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The Influence of Postweaning Housing Conditions on Drug-Induced Conditioned Taste Aversion

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SMITH, J. K., J. C. NEILL AND B. COSTALL. *The influence of postweaning housing conditions on drug-induced conditioned taste aversion.* PHARMACOL BIOCHEM BEHAV **59**(2) 379–386, 1998.—Postweaning social isolation can influence the sensitivity of rats to several effects of drugs of abuse. The present study investigated the influence of postweaning housing conditions on the sensitivity of rats to the aversive effects of a number of psychoactive agents using a conditioned taste aversion (CTA) test procedure. Development of a CTA was assessed by pairing administration of the drug with the consumption of a 0.05% (weight/volume) saccharin solution in water-deprived (18 h) rats in a 20 min drinking period. Saccharin consumption was then measured in 20 min test sessions over the next 4 consecutive days. Consumption of saccharin solution was significantly reduced in both isolated and enriched rats following administration of *d*-amphetamine (2 mg/kg), cocaine (30 mg/kg), morphine (10 mg/kg), nicotine (1.0 mg/kg), caffeine (20 mg/kg), alcohol (1.5 g/kg), and LiCl (0.15 M, 4 ml/kg). There was no significant effect of housing conditions on the CTA induced by cocaine, nicotine, alcohol, or LiCl; however, isolation-reared rats were found to be less sensitive to the aversive effects of *d*-amphetamine, morphine, and caffeine in this paradigm. These results suggest that rearing rats in social isolation induces an attenuation in sensitivity to the aversive effects of some psychoactive agents. © 1998 Elsevier Science Inc.

Social isolation Environmental enrichment Rat Conditioned taste aversion Drugs of abuse

DEVELOPMENTAL variables influence sensitivity to the effects of drugs of abuse and rats reared in social isolation have been shown to be more sensitive to the behavioral effects of the psychostimulants *d*-amphetamine (33,42) and cocaine (30,42) In some studies rats isolated from weaning have an enhanced sensitivity to the reinforcing effects of drugs of abuse and will self-administer cocaine (7,35), morphine (1,25), and heroin (8) more readily in an operant paradigm, although there have been conflicting reports (18,30). In addition, isolated rats have been found to be more sensitive to the reinforcing effects of *d*-amphetamine administration as assessed using drug discrimination (14) and conditioned reinforcement (21,42) paradigms.

It has been suggested that the enhanced sensitivity of rats to the reinforcing effects of these drugs is mediated via increased dopaminergic function. Consistent with this suggestion, isolated rats show elevated dopamine levels within the prefrontal cortex (5,22) as well as enhanced D_2 receptor binding in the striatum (17). In addition, isolates exhibit greater dopamine release in the nucleus accumbens on systemic administration of *d*-amphetamine, as well as increased locomotor activation and responding for a conditioned reinforcer following direct administration of dopamine into the nucleus accumbens compared with their socially reared counterparts (21,22).

Drugs that act as reinforcers can also have aversive properties as measured in a CTA paradigm, a feature of many addictive drugs, and such effects may counteract the tendency towards self-administration (43). When administration of a psychoactive drug that serves as a reinforcer in other paradigms is paired with a flavored solution, the solution is subsequently avoided; a phenomenon referred to as conditioned taste aversion (CTA) (16). Development of CTA is a robust phenomenon that can be induced following a single pairing session (40) and is typically measured in terms of a reduced intake of the test solution.

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The paradoxical ability of drugs to induce a CTA within a dose range similar to that which is reinforcing was first demonstrated by Reicher and Holman (31), who showed that rats injected with *d*-amphetamine immediately before they consumed a flavored solution in a distinctive location approached the location, but avoided consuming the flavored solution. The *d*-amphetamine–induced state was, therefore, considered to be aversive when paired with drinking, and reinforcing when paired with motor responses. The ability of drugs to serve simultaneously, in the same animal, as a reinforcer and to induce a CTA has been demonstrated for a number of psychoactive drugs including *d*-amphetamine (31) and morphine (39,44).

