-min access to water. No injections were given following water access on these sessions.

Phase III. Conditioning: following the second water-recovery session, all subjects were given 20-min access to a novel saccharin solution. Immediately following saccharin access, subjects in each preexposure group within each experiment were matched on consumption and given an SC injection of either cocaine (32 mg/kg) or distilled water. On the following 3 water-recovery days, all subjects were given 20-min access to water. No injections were given following water access on these days. This alternating procedure of conditioning/water recovery was repeated until all subjects had received four complete cycles. On the day following the final water-recovery session, all subjects were given 20-min access to saccharin in a final one-bottle test of the aversion to saccharin. No injections were given following this test. The specific dose of cocaine used in conditioning (i.e., 32 mg/kg) was based on prior dose–response assessments of cocaine-induced taste aversions in which various doses of cocaine (0, 18, 32, and 50 mg/kg) were given SC following saccharin consumption [(28); see also (26,35,77)]. In that analysis, 18 mg/kg was generally ineffective in inducing aversions, whereas 32 and 50 mg/kg produced aversions of comparable strength. Given that 32 mg/kg was the minimally effective dose in inducing aversions, it was used in the present experiment. Aversions to this dose are gradually acquired and do not result in complete suppression of consumption, even with repeated conditioning trials. As such, aversions at this dose provide a baseline to assess the strengthening or weakening effects of cocaine preexposure.

Statistical Analysis

Between-group comparisons in consumption on each conditioning trial were assessed using a one-tailed Kruskal–Wallis one-way analysis of variance. The specific H generated from each test represents comparisons among all groups for each trial and do not represent specific group contrasts. All determinations of statistical significance are based on $p \leqslant 0.05$.

EXPERIMENT 1: MULTIPLE COCAINE PREEXPOSURES

Specific Procedure

During drug preexposure, subjects were given an IP injection of cocaine or its distilled water vehicle once a day for a total of 10 preexposures. During taste aversion conditioning, subjects preexposed to cocaine were divided into two groups and injected SC with either cocaine or equivolume distilled water. Similarly, subjects preexposed to water were divided into two groups and injected SC with either cocaine or water. This two-by-two preexposure/conditioning design yielded four groups of subjects (n = 6 per group): groups CC, CW, WC, and WW. The first letter in each group designation refers to the compound given during preexposure, i.e., cocaine (C) or water (W). The second letter refers to the compound given during conditioning, i.e., C or W.

EXPERIMENT 2: SINGLE COCAINE PREEXPOSURE

Specific Procedure

During drug preexposure, subjects were given a single IP injection of cocaine or its distilled water vehicle. During taste aversion conditioning, subjects preexposed to cocaine were divided into two groups and injected SC with either cocaine or equivolume distilled water. Similarly, subjects preexposed to water were divided into two groups and injected SC with either cocaine or water. This two-by-two preexposure/conditioning design yielded four groups of subjects (n = 6 per group): groups CC, CW, WC, and WW. The first letter in each group designation refers to the compound given during preexposure, i.e., cocaine (C) or water (W). The second letter refers to the compound given during conditioning, i.e., C or W.

RESULTS

Experiment 1: Multiple Cocaine Preexposures

At no point during the preexposure phase did subjects receiving the multiple cocaine or vehicle injections drink significantly different amounts of water. The mean amount consumed by each group over the 10-day preexposure period was approximately 11 ml. Further, there were no significant differences in water consumption between groups immediately following preexposure. The mean amount consumed by each group on the 2 days prior to conditioning was 11 ml.

Figure 1 illustrates the mean (±SEM) amount of saccharin consumed over the repeated conditioning trials for subjects in groups CC, CW, WC, and WW. As illustrated, subjects given water preexposure and injected with cocaine during conditioning (group WC) acquired robust aversions to saccharin. These subjects decreased consumption by approximately 50% following only a single conditioning trial, and drank less than 2 ml (an 85% reduction in saccharin consumption) on the final aversion test. Subjects injected with cocaine during both preexposure and conditioning (group CC) displayed no clear change in saccharin consumption following the initial conditioning trial (a reduction of approximately 5%). With repeated conditioning, these subjects also acquired an aversion to saccharin, drinking approximately 4 ml on the final aversion test (a 70% reduction in saccharin consumption from the initial conditioning trial). Control subjects injected with water during conditioning maintained a high level of saccharin consumption during conditioning, independent of whether they had been exposed to cocaine or water during preexposure (see groups CW and WW). For both control groups, consumption increased with repeated access to saccharin.

