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The Effects of Cocaine Preexposure on the Acquisition of Cocaine-Induced Taste Aversions

ANTHONY L. RILEY AND HILARY F. DIAMOND

Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016

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RILEY, A. L. AND H. F. DIAMOND. *The effects of cocaine preexposure on the acquisition of cocaine-induced taste aversions.* PHARMACOL BIOCHEM BEHAV **60**(3) 739–745, 1998.—In separate experiments, rats received either five intraperitoneal or five subcutaneous injections of cocaine (once daily or spaced every fourth day) prior to receiving repeated saccharin–cocaine pairings (during taste aversion conditioning). Both spaced and massed subcutaneous cocaine preexposure attenuated the subsequent acquisition of taste aversions induced by cocaine. Specifically, aversions in the preexposed subjects were acquired at a slower rate and/or to a lesser degree than those acquired by subjects preexposed to the cocaine vehicle and injected with cocaine during conditioning. Spaced and massed intraperitoneal cocaine preexposure had only a weak or no effect, respectively, on the subsequent acquisition of cocaine-induced taste aversions. Specifically, subjects receiving spaced intraperitoneal injections of cocaine during preexposure differed from nonpreexposed subjects on only a single conditioning trial, and subjects receiving massed intraperitoneal injections of cocaine during preexposure displayed aversions comparable to those of nonpreexposed subjects. Although the effects of subcutaneous cocaine preexposure were similar to those reported with other drugs within the aversion design, it is clear that the preexposure effect with cocaine is dependent upon the specific parameters of preexposure. Several possibilities for these differential effects of cocaine preexposure were discussed, including the influence of changing the route of administration from preexposure to conditioning (i.e., from IP to SC) and the differential masking of the aversive effects of cocaine during conditioning by differential sensitization to cocaine's reinforcing properties following SC and IP preexposure. Although the present series of experiments did not directly address the mechanism(s) underlying the attenuating effects of cocaine peexposure on aversion learning, several possibilities were noted, including adaptation or tolerance to the aversive effects of cocaine and sensitization to its rewarding effects. © 1998 Elsevier Science Inc.

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 compounds [(29,54,60); for a bibliography, see (58)], such conditioned taste aversions are significantly attenuated if they have received exposure to the drug prior to conditioning [for reviews, see (6,28)]. Several possible explanations of the unconditioned stimulus (UCS) preexposure effect in aversion learning have been proposed [e.g., associative blocking, tolerance, habituation; see (2,5,7,9,10,15,16,18,26,35,42,55,56)]. Although there is no consensus on its mechanism, the fact that aversions are weakened by such prior exposure is well documented.

Since its initial demonstration with apomorphine (8), a wide range of compounds have been shown to produce the UCS preexposure effect, for example, amphetamine (32), chlordiazepoxide (28), cyclophosphamide (19), Δ^9-THC (25), diazepam (72), estradiol (47), ethanol (3), fenfluramine (32), LiCl (57), morphine (14), methamphetamine (33), and nicotine (37). Although the UCS preexposure effect has been demonstrated with a variety of drugs with different biochemical, physiological, and behavioral effects, little is known about the effects of such exposure on the acquisition of cocaine-induced taste aversion. This is surprising, given the fact that the effects of cocaine exposure on subsequent cocaine responsivity have been well documented in other preparations (20–22,36,38–41,43,44,46,49,51–53,61,65,69,70,73,74,78–80) and that the consequences of chronic cocaine exposure have been implicated in drug use and abuse [see (1,4,50,59,76)].

Although there have been no specific assessments of the effects of noncontingent cocaine exposures on subsequent cocaine-induced aversions, Glowa and his colleagues have recently reported that a single squirrel monkey with a history of cocaine self-administration continued to respond for banana

Requests for reprints should be addressed to Anthony L. Riley, Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016.

pellets that were paired with the subsequent injection of cocaine, i.e., exposure to cocaine via a self-administration preparation appeared to attenuate subsequent cocaine-induced taste aversions relative to subjects without the self-administration history [see (31)]. Although consistent with the aforementioned effects of preexposure to other psychoactive drugs on taste aversion learning, it should be noted that these findings with cocaine were limited to a single subject. Further, it is not clear to what extent the attenuation of taste aversion learning was a function of the cocaine preexposure or exposure to the self-administration preparation. Accordingly, it remains unknown to what degree (if any) noncontingent cocaine exposure affects aversion learning.