Whereas the CTA induced by drugs that do not possess reinforcing properties is mediated via a toxicity effect, the aversive effects of self-administered drugs are thought to be mediated via an interaction with the same neural mechanisms as the reinforcing properties of these drugs. Thus, pharmacological manipulations that disrupt self-administration of psychoactive drugs also disrupt the CTA that develops following their administration, but have no effect on the CTA induced by drugs that are not self-administered and are not thought to act as reinforcers, such as LiCl (3,19,41).

In a recent study it was demonstrated that isolation rearing attenuated the CTA induced by morphine in rats (38). We have recently shown that isolation rearing enhances the sensitivity of rats to the behavioral and reinforcing effects of the psychomotor stimulants *d*-amphetamine and cocaine (42). To further investigate the influence of postweaning housing conditions on sensitivity to drugs of abuse, and the relationship between environmental factors and the reinforcing and aversive properties of such drugs, it was considered important to determine whether isolation rearing influences the aversive properties of these psychostimulants, as well as other psychoactive agents. Thus, the aim of the present study was to examine the influence of postweaning housing conditions on the sensitivity of rats to the aversive properties of a range of psychoactive drugs and LiCl using a CTA paradigm. A one-bottle procedure was used, as this has been shown to be a more sensitive measure of differential taste aversions (4).

METHOD

Subjects and Housing Conditions

Twenty-four female Hooded Lister rats (250–300 g, University of Bradford strain) were used as subjects. Rats were obtained at weaning (21 days) and randomly allocated to one of two housing conditions where they remained for a period of 12 weeks before experimentation began, and for the duration of the experiments reported here. Isolated rats ($n = 12$) were housed in individual cages (38 × 24 × 18 cm) such that they could see, hear, and smell rats in adjacent cages, but were prevented from physical contact. Handling of isolated animals occurred once weekly for cage cleaning purposes only. The social animals ($n = 12$) were housed in groups of six (cages measured 38 × 59 × 24 cm), and were environmentally enriched with various objects, such as Cardboard and Perspex tubes, ladders, ping-pong balls, marbles, and various animal toys, and were handled daily. Socially housed animals in the study were maintained within an enriched environment, in accordance with a number of similar studies (14,18), as this is thought to enhance differences induced by housing and rearing conditions (6). Food and water were available to all rats *ad lib*, unless otherwise stated, and rats were maintained under a 12 h L:12 h D cycle (lights on at 0700 h). All experiments were conducted between 0900 and 1200 h.

Procedure

Habituation. Rats were water deprived overnight (18 h) throughout the experimental procedure. Immediately following this deprivation period rats were transferred to individual cages (38 × 24 × 18 cm) and given access to a 0.05% saccharin solution (weight/volume) for a period of 20 min. Because rats did not drink sufficient quantities of the solution to enable a significant reduction in consumption during this first exposure, rats were given the solution for 20 min daily over a 5 day period. Fluid consumption was monitored in all rats by weighing bottles before and after each test during this habituation period. This 5 day period was followed by 10 days during which animals were given access to water during the drinking period to allow fluid consumption to stabilize.

Pairing. Rats were water deprived for 18 h and given access to a 0.05% saccharin solution as in habituation. On day 1, 20 min following presentation of the saccharin solution, rats were removed from the test cage and injected with either drug or vehicle. Rats were then placed in the test cage for a further 30 min, before being returned to the home cage. Saccharin consumption was then measured in a daily 20 min test session for the next 4 consecutive days (days 2–5). As saccharin intake was not significantly reduced following the first pairing session with LiCl (Fig. 1) the pairing procedure was repeated on day 2. Following the 5 day test period, animals were given access to the saccharin solution for 20 min daily until fluid