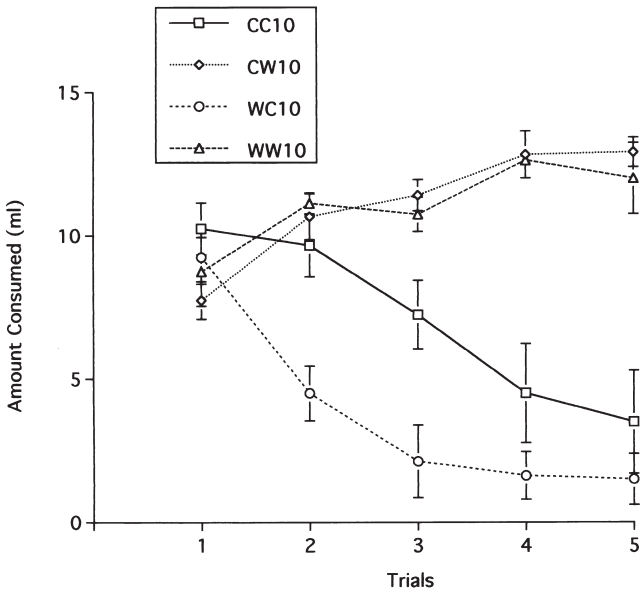

FIG. 1. Mean (±SEM) saccharin consumption by subjects receiving saccharin–cocaine (groups CC and WC) or saccharin–distilled water (groups CW and WW) pairings during taste aversion conditioning. The first letter in the group designation refers to the drug received during preexposure, i.e., cocaine (C) or water (W); the second letter refers to the drug received during conditioning, i.e., C or W. During preexposure, cocaine (10 mg/kg) was given IP once a day for 10 consecutive days.

Post hoc comparisons revealed that subjects in group WC drank significantly less saccharin than both control groups on the second, third, fourth, and fifth conditioning trials [all $Hs(3) > 9.092$]. Group CC drank significantly less than control groups on the third, fourth, and fifth trials [all $Hs(3) > 12.997$]. Subjects in group WC drank significantly less than subjects in group CC on conditioning trials 2 and 3 [$H(3) = 9.092$ for trial 2 and $H(3) = 12.997$ for trial 3]. At no point in conditioning did subjects in the two control groups differ in the amount of saccharin consumed. Further, at no point during this phase did subjects in any group differ in the amount of water consumed on recovery sessions.

Experiment 2: Single Cocaine Preexposure

There were no significant differences in water consumption between groups immediately following cocaine or water preexposure. The mean amount consumed by each group on the 2 days prior to conditioning was 10.5 ml.

Figure 2 illustrates the mean (±SEM) amount of saccharin consumed over the repeated conditioning trials for subjects in groups CC, CW, WC, and WW. As illustrated, subjects given water preexposure and injected with cocaine during conditioning (group WC) acquired robust aversions to saccharin. These subjects decreased consumption by approximately 35% following only a single conditioning trial, and drank less than 4 ml (a 70% reduction in saccharin consumption) on the final aversion test. Subjects injected with cocaine during both preexposure and conditioning (group CC) displayed no clear change in saccharin consumption following the initial conditioning trial (a reduction of approximately 5%). With repeated conditioning, these subjects also acquired an aversion to saccharin, drinking approximately 5 ml on the final aver-

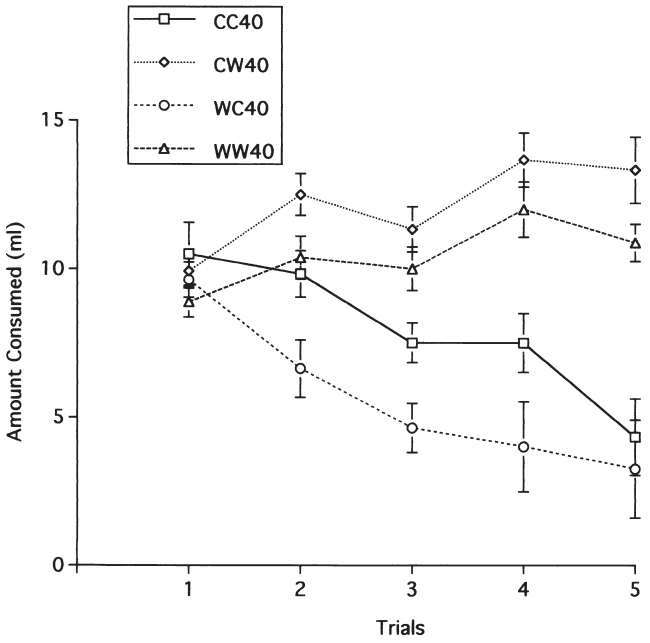

FIG. 2. Mean (±SEM) saccharin consumption by subjects receiving saccharin–cocaine (groups CC and WC) or saccharin–distilled water (groups CW and WW) pairings during taste aversion conditioning. The first letter in the group designation refers to the drug received during preexposure, i.e., cocaine (C) or water (W); the second letter refers to the drug received during conditioning, i.e., C or W. During preexposure, a single IP injection of cocaine (40 mg/kg) was given.

sion test (a 65% reduction in saccharin consumption from the initial conditioning trial). Control subjects injected with water during conditioning maintained a high level of saccharin consumption during conditioning, independent of whether they had been exposed to cocaine or water during preexposure (see groups CW and WW). For both control groups, consumption increased with repeated access to saccharin.