The present series of experiments directly assessed the effects of noncontingent cocaine preexposures on cocaine-induced taste aversions. For other compounds, the UCS preexposure effect has been reported following both spaced (5,13) and massed (11,12) as well as following both intraperitoneal (16) and SC (37) drug administration. To assess the degree to which the effects of cocaine preexposure parallel those of other psychoactive drugs, cocaine preexposure was either SC (Experiments 1 and 2) or intraperitoneal (Experiments 3 and 4) and either spaced (i.e., every fourth day for five exposures; Experiments 1 and 3) or massed (i.e., once a day for 5 consecutive days; Experiments 2 and 4). For all studies, cocaine was administered subcutaneously during aversion training, the route most effective in inducing taste aversions [see (23,24,30)].

GENERAL METHOD

Subjects

The subjects were 108 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 28°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.) 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 a subcutnaeous (SC; Experiments 1 and 2) or intraperitoneal (IP; Experiments 3 and 4) injection of 32 mg/kg cocaine or of equivolume distilled water. These preexposure injections were given either every fourth day (Experiments 1 and 3) or daily (Experiments 2 and 4) for a total of five drug exposures. For subjects receiving the spaced preexposures, 20-min access to water was given between preexposure injections. No injections were given following water access on these days.

Phase III: conditioning. On the day following the final drug preexposure or water-recovery session of Phase II, 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 subcutaneously injected with either cocaine (32 mg/kg, SC) 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 subcutaneously following saccharin consumption [see (24)]. 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 at 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 $p < 0.05$.

EXPERIMENT 1: SPACED SUBCUTANEOUS PREEXPOSURE

Specific Procedure

During drug preexposure, subjects were given a SC injection of cocaine (group C; $n = 14$) or its distilled water vehicle (group W; $n = 14$) every fourth day for a total of five drug preexposures. During taste aversion conditioning, subjects in group C were injected with either cocaine or equivolume distilled water, yielding groups CC and CW. Similarly, subjects in group W were injected with either cocaine or distilled water, yielding groups 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: MASSED SUBCUTANEOUS PREEXPOSURE

Specific Procedure

During drug preexposure, subjects were given a SC injection of cocaine (group C; $n = 8$) or its distilled water vehicle

(group W; $n = 4$) once a day for a total of five drug preexposures. During taste aversion conditioning, subjects in group C were injected with either cocaine or equivolume distilled water, yielding groups CC and CW and subjects in group W were injected with cocaine, yielding group WC.

EXPERIMENT 3: SPACED INTRAPERITONEAL PREEXPOSURE

Specific Procedure

During drug preexposure, subjects were given an IP injection of cocaine (group C; $n = 14$) or its distilled water vehicle (group W; $n = 14$) every fourth day for a total of five drug preexposures. During taste aversion conditioning, subjects in group C were injected with either cocaine or equivolume distilled water, yielding groups CC and CW. Similarly, subjects in group W were injected with either cocaine or distilled water, yielding groups WC and WW.

EXPERIMENT 4: MASSED INTRAPERITONEAL PREEXPOSURE

Specific Procedure

During drug preexposure, subjects were given an IP injection of cocaine (group C; $n = 24$) or its distilled water vehicle (group W; $n = 16$) once a day for a total of five drug preexposures. During taste aversion conditioning, subjects in group C were injected with either cocaine or equivolume distilled water, yielding groups CC and CW. Similarly, subjects in group W were injected with either cocaine or distilled water, yielding groups WC and WW.

RESULTS

At no point did subjects receiving cocaine or vehicle during the preexposure phase of each experiment drink significantly different amounts of water. The mean amount consumed for each group was approximately 12 ml.