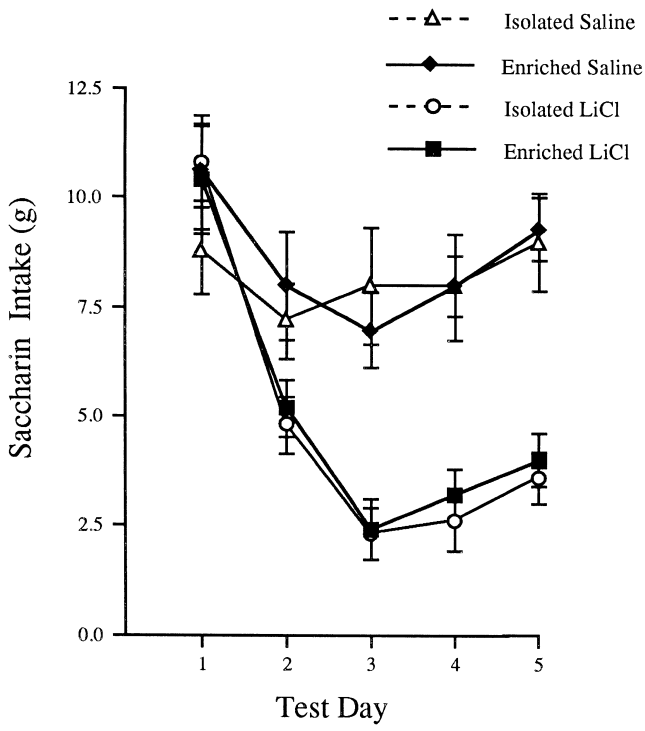

FIG. 1. The influence of postweaning housing conditions on LiCl induced CTA. Data are expressed as the mean ± SEM ($n = 5$ per group) saccharin intake in a 20 min test. LiCl (0.15 M, 4 ml/kg) or saline vehicle were administered following the drinking period on days 1 and 2.

consumption returned to basal levels, before the procedure was repeated for the next drug test. Drug pairing sessions were separated by at least 10 days.

Drugs

d-Amphetamine sulphate (Sigma, UK), Cocaine hydrochloride (Sigma), and Morphine hydrochloride (Sigma) were dissolved in 0.9% NaCl. Caffeine (Sigma), Nicotine sulphate (BDH, UK) and Lithium Chloride (LiCl, Sigma) were dissolved in distilled water. Absolute alcohol (Merck Ltd, UK) was diluted using 0.9% NaCl to give a 20% volume/volume solution. Saccharin (Sigma) was diluted using distilled water to give a 0.05% weight/volume solution. All drugs and vehicle were injected via the intraperitoneal route (IP) with the exception of nicotine, which was injected subcutaneously (SC). Injection volumes of 1 ml/kg were used for all drugs and vehicle, except LiCl (0.15 M), which was injected in a volume of 4 ml/kg and alcohol. Alcohol injection volumes were calculated according to the equation: g/kg = (x ml ethanol × 0.158)/body wt (kg). Drugs were administered in the order; *d*-amphetamine, cocaine, morphine, nicotine, caffeine, alcohol, LiCl. Drug doses were calculated as base equivalent weight and were chosen from studies demonstrating a significant CTA following a single pairing session (9,15,26,28,40).

Statistical Analysis

Data were subjected to a three-way analysis of variance (ANOVA) with two between-subjects factors; housing (two levels) and drug (two levels), and one within-subjects factor; time (five levels), followed by post hoc analysis using a two-tailed Dunnett's *t*-test.

RESULTS

A two-way ANOVA revealed no significant difference in the volume of saccharin consumed by isolated and enriched rats during the initial 5 day habituation period, $F(4, 80) = 0.43$, NS. Similarly, during all the test procedures isolated and enriched rats did not exhibit differences in the volume of solution consumed during the test period either on day 1, before administration of drug, or on days 2–5 following administration of vehicle.

LiCl

Administration of LiCl (0.15 M, 4 ml/kg) on day 1 did not have a significant effect on saccharin intake on the following test day; however, a repeated pairing session on day 2 led to a reduction in saccharin intake in both isolated and enriched rats. A three-way ANOVA revealed a significant effect of drug, $F(1, 20) = 34.7$, $p < 0.001$, a significant effect of time, $F(4, 80) = 13.3$, $p < 0.001$, and a significant drug × time interaction, $F(4, 80) = 4.7$, $p < 0.01$. Post hoc analysis revealed that saccharin intake was significantly reduced on days 3 and 4 ($p < 0.05$). There was no effect of housing, however, $F(1, 20) = 3.3$, NS, and no housing × drug interaction, $F(1, 20) = 2.5$, NS, suggesting that there was no difference in sensitivity to the CTA induced by LiCl in isolated and enriched rats (Fig. 1).