Post hoc comparisons revealed that subjects in group WC drank significantly less saccharin than both control groups on the second, third, fourth, and fifth conditioning trials [all $H(3) > 11.549$]. Group CC drank significantly less than group CW on the second trial [$H(3) = 11.48$] and groups CW and WW on the third, fourth, and fifth trials [all Hs$(3) > 14.301$]. Subjects in group WC drank significantly less than subjects in group CC on trials 2 and 3 [$H(3) = 11.549$ for trial 2 and $H(3) = 14.468$ for trial 3]. At no point in conditioning did subjects in the two control groups differ in the amount of saccharin consumed. Further, at no point during this phase did subjects in any group differ in the amount of water consumed on recovery sessions.

GENERAL DISCUSSION

Previously, we reported that preexposure to cocaine attenuated the subsequent acquisition of cocaine-induced taste aversions (77). This attenuation was evident when cocaine was given SC (every day for 5 consecutive days or every fourth day for five total injections) and IP (every fourth day). IP preexposures given every day for 5 consecutive days resulted in a nonsignificant attenuation of taste aversion learning. Although the effects of cocaine preexposure were clearly parameter dependent, it is important to note that under none of the four conditions was there any evidence of sensitized aversions, i.e., aversions in the preexposed subjects were never greater than those in subjects preexposed to the cocaine vehicle.

Given that the attenuating effects of cocaine preexposure on the subsequent acquisition of cocaine-induced taste aversions were dependent upon the specific parameters of drug preexposure, it is possible that the display of sensitized aversions would be parameter dependent as well. That is, if the preexposures were given under parameters that more closely parallel those under which sensitization has been reported within other preparations, cocaine preexposure may result in sensitized aversions. This was tested in the present experiment in which rats were given either a daily injection of a low dose of cocaine (10 mg/kg) for 10 consecutive days or a single injection of a high dose of cocaine (40 mg/kg) [for descriptions of comparable parametric conditions producing sensitization, see (45,67,72,73,85,94)]. As described, independent of whether subjects were exposed to the low dose of cocaine repeatedly or the high dose acutely, aversions were attenuated. Cocaine preexposed subjects drank significantly greater amounts of saccharin than vehicle-exposed subjects on the second and third conditioning trials. Further, cocaine preexposed subjects differed from control subjects on fewer trials than subjects preexposed to the cocaine vehicle. Both of these indices suggest that aversion learning was retarded in the cocaine-preexposed subjects.

Thus, similar to our previous work assessing the effects of cocaine preexposure on aversion learning (77), there was no evidence of sensitization to the aversive effects of cocaine (as indexed by taste aversion learning). Similar to other psychoactive drugs assessed within this design, aversion learning was attenuated by such preexposure. Given that taste aversions are generally assumed to reflect the aversive properties of the drug paired with the taste [see (79)], the present results with cocaine are consistent with the position that preexposure to cocaine reduced its aversive effects, possibly through habituation, adaptation, or tolerance [for related discussions with other compounds, see (13–17,19–21,30,38,39,42,57,75,76,78); though see (10,89)]. Although consistent with this position, there was no independent assessment of such processes in the present experiment. Several sources of evidence, however, suggest that tolerance may have mediated the weaker aversions following cocaine preexposure. First, cocaine-induced aversions are dose dependent [see (28,35,53)]. Specifically, as the dose of cocaine increases aversions increase. Interestingly, the aversions induced in subjects preexposed to cocaine (either 10 daily exposures of 10 mg/kg or a single exposure of 40 mg/kg) in the present experiments resemble those induced by lower doses of cocaine [for comparison, see (26)], i.e., the dose–response function for cocaine appears to be shifted to the right by the cocaine preexposure, a shift generally suggestive of the development of tolerance. Again, it is important to note that these descriptions are based on cross-study comparisons, and there was no independent assessment of tolerance in the present series of studies. Exposure to cocaine under other parametric conditions, however, has been reported to produce tolerance, indicating that such a process can occur with cocaine. For example, Emmett-Oglesby and Lane (24) reported that cocaine exposure (5 mg every 8 h for a week) resulted in a decrease in the interreinforcer time for cocaine self administration, an effect indicative of the loss in the reinforcing effects of cocaine with chronic exposure. Under similar conditions, cocaine exposure shifted to the right the dose-response function for the threshold dose supporting self-administration. Such tolerance develops under both contingent