Experiment 1: Spaced Subcutaneous Preexposure

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, drinking less than 4 ml by the final conditioning trial. On the other hand, subjects injected with cocaine during both preexposure and conditioning (group CC) maintained a high level of saccharin consumption over conditioning trials. Control subjects injected with water during conditioning also 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).

Post hoc comparisons revealed that subjects in group WC drank significantly less saccharin than both control groups on the third, fourth, and fifth conditioning trials and significantly less than subjects in group CC on conditioning trials 3 and 4, $H(3) = 7.936$ for trial 3, and $H(3) = 10.437$ for trial 4. Groups CC, CW, and WW did not differ in saccharin consumption until the final conditioning trial, at which point subjects in group CW drank significantly more saccharin than subjects in groups CC and WW, $H(3) = 16.533$ for trial 5.

Experiment 2: Massed Subcutaneous Preexposure

Figure 2 illustrates the mean (±SEM) amount of saccharin consumed over the repeated conditioning trials for subjects in groups CC, CW and WC. As illustrated, subjects given water preexposure and injected with cocaine during conditioning (group WC) acquired the aversion to saccharin, drinking less than 7 ml by the final conditioning trial. Control subjects given cocaine during preexposure and injected with water during conditioning maintained a high level of saccharin consumption (see group CW). Subjects injected with cocaine during both preexposure and conditioning (group CC) maintained levels of saccharin consumption intermediate to those of subjects in group WC and in group CW, drinking approximately 12 ml on the final conditioning trial.

Post hoc comparisons revealed that subjects in group WC drank significantly less saccharin than those in group CW on the second, third, fourth, and fifth conditioning trials and significantly less saccharin than subjects in group CC on conditioning trials 2–4, $H(2) = 7.471$ for trial 2; $H(2) = 7.269$ for trial 3; $H(2) = 9.24$ for trial 4; $H(2) = 8.163$ for trial 5. Groups CC and CW did not differ in saccharin consumption until the

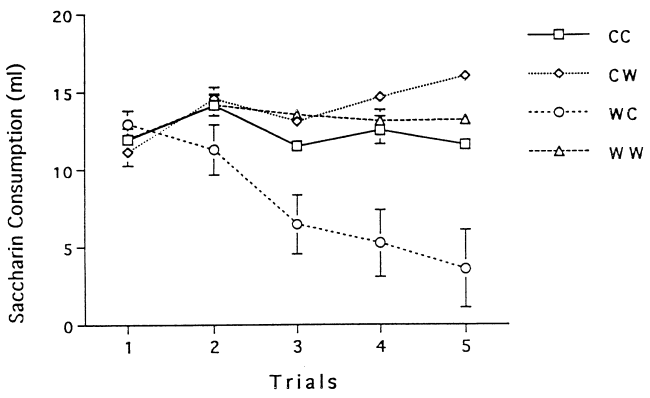

FIG. 1. Mean (±SEM). saccharin consumption by subjects receiving saccharin–cocaine (groups CC and WC) or saccharin–distilled water (groups CW and WW) pairings during taste aversion conditioning. The first letter in the group designation refers to the drug received during preexposure, i.e., cocaine (C) or water (W); the second letter refers to the drug received during conditioning, i.e., C or W. All preexposure injections were given subcutaneously, every fourth day.

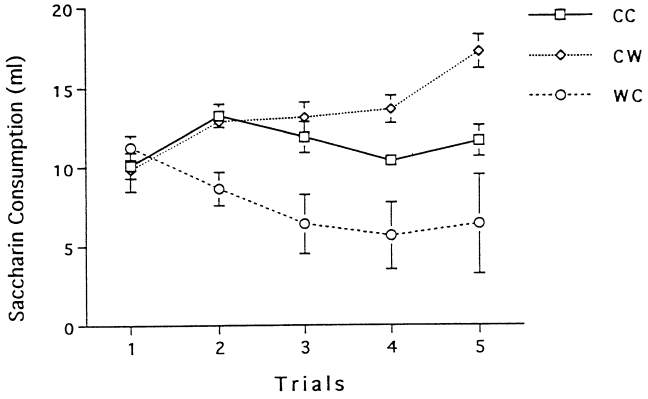

FIG. 2. Mean (±SEM) saccharin consumption by subjects receiving saccharin–cocaine (groups CC and WC) or saccharin–distilled water (groups CW) pairings during taste aversion conditioning. The first letter in the group designation refers to the drug received during preexposure, i.e., cocaine (C) or water (W); the second letter refers to the drug received during conditioning, i.e., C or W. All preexposure injections were given subcutaneously, once daily.

final conditioning trial, at which point subjects in group CW drank significantly more saccharin than subjects in group CC, $H(2) = 8.163$ for trial 5.