Drug-Induced CTA Affected by Housing Conditions

d-Amphetamine. A significant effect of drug, $F(1, 20) = 342.6$, $p < 0.001$, time, $F(4, 80) = 10.38$, $p < 0.001$, and a drug × time interaction, $F(4, 80) = 24.14$, $p < 0.001$, showed that administration of *d*-amphetamine (2 mg/kg) led to a significant reduction in the intake of saccharin solution in both groups of animals on days 2, 3, 4, and 5 ($p < 0.01$). Furthermore, a significant effect of housing, $F(1, 20) = 4.5$, $p < 0.05$, and a housing × drug interaction, $F(1, 20) = 7.29$, $p < 0.05$, suggests that the extent to which saccharin intake was reduced varied according to the housing conditions under which the rats were maintained. Post hoc analysis revealed that enriched rats exhibited a significantly greater reduction in saccharin intake following drug treatment on days 2 ($p < 0.05$), 3, ($p < 0.01$), and 4 ($p < 0.05$) compared to isolated animals; thus, enriched animals showed a greater *d*-amphetamine induced CTA (Fig. 2a).

Morphine. Similarly, morphine (10 mg/kg) induced a CTA that was considerably greater in enriched compared to isolated rats. A significant effect of drug, $F(1, 20) = 70.95$, $p < 0.001$, time, $F(4, 80) = 6.9$, $p < 0.05$, and a significant drug × time interaction, $F(4, 80) = 9.2$, $p < 0.001$, suggests that morphine induced a CTA in both isolated and enriched rats on days 2–5 inclusive ($p < 0.01$). Furthermore, a significant effect of housing, $F(1, 20) = 6.23$, $p < 0.05$, as well as a housing × drug interaction, $F(1, 20) = 5.11$, $p < 0.05$, indicates that the reduction in consumption of saccharin solution induced by morphine was greater in enriched rats when compared with isolates. Post hoc analysis revealed that the decrease in saccharin intake was significantly greater in enriched compared to isolated rats on days 2–4 ($p < 0.01$) and day 5 ($p < 0.05$) (Fig. 2b).

Caffeine. A significant effect of both drug, $F(1, 20) = 13.5$, $p < 0.05$, and time, $F(4, 80) = 7.9$, $p < 0.001$, show that administration of caffeine (20 mg/kg) induced a CTA in all rats. Post hoc analysis showed that saccharin intake was significantly reduced on days 2, 3, 4, and 5 ($p < 0.01$). In addition, a significant effect of housing, $F(1, 20) = 6.4$, $p < 0.05$, and a housing × drug interaction, $F(1, 20) = 6.8$, $p < 0.05$, suggests that this reduction was greater in enriched animals when compared to those housed in isolation following administration of caffeine on days 2 and 3 ($p < 0.01$) and 4 ($p < 0.05$) (Fig. 2c).

Drug-Induced CTA Not Affected by Housing Conditions

Cocaine. Administration of cocaine (30 mg/kg) on day 1 similarly led to a reduction in saccharin consumption in both isolated and enriched rats from day 2 onwards. A three-way ANOVA revealed a significant effect of drug, $F(1, 20) = 174.0$, $p < 0.001$, time, $F(4, 80) = 16.91$, $p < 0.001$, as well as a drug × time interaction, $F(4, 80) = 13.02$, $p < 0.001$. Post hoc analysis revealed that saccharin consumption was significantly reduced on days 2, 3, 4, and 5 ($p < 0.01$). There was no effect of housing, however, $F(1, 20) = 0.01$, NS, and no housing × drug interaction, $F(1, 20) = 0.8$, NS, suggesting that both groups of animals were equally sensitive to the CTA produced following cocaine administration (Fig. 3a).

Nicotine. Administration of nicotine (1 mg/kg) significantly reduced saccharin intake in both isolated and enriched rats. A significant effect of both drug, $F(1, 20) = 22.1$, $p < 0.001$, and time, $F(4, 80) = 3.31$, $p < 0.05$, were observed, and post hoc analysis revealed a significant reduction in saccharin intake on days 2 and 3 ($p < 0.05$). However, the lack of effect of housing, $F(1, 20) = 0.26$, NS, and housing × drug interaction, $F(1, 20) = 1.18$, NS, suggests that both groups of rats were equally sensitive to the CTA produced following treatment with nicotine (Fig. 3b).