and noncontingent cocaine administration within a cocaine self-administration procedure, using either single or multiple dose methods (25). Tolerance is not limited to the reinforcing effects of cocaine. For example, Katz et al. (51) have reported tolerance to the suppressive effects of cocaine on schedule-controlled responding, i.e., on an FR30 schedule for food reinforcement. Specifically, chronic exposure to 10 mg/kg/day shifted the ED_{50} for behavioral suppression to the right. Kleven and Woolverton (52) have also found that tolerance develops to the rate-decreasing effects of chronic cocaine (between 4.0–32.0 mg/kg/day) on FR (50–100) schedules of reinforcement. Similar tolerance has been demonstrated on fixed-interval schedules following chronic exposure to 13 mg/kg cocaine (87). Cocaine-induced stereotypy is also reduced to baseline levels after 5 days of cocaine exposure (47). Although the extent to which such results apply to the present findings remains unknown given the different parametric conditions under which tolerance was assessed among the various studies, these examples and others [see (37,41,43,59,82,83,92,96)] clearly indicate that tolerance can occur with cocaine exposure.

Although exposure to cocaine under some conditions has been reported to produce tolerance (see above), under other conditions and with other measures cocaine reliably produces sensitization, i.e., responsivity to cocaine increases with repeated exposure to cocaine [see (1,8,44,48–50,58,88,95)]. The failure to demonstrate a sensitizing effect of cocaine preexposure on aversion learning is, thus, inconsistent with these reports of cocaine sensitization [for an alternative interpretation of the UCS preexposure effect that assumes sensitization to the reinforcing effects of psychoactive drugs, see (31) and (32); for related discussions, see (27,69,86)]. It is possible that this failure of sensitization is a function of the relative insensitivity of the aversion design to such an effect. As noted above, however, cocaine-induced taste aversion learning can be sensitized by a number of pharmacological manipulations, and amphetamine- and ethanol-induced taste aversions have been sensitized by shock (9) and dizolcilpine (6), respectively, within a crossdrug preexposure design. Thus, the failure is unlikely an insensitivity of the design to such potentiation. The failure to see sensitization may also reflect the specific parameters of drug preexposure used in the present experiments. As noted above, the specific parameters chosen were based on reports that cocaine (given at these doses and injection frequencies) produced sensitization (see above). Although such parameters did not support sensitization to cocaine's aversive effects, the fact that under identical parametric conditions different behavioral and physiological responses become sensitized at different rates (or to different degrees) [see (2,3,8,43, 44,48,60,66,67)] suggests that it is possible that under different parametric conditions sensitization may occur to the aversive effects of cocaine [see also (7,64)].

Although the basis for the effect of cocaine preexposure on the acquisition of cocaine-induced taste aversions is not known, it is nonetheless clear that such aversions are attenuated with cocaine preexposure, and that there is no evidence that cocaine preexposure increases its aversiveness within the taste aversion design, i.e., cocaine-induced taste aversion learning is not sensitized by cocaine preexposure.