Experiment 3: Spaced Intraperitoneal Preexposure

Figure 3 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, drinking less than 5 ml by the final conditioning trial. Control subjects injected with the distilled water vehicle during conditioning (groups CW and WW) maintained high levels of saccharin consumption during conditioning, increasing consumption from the first to last trial. Subjects injected with cocaine during both preexposure and conditioning (group CC) maintained levels of saccharin consumption intermediate to those of subjects in group WC and in groups CW and WW, drinking approximately 8 ml on the final conditioning trial.

Post hoc comparisons revealed that subjects in group WC consumed significantly less saccharin than control subjects (groups CW and WW) on the second, fourth, and fifth conditioning trials, $H(3) = 10.533$ for trial 2; $H(3) = 12.969$ and 16.161 for trials 4 and 5, respectively. In addition, subjects in group WC drank significantly less saccharin than subjects in group CC on the second conditioning trial, $H(3) = 10.533$. Group CC did not differ significantly from controls until the fourth trial, $H(3) = 12.969$.

Experiment 4: Massed Intraperitoneal Preexposure

Figure 4 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) decreased saccharin consumption with repeated conditioning trials, drinking less than 6 ml by the final conditioning trial. Similarly, subjects injected with cocaine during both preexposure and conditioning (group CC) displayed aversions comparable to subjects in group WC, decreasing saccharin consumption with repeated conditioning trials and drinking 8 ml by the final trial. Control subjects injected with the distilled water vehicle during conditioning (groups CW and WW) maintained high levels of saccharin consumption over trials, increasing consumption from the first to the last conditioning trial.

Post hoc comparisons revealed that subjects in group WC and group CC drank significantly less saccharin than control subjects (groups CW and WW) on all but the initial conditioning trial [all $H(2)$s > 17.737]. There were no significant differences in consumption between groups CC and WC on any trial.

GENERAL DISCUSSION

Preexposure to a wide variety of psychoactive compounds has been reported to attenuate subsequent conditioned taste aversion learning induced by those compounds (see above). Interestingly, the effects of cocaine have not been evaluated within this preparation [although see (31)]. As described, exposure to cocaine prior to aversion conditioning clearly attenuated the acquisition of cocaine-induced taste aversions under two of the four preexposure conditions examined in the present series of experiments, specifically, when cocaine was administered subcutaneously (either spaced or massed; Experiments 1 and 2, respectively). The two conditions under which preexposure produced weak attenuation was when cocaine was administered intraperitoneally (either spaced or massed; Experiments 3 and 4, respectively). These differences between the SC and IP conditions were evident both in terms of the number of trials on which preexposed subjects drank significantly more than nonpreexposed subjects (a mean of 2.5 vs. 0.5 for SC and IP, respectively), as well as the number of trials preexposed subjects drank significantly less than controls (a mean of 1 vs. 3 for SC and IP, respectively). Thus, although cocaine preexposure can attenuate subsequent aversion learning, an effect consistent with other demonstrations of UCS preexposure on taste aversion learning, the attenuating effects of cocaine preexposure on aversion learning are clearly dependent on the specific parameters of cocaine preexposure.