Alcohol. A significant effect of drug, $F(1, 20) = 11.3$, $p < 0.01$, and time, $F(4, 80) = 5.9$, $p < 0.05$, indicates that administration of alcohol (1.5 g/kg) induced a CTA in both groups of rats, and post hoc analysis showed that saccharin intake was significantly reduced on days 2 and 3 ($p < 0.05$). Further anal-

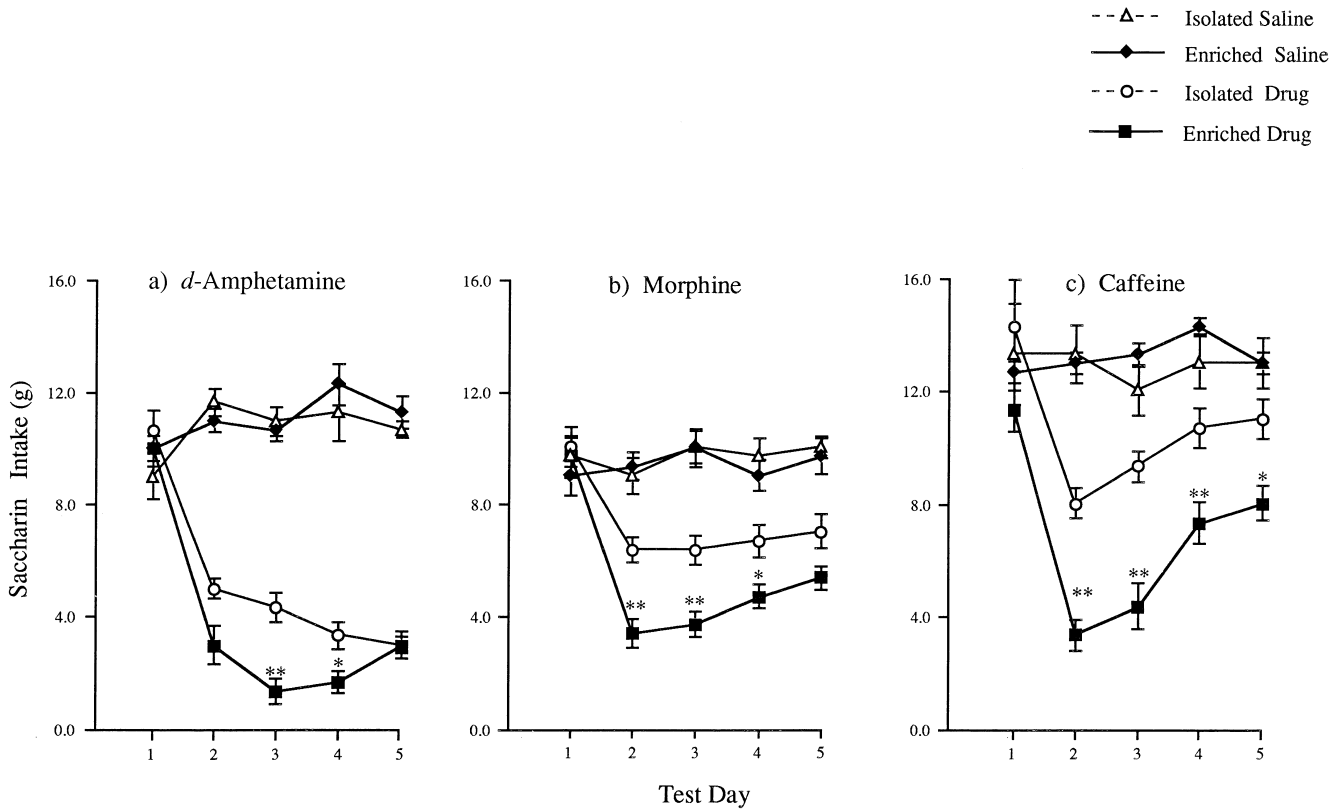

FIG. 2. (a–c) The influence of postweaning housing conditions on (a) *d*-amphetamine, (b) morphine, and (c) caffeine induced CTA. Data are expressed as the mean ± SEM ($n = 6$ per group) saccharin intake in a 20 min test. *d*-Amphetamine (2 mg/kg), morphine (10 mg/kg), caffeine (20 mg/kg), or saline vehicle were administered following the drinking period on day 1. Significant effect of housing conditions: $*p < 0.05$, $**p < 0.01$ (Dunnett's *t*-test).

ysis showed that there was no significant effect of housing; however, $F(1, 20) = 0.4$, NS, and no housing × drug interaction, $F(1, 20) = 0.12$, NS), suggesting that both groups of rats were equally sensitive to alcohol-induced CTA (Fig. 3c).