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REFERENCES

1. Badiani, A.; Browman, K. E.; Robinson, T. E.: Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res. 674:291–298; 1985.
2. Bartlett, E.; Hallin, A.; Chapman, B.; Angrist, B.: Selective sensitization to the psychosis-inducing effects of cocaine: A possible marker for addiction relapse vulnerability? Neuropsychopharmacology 16:77–82; 1997.
3. Bauco, P.; Wise, R. A.: Synergistic effects of cocaine with lateral hypothalamic brain stimulation reward: Lack of tolerance or sensitization. J. Pharmacol. Exp. Ther. 283:1160–1167; 1997.
4. Bell, I. R.; Rossi, J., III; Gilbert, M. E.; Kobal, G.; Morrow, L. A.; Newlin, D. B.; Sorg, B. A.; Wood, R. W.: Testing the neural sensitization and kindling hypothesis for illness from low levels of environmental chemicals. Environ. Health Perspect. 105:539–547; 1997.
5. Berman, R. F.; Cannon, D. S.: The effect of prior ethanol experience on ethanol-induced saccharin aversions. Physiol. Behav. 12:1041–1044; 1974.
6. Bienkowski, P.; Koros, E.; Piasecki, J.; Kostowski, W.: Prior exposure to MK-801 sensitizes rats to ethanol-induced conditioned taste aversion. Alcohol Alcohol. 33:116–120; 1998.
7. Borowski, T. B.; Kokkinidis, L.: Cocaine preexposure sensitizes conditioned fear in a potentiated acoustic startle paradigm. Pharmacol. Biochem. Behav. 49:935–942; 1994.
8. Borowsky, B.; Kuhn, C. M.: Chronic cocaine administration sensitizes behavioral but not neuroendocrine responses. Brain Res. 543:301–306; 1991.
9. Bowers, W. J.; Gingras, M. A.; Amit, Z.: Time-dependent exacerbation of amphetamine-induced taste aversions following exposure to footshock. Psychopharmacology (Berlin) 125:43–49; 1996.
10. Braveman, N. S.: Formation of taste aversions in rats following prior exposure to sickness. Learn. Motiv. 6:512–534; 1975.
11. Braveman, N. S.: What studies on pre-exposure to pharmacological agents tell us about the nature of the aversion-inducing treatment. In: Barker, L. M.; Best, M. R.; Domjan, M., eds. Learning mechanisms in food selection. Waco, TX: Baylor University Press; 1977:511–530.
12. Brookshire, K. H.; Brackbill, R. M.: Habituation to illness: Effects on acquisition and retention of a conditioned taste aversion. Paper presented at the meeting of the Psychonomic Society; 1971.
13. Brookshire, K. H.; Brackbill, R. M.: Formation and retention of conditioned taste aversions and UCS habituation. Bull. Psychon. Soc. 7:125–128; 1976.
14. Cain, N. W.; Baenninger, R.: Habituation to illness: Effects of prior experience with the US on the formation of learned taste aversions in rats. Anim. Learn. Behav. 5:359–364; 1977.
15. Cannon, D. S.; Baker, T. B.; Berman, R. F.: Taste aversion disruption by drug pretreatment: Dissociative and drug specific effects. Pharmacol. Biochem. Behav. 6:93–100; 1977.
16. Cannon, D. S.; Berman, R. F.; Baker, T. B.; Atkinson, C. A.: Effect of preconditioning unconditioned stimulus experience on learned taste aversions. J. Exp. Psychol. Anim. Behav. Proc. 104:270–284; 1975.
17. Cappell, H.; LeBlanc, A. E.: Parametric investigations of the effects of prior exposure to amphetamine and morphine on conditioned gustatory aversion. Psychopharmacology (Berlin) 51:265–271; 1977.
18. Cappell, H.; LeBlanc, A. E.; Herling, S.: Modification of the punishing effects of psychoactive drugs in rats by previous drug experience. J. Comp. Physiol. Psychol. 89:347–356; 1975.
19. Cappell, H. D.; Poulos, C. X.: Associative factors in drug pretreatment effects on gustatory conditioning: Cross-drug effects. Psychopharmacology (Berlin) 64:209–213; 1979.