The basis for this effect of the route of cocaine preexposure is not immediately evident. The UCS preexposure effect has been reported following SC, IP, and oral administration of

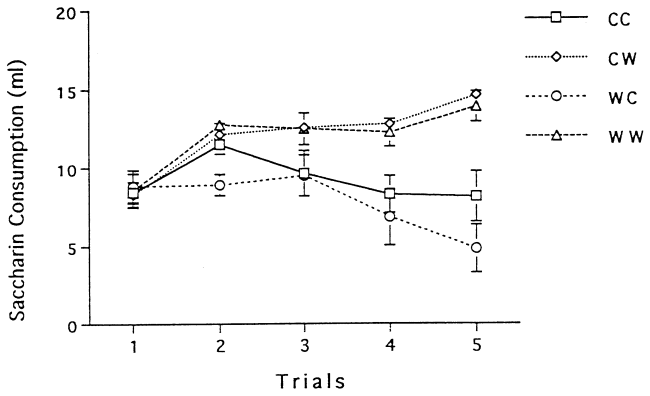

FIG. 3. Mean (±SEM) saccharin consumption by subjects receiving saccharin–cocaine (groups CC and WC) or saccharin–distilled water (groups CW and WW) pairings during taste aversion conditioning. The first letter in the group designation refers to the drug received during preexposure, i.e., cocaine (C) or water (W); the second letter refers to the drug received during conditioning, i.e., C or W. All preexposure injections were given intraperitoneally, every fourth day.

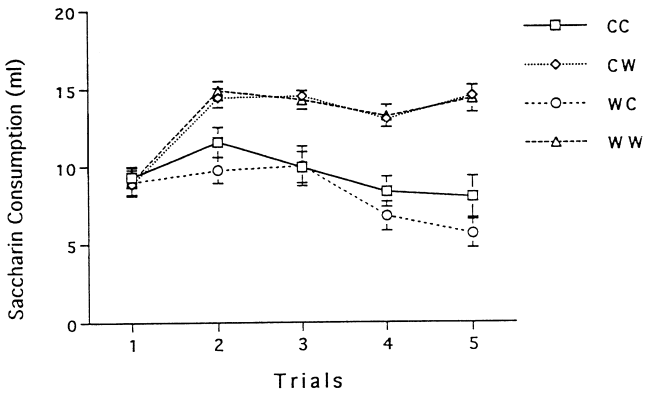

FIG. 4. Mean (±SEM) saccharin consumption by subjects receiving saccharin–cocaine (groups CC and WC) or saccharin–distilled water (groups CW and WW) pairings during taste aversion conditioning. The first letter in the group designation refers to the drug received during preexposure, i.e., cocaine (C) or water (W); the second letter refers to the drug received during conditioning, i.e., C or W. All preexposure injections were given intraperitoneally, once daily.

a number of psychoactive agents (see above). Thus, the relatively weaker attenuating effects following spaced IP preexposure and the absence of such effects following massed IP preexposures can not be a simple function of route of administration. It is interesting that the weaker attenuating effects of cocaine preexposure occurred when the preexposure injections were given by a different route than the conditioning injections, i.e., IP vs. SC, respectively. In the single arrticle examining route of administration in the UCS preexposure effect, Domjan and Best (17) reported that although both intragastric and IP LiCl preexposures were effective in attenuating LiCl-induced taste aversions, the attenuating effects of LiCl preexposure were eliminated if the route of administration was changed from preexposure to conditioning. The present findings that weaker attenuation was evident when the preexposure and conditioning routes were different is, thus, consistent with the work by Domjan and Best (17). The fact that massed IP preexposures produced even less attenuation than spaced IP preexposures may be a function of the additional shift in the temporal patterning of the injections between the preexposure and conditioning phases (i.e., from once a day to every fourth day in the massed group). Given that the attenuation was not weaker in the massed SC condition (relative to the spaced SC condition), however, questions such an influence of temporal factors.