DISCUSSION

Results of the present study demonstrate that postweaning housing conditions had no influence on the CTA induced following administration of the toxic agent LiCl or the psychoactive agents cocaine, nicotine, and alcohol. In contrast, however, rats deprived of social contact from weaning had an attenuated sensitivity to the conditioned aversive effects of *d*-amphetamine, morphine, and caffeine when compared with rats reared in an enriched environment.

One potential problem with interpretation of the present results is the use of a within-subjects design. Thus, the same animals were tested repeatedly throughout this study. Primarily, it may be predicted that with the present design, repeated exposure to saccharin in the same animals would weaken the strength of an association between the conditioned stimulus CS (taste of the saccharin) and unconditioned stimulus UCS (effects of a drug). In this case, the magnitude of the CTA produced by drugs tested towards the end of the study would be expected to be greatly reduced (or undetectable) compared with those tested at the start. However, results of the present studies do not support this prediction. Thus, all drugs induced a measurable CTA, regardless of the order in which they were tested. In addition, the strength of the CTA produced by the drugs tested towards the end of the study (caffeine and alcohol) did not appear to be markedly reduced when compared with that produced by drugs tested at the beginning (*d*-amphetamine and cocaine). Therefore, it seems that the period of access to saccharin given in between each drug test to bring intakes back to baseline levels was sufficient to lose, or reduce, the previous CS-UCS association to allow for the testing of a new drug-induced CTA. Another potential problem with the reuse of animals is that the effect of rearing conditions on a particular drug-induced CTA may be influenced by previous drug–saccharin pairings. It is difficult to determine whether the interactions between drug effects and rearing conditions were indeed influenced by previous drug–saccharin pairings. However, differences between the two groups in the magnitude of the drug-induced CTA were observed regardless of the order in which the drugs were tested, for example, with *d*-amphetamine, tested first, morphine, tested third, and caffeine, tested fifth. The use of a different group of animals for testing the effects of each drug would have eliminated these potential problems with interpretation of the data and does represent the ideal situation. However, this would have meant using a very large experimental group of animals, which was not considered absolutely necessary in view of the results obtained.

Pairing administration of LiCl with the availability of a distinctive tasting solution has previously been shown to induce a CTA that is blocked by prior lesioning of the area postrema (32) as well as by administration of antiemetic agents like sco-