20. Dacanay, R. J.; Riley, A. L.: The UCS preexposure effect in taste aversion learning: Tolerance and blocking are drug specific. Anim. Learn. Behav. 10:91–96; 1982.
21. Domjan, M.; Siegel, S.: Attenuation of the aversive and analgesic effects of morphine by repeated administration: Different mechanisms. Physiol. Psychol. 11:155–158; 1983.
22. Elkins, R. L.: Bait-shyness acquisition and resistance to extinction as functions of the US exposure prior to conditioning. Physiol. Psychol. 2:341–343; 1974.
23. Ellenbroek, B. A.; Cools, A. R.: Maternal separation reduces latent inhibition in the conditioned taste aversion paradigm. Neurosci. Res. Commun. 17:27–33; 1995.
24. Emmett-Oglesby, M. W.; Lane, J. D.: Tolerance to the reinforcing effects of cocaine. Behav. Pharmacol. 3:193–200; 1992.
25. Emmett-Oglesby, M. W.; Peltier, R. L.; Depoortere, R. Y.; Pickering, C. L.; Hooper, M. L.; Gong, Y. H.; Lane, J. D.: Tolerance to self-administration of cocaine in rats: Time course and dose–response determination using a multi-dose method. Drug Alcohol Depend. 32:247–256; 1993.
26. Etkind, S. A.; Fantegrossi, W. E.; Riley, A. L.: Cocaine and alcohol synergism in taste aversion learning. Pharmacol. Biochem. Behav. 59:649–655; 1998.
27. Ettenberg, A.; Sgro, S.; White, N.: Algebraic summation of the affective properties of a rewarding and an aversive stimulus in the rat. Physiol. Behav. 28:873–877; 1982.
28. Ferrari, C. M.; O'Connor, D. A.; Riley, A. L.: Cocaine-induced taste aversions: Effect of route of administration. Pharmacol. Biochem. Behav. 38:267–271; 1991.
29. Fisher, G. J.; Vail, B. J.: Preexposure to delta-9-THC blocks THC-induced conditioned taste aversion in rats. Behav. Neural. Biol. 30:191–196; 1980.
30. Ford, K. A.; Riley, A. L.: The effects of LiCl preexposure on amphetamine-induced taste aversions: An assessment of blocking. Pharmacol. Biochem. Behav. 20:643–645; 1984.
31. Gaiardi, M.; Bartoletti, M.; Bacchi, A.; Gubellini, C.; Costa, M.; Babbini, M.: Role of repeated exposure to morphine in determining its affective properties: Place and taste conditioning studies in rats. Psychopharmacology (Berlin) 103:183–186; 1991.
32. Gaiardi, M.; Bartoletti, M.; Gubellini, C.; Bacchi, A.; Babbini, M.: Modulation of the stimulus effects of morphine by *d*-amphetamine. Pharmacol. Biochem. Behav. 59:249–253; 1998.
33. Gamzu, E.: The multifaceted nature of taste-aversion-inducing agents: Is there a single common factor? In: Barker, L. M.; Best, M. R.; Domjan, M., eds. Learning mechanisms in food selection. Waco, TX: Baylor University Press; 1977:477–509.
34. Garcia, J.; Ervin, F. R.: Gustatory-visceral and telereceptor-cutaneous conditioning: Adaptation in internal and external milieus. Commun. Behav. Biol. 1:389–415; 1968.
35. Glowa, J. R.; Shaw, A. E.; Riley, A. L.: Cocaine-induced conditioned taste aversions: Comparisons between effects in LEW/N and F344/N rat strains. Psychopharmacology (Berlin) 114:229–232; 1994.
36. Glowa, J. R.; Williams, A. N.: Effects of prior exposure to cocaine: Interaction of reinforcing and suppressant effects. Life Sci. 51:987–994; 1992.
37. Goeders, N. E.; Irby, B. D.; Shuster, C. C.; Guerin, G. F.: Tolerance and sensitization to the behavioral effects of cocaine in rats: Relationship to benzodiazepine receptors. Pharmacol. Biochem. Behav. 57:43–56; 1997.
38. Goudie, A. J.; Taylor, M.; Atherton, H.: Effects of prior drug experience on the establishment of taste aversions in rats. Pharmacol. Biochem. Behav. 3:947–952; 1975.
39. Goudie, A. J.; Thorton, E. W.; Wheeler, T. J.: Drug pretreatment effects in drug induced taste aversions: Effect of dose and duration of pretreatment. Pharmacol. Biochem. Behav. 4:629–633; 1976.
40. Heinrichs, S. C.; Klaassen, A.; Koob, G. F.; Schulteis, G.; Ahmed, S.; De Souza, E. B.: Corticotropin-releasing factor receptor blockade enhances conditioned aversive properties of cocaine in rats. Psychopharmacology (Berlin) 136:247–255; 1998.