A second explanation for the differential effects of SC vs. IP cocaine preexposure on aversion learning is related to sensitization and how such a process may vary with route of administration. Although the attenuating effects of preexposure for drugs other than cocaine are often described as resulting from adaptation to the aversive effects of the drug (9,10,28, 32,35,71) or the development of tolerance to these effects (3,11,13,16,42,56), Gaiardi, Bartoletti, Bacchi, Gubellini, Costa and Babbini (27) have recently offered an alternative explanation of the UCS preexposure effect that might be relevant to the present data. Specifically, they suggested that the UCS preexposure effect with some drugs may be a function of the drug's reinforcing effects increasing over repeated injections (via sensitization), an increase that counters the aversive effects of the drug. The interaction of the increasing reinforcing effects with the aversive effects renders the drug ineffective in inducing an aversion, i.e., produces the UCS preexposure effect. This suggestion was based on a study in which animals given the same number of morphine preexposures that attenuated morphine-induced taste aversions displayed greater conditioned place preferences, an indication to the authors that under these conditions the reinforcing properties of morphine had been sensitized by the drug preexposure. That a drug may simultaneously produce both reinforcing and aversive properties has been previously demonstrated with a number of compounds, including morphine and amphetamine (63,68,77). Further, the interaction of these properties has been offered as a basis to account for specific characteristics of aversion conditioning [e.g., the weakening of morphine-induced taste aversions with repeated conditioning trials; see (66); for a related discussion, see (48).

Like morphine and amphetamine, cocaine also appears to produce both reinforcing and aversive effects (as indexed by its ability to support both self-administration and taste aversions, respectively). Further, repeated exposures to cocaine have been reported to increase its reinforcing properties, as measured by the rate of acquisition of cocaine self-administration or conditioned place preferences [see (36,44,62,64). Accordingly, the attenuating effects of cocaine preexposure may also be due to a masking or overshadowing of its aversive effects by the increase in its reinforcing properties rather than to a direct weakening of its aversiveness as a result or adaptation or tolerance. If sensitization to cocaine is a function of the route of administration, this explanation may be able to account for the different effects of IP and SC cocaine preexposure on aversion learning. Specifically, if repeated SC exposure to cocaine produces greater sensitization than repeated IP exposure, one would expect to see a greater preexposure effect under the SC condition. That is, there would be greater sensitization of the reinforcing effects of cocaine following SC exposure and thus a greater masking of cocaine's aversive effects.

Although sensitization to cocaine has been reported following both SC and IP exposure within other designs (see above), there is limited work addressing the relative strength of sensitization under the two conditions. In one study directly comparing the two routes [see (80)], repeated exposure to IP cocaine (twice daily for 7 consecutive days) induced greater sensitization than SC exposure (as indexed by the shift in peak horizontal and ambulatory activity in response to an injection of cocaine prior to and following chronic injections). The majority of the sensitized locomotor activity was produced within the first half of the testing period following the injection of cocaine (the testing periods were 120 and 300 min in duration for the IP and SC conditions, respectively). Later in the testing period there was no evidence of sensitization in subjects receiving chronic IP cocaine. That is, the amount of activity induced by cocaine further into the testing period did not differ prior to and following the chronic IP exposure to cocaine. Interestingly, cocaine-induced locomotor activity decreased in this interval for subjects receiving chronic SC cocaine. That is, the amount of activity induced by cocaine further into the testing period was less following the chronic exposure to SC cocaine. It appeared that following chronic SC cocaine, locomotor activity was "desensitized" late in testing. Although it is difficult to make comparisons between the degree of sensitization following SC and IP administration of cocaine, there does not appear to be evidence for greater sensitization following SC (relative to IP) administration. Therefore, the extent to which the effects in the present experiment are due to differential sensitization following the different routes of administration remains unknown.

The discussion has focused primarily on accounting for the differences between the effects of SC and IP cocaine exposure on taste aversion learning and less on the basis for the preexposure that was evident. As noted, it is possible that the weaker aversions were a function of adaptation or tolerance to the aversive effects of cocaine [for discussions of tolerance to a range of effects of cocaine following chronic exposure, see (21,22,34,38,45,61,67,75,81). It is also possible that the weaker aversions were a function of the above-mentioned sensitization of its reinforcing effects. Neither explanation, however, provides a clear account of the differences in the effects of preexposure following SC and IP administration without assuming a yet-to-be demonstrated interaction of tolerance (or sensitization) and route of administration. What is clear is that under some conditions preexposure to cocaine can attenuate cocaine-induced taste aversion learning. Further work is needed to address the specific mechanism underlying the preexposure effect, as well as to determine the basis for the effect of route of administration.

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