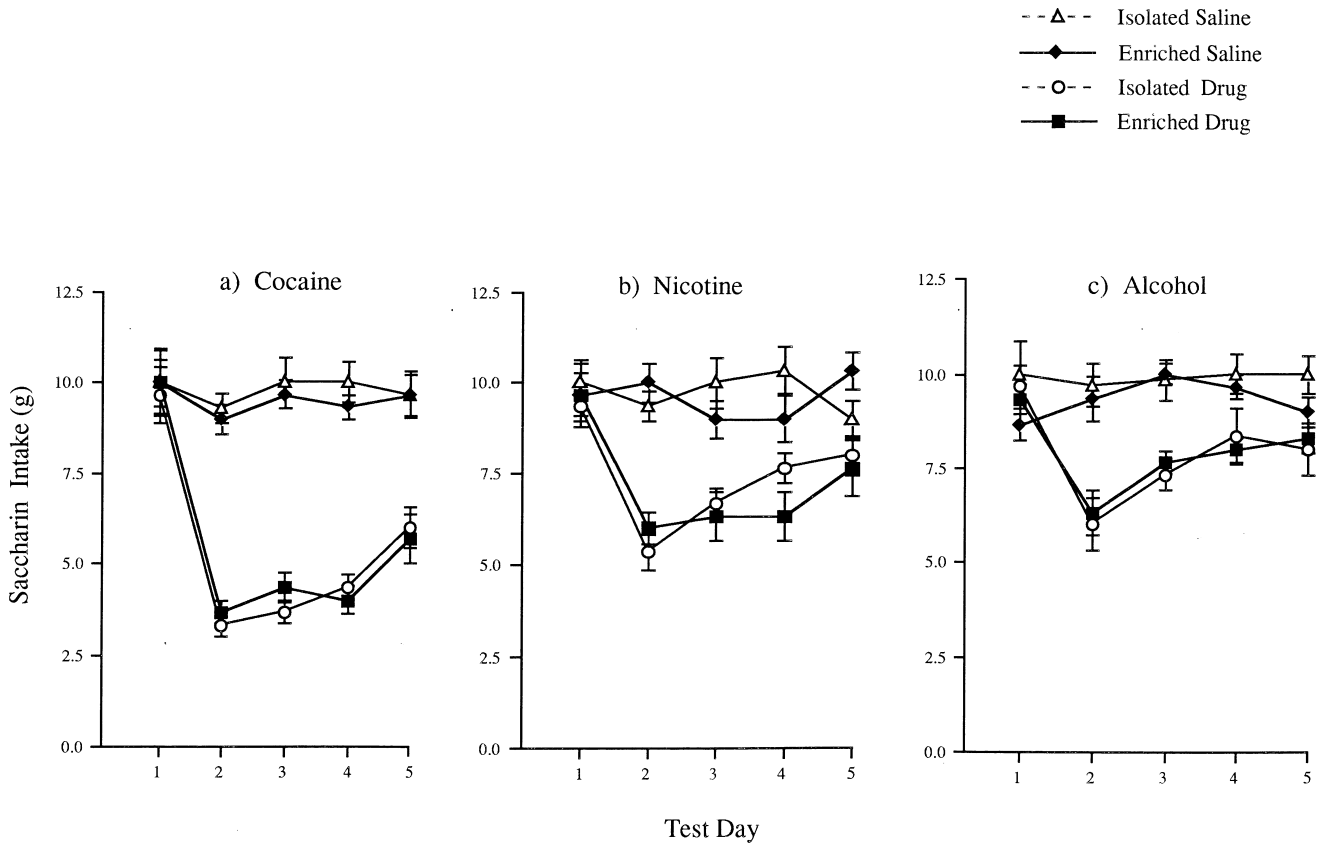

FIG. 3. (a–c) The influence of postweaning housing conditions on (a) cocaine, (b) nicotine, and (c) alcohol-induced CTA. Data are expressed as the mean ± SEM (n = 6 per group) saccharin intake in a 20 min test. Cocaine (30 mg/kg), nicotine (1 mg/kg), alcohol (1.5 g/kg), or saline vehicle were administered following the drinking period on day 1.

polamine (11). In agreement with previous studies (13), rearing conditions did not affect the CTA induced by LiCl, suggesting that postweaning housing conditions have no influence on the sensitivity of rats to the illness-inducing effects of the toxic agent LiCl. Thus, differential housing conditions may selectively alter the sensitivity of rats to the aversive properties of psychoactive drugs while having no influence on CTA produced by emetic agents, although the present study only tested one such agent. This finding further demonstrates that isolation rearing is without effect to impair this form of associative learning, in contrast to the disruptive influence of isolation rearing on other forms of learning (33). This finding is further supported by the demonstration that isolation rearing does not alter the acquisition of a stimulus reward association in conditioned reward paradigms (21,42).

Both groups of animals exhibited a significant CTA on administration of all the psychoactive agents examined in the present study. The ability of these agents to induce a CTA has been demonstrated in a number of previous studies [for review see (16)]. In contrast to the number of studies investigating the influence of rearing conditions on the reinforcing properties of drugs of abuse, only one study has previously examined the effects of social isolation on drug induced CTA, where it was found that isolated animals were less sensitive to the aversive effects of morphine (38). The present study similarly demonstrated an attenuation in sensitivity to the effects of morphine and, in addition, showed similar decreases in the extent to which a CTA was observed following administration of *d*-amphetamine and caffeine.

The demonstration that drugs that possess reinforcing properties in a number of paradigms are also active to produce a CTA at similar doses has been described as paradoxical by a number of workers. At first sight the findings of