41. Hoffman, S. H.; Branch, M. N.; Sizemore, G. M.: Cocaine tolerance: Acute versus chronic effects as dependent upon fixed-ratio size. J. Exp. Anal. Behav. 47:363–376; 1987.
42. Holman, E. W.: The effect of drug habituation before and after taste aversion learning in rats. Anim. Learn. Behav. 4:329–332; 1976.
43. Hooks, M. S.; Duffy, P.; Striplin, C.; Kalivas, P. W.: Behavioral and neurochemical sensitization following cocaine self-administration. Psychopharmacology (Berlin) 115:265–272; 1994.
44. Hooks, M. S.; Jones, G. H.; Hemby, S. E.; Justice, J. B.: Environmental and pharmacological sensitization: Effects of repeated administration of systemic or intra-nucleus accumbens cocaine. Psychopharmacology (Berlin) 111:109–116; 1993.
45. Horger, B. A.; Shelton, K.; Schenk, S.: Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav. 37:707–711; 1990.
46. Iwamoto, E. T.; Williamson, E. C.: Nicotine-induced taste aversion: Characterization and preexposure effects in rats. Pharmacol. Biochem. Behav. 21:527–532; 1984.
47. Johansson, E. K.; Tucker, S. M.; Ginn, H. B.; Martin, B. R.; Aceto, M. D.: Functional and dispositional tolerance develops during continuous exposure. Eur. J. Drug Metab. Pharmacokinet. 17:155–162; 1992.
48. Kalivas, P. W.; Duffy, P.; DuMars, L. A.; Skinner, C.: Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J. Pharmacol. Exp. Ther. 245:485–492; 1988.
49. Kalivas, P. W.; Sorg, B. A.; Hooks, M. S.: The pharmacology and neural circuitry of sensitization to psychostimulants. Behav. Pharmacol. 4:315–334; 1993.
50. Kalivas, P. W.; Stewart, J.: Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16:223–244; 1991.
51. Katz, J. L.; Griffiths, J. W.; Sharpe, L. G.; De Souza, E. B.; Witkin, J. M.: Cocaine tolerance and cross-tolerance. J. Pharmacol. Exp. Ther. 264:183–192; 1993.
52. Kleven, M. S.; Woolverton, W. L.: Effects of continuous cocaine administration on schedule-controlled behavior in rhesus monkeys. Behav. Pharmacol. 2:471–480; 1991.
53. Kosten, T. A.; Miserendino, M. J. D.; Chi, S.; Nestler, E. J.: Fischer and Lewis rat strains show differential cocaine effects in conditioned place preference and behavioral sensitization but not in locomotor activity or conditioned taste aversion. J. Pharmacol. Exp. Ther. 269:137–144; 1994.
54. Kuribara, H.: Effects of interdose interval on ambulatory sensitization to methamphetamine, cocaine and morphine in mice. Eur. J. Pharmacol. 316:1–5; 1996.
55. Kuribara, H.: Importance of post-drug environmental factors for induction of sensitization to the ambulation-increasing effects of methamphetamine and cocaine in mice. Psychopharmacology (Berlin) 126:293–300; 1996.
56. Lasiter, P. S.; Braun, J. J.: Shock facilitation of taste aversion learning. Behav. Neural. Biol. 32:277–281; 1981.
57. LeBlanc, A. E.; Cappell, H.: Attenuation of punishing effects of morphine and amphetamine by chronic prior treatment. J. Comp. Physiol. Psychol. 87:691–698; 1974.
58. Lett, B. T.: Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. Psychopharmacology (Berlin) 98:357–362; 1989.
59. Li, D.-H.; Depoortere, R. Y.; Emmett-Oglesby, M. W.: Tolerance to the reinforcing effects of cocaine in a progressive ratio paradigm. Psychopharmacology (Berlin) 116:326–332; 1994.
60. Lienau, A.-K.; Kuschinsky, K.: Sensitization phenomena after repeated administration of cocaine or *d*-amphetamine in rats: Associative and non-associative mechanisms and the role of dopamine in the striatum. Naunyn Schmiedebergs Arch. Pharmacol. 355:531–537; 1997.
61. Lipinski, W. J.; Rusiniak, K. W.; Hilliard, M.; Davis, R. E.: Nerve growth factor facilitates conditioned taste aversion learning in normal rats. Brain Res. 692:143–153; 1995.
62. Merwin, A.; Doty, R. L.: Early exposure to low levels of estradiol (E_2) mitigates E_2-induced conditioned taste aversions in prepubertally ovariectomized female rats. Physiol. Behav. 55:185–187; 1994.
63. Miller, C. S.: Toxicant-induced loss of tolerance: An emerging theory of disease? Environ. Health Perspect. 105:445–453; 1997.

64. Morrow, B. A.; Taylor, J. R.; Roth, R. H.: Prior exposure to cocaine diminishes behavioral and biochemical responses to aversive conditioning: Reversal by glycine/*N*-methyl-D-aspartate antagonist co-treatment. Neuroscience 69:233–240; 1995.
65. Newlin, D. B.: Drug sensitization, substance abuse, and chemical sensitivity. Toxicol. Ind. Health 10:463–480; 1994.
66. O'Dell, L. E.; Khroyan, T. V.; Neisewander, J. L.: Dose-dependent characterization of the rewarding and stimulant properties of cocaine following IP and intravenous administration in rats. Psychopharmacology (Berlin) 123:144–153; 1996.
67. Orona, R. A.; Mayfield, R. D.; Cline, E. J.; Zahniser, N. R.: Repeated intravenous cocaine administration to rats produces behavioral sensitization without changing brain cocaine levels. Neurosci. Lett. 167:121–124; 1994.
68. Pilcher, C. W. T.; Jones, S. M.: Social crowding enhances aversiveness of naloxone in rats. Pharmacol. Biochem. Behav. 14:299–303; 1981.
69. Pizzi, W. J.; Cook, D. F.: Conditioned taste aversion is a confound in behavioral studies that report a reduction in the reinforcing effects of drugs. Pharmacol. Biochem. Behav. 53:243–247; 1996.
70. Post, R. M.; Contel, N. R.: Human and animal studies of cocaine: Implications for development of behavioral pathology. In: Creese, I., ed. Stimulants: Neurochemical, behavioral, and clinical perspectives. New York: Raven Press; 1983:169–203.
71. Post, R. M.; Rose, H.: Increasing effects of repetitive cocaine administration in the rat. Nature 260:731–732; 1976.
72. Post, R. M.; Weiss, S. R. B.; Pert, A.: The role of context and conditioning in behavioral sensitization to cocaine. Psychopharmacol. Bull. 23:425–429; 1987.
73. Post, R. M.; Weiss, S. R. B.; Fontana, D.; Pert, A.: Conditioned sensitization to the psychomotor stimulant cocaine. Ann. NY Acad. Sci. 654:386–399; 1992.
74. Revusky, S. H.; Garcia, J.: Learned associations over long delays. In: Bower, G. H.; Spence, J. J., eds. The psychology of learning and motivation: Advances in research and theory. New York: Academic Press; 1970:1–83.
75. Riccio, D. C.; Haroutunian, V.: Failure to learn in a taste aversion paradigm: Associative or performance deficit? Bull. Psychon. Soc. 10:219–222; 1977.
76. Riley, A. L.; Dacanay, R. J.; Mastropaolo, J. P.: The effect of morphine preexposure on the acquisition of morphine-induced taste aversions: A nonassociative effect. Anim. Learn. Behav. 12:157–162; 1984.
77. Riley, A. L.; Diamond, H. F.: The effects of cocaine preexposure on the acquisition of cocaine-induced taste aversions. Pharmacol. Biochem. Behav. 60:739–745; 1998.
78. Riley, A. L.; Jacobs, W. J.; LoLordo, V. M.: Drug exposure and the acquisition and retention of a conditioned taste aversion. J. Comp. Physiol. Psychol. 90:799–807; 1976.
79. Riley, A. L.; Tuck, D. L.: Conditioned taste aversions: A behavioral index of toxicity. Ann. NY Acad. Sci. 443:272–292; 1985.
80. Riley, A. L.; Tuck, D. L.: Conditioned food aversions: A bibliography. Ann. NY Acad. Sci. 443:381–437; 1985.
81. Rozin, P.; Kalat, J. W.: Specific hungers and poison avoidance as adaptive specializations of learning. Psychol. Rev. 78:459–486; 1971.
82. Schama, K. F.; Branch, M. N.: Tolerance to cocaine's rate-increasing effects upon repeated administration. J. Exp. Anal. Behav. 62:45–56; 1994.
83. Schenk, S.; Partridge, B.: Sensitization and tolerance in psychostimulant self-administration. Pharmacol. Biochem. Behav. 57:543–550; 1997.
84. Shippenberg, T. S.; Heidbreder, C.: Sensitization to the conditioned rewarding effects of cocaine: Pharmacological and temporal characteristics. J. Pharmacol. Exp. Ther. 273:808–815; 1995.
85. Shippenberg, T. S.; Rea, W.: Sensitization to the behavioral effects of cocaine: Modulation by dynorphin and κ-opioid receptor agonists. Pharmacol. Biochem. Behav. 57:449–455; 1997.
86. Siegel, S.; Parker, L. A.; Moroz, I.: Morphine-induced taste avoidance is attenuated with multiple conditioning trials. Pharmacol. Biochem. Behav. 50:299–303; 1995.
87. Smith, J. B.: Situational specificity of tolerance to decreased operant responding by cocaine. Pharmacol. Biochem. Behav. 36:473–477; 1990.
88. Stewart, J.; Badiani, A.: Tolerance and sensitization to the behavioral effects of drugs. Behav. Pharmacol. 4:289–312; 1993.
89. Suarez, E. M.; Barker, L. M.: Effects of water deprivation and prior LiCl exposure in conditioning taste aversions. Physiol. Behav. 17:555–559; 1976.
90. Switzman, L.; Fishman, B.; Amit, Z.: Pre-exposure effects of morphine, diazepam and Δ^9-THC on the formation of conditioned taste aversions. Psychopharmacology (Berlin) 74:149–157; 1981.
91. Unterwald, E. M.; Ho, A.; Rubenfeld, J. M.; Kreek, M. J.: Time course of the development of behavioral sensitization and dopamine receptor up-regulation during binge cocaine administration. J. Pharmacol. Exp. Ther. 270:1387–1396; 1994.
92. van Haaren, F.; Anderson, K. G.: Behavioral effects of acute and chronic cocaine administration in male and female rats: Effects of fixed-ratio schedule parameters. Behav. Pharmacol. 5:607–614; 1994.
93. Weiss, B.: Experimental strategies for research on multiple chemical sensitivity. Environ. Health Perspect. 105:487–494; 1997.
94. Weiss, S. R. B.; Post, R. M.; Pert, A.; Woodward, R.; Murman, D.: Context-dependent cocaine sensitization: Differential effect of haloperidol on development versus expression. Pharmacol. Biochem. Behav. 34:655–661; 1989.
95. Yeh, S. Y.; Haertzen, C. A.: Cocaine-induced locomotor activity in rats. Pharmacol. Biochem. Behav. 39:723–727; 1991.
96. Yu, Z. J.; Jin, C.; Rochold, R. W.; Hoskins, B.; Ho, I. K.: Site and mechanism of behavioral tolerance to cocaine: A study of dopamine release in Wistar–Kyoto and spontaneously hypertensive rats. Neurochem. Res. 18:1203–1209; 1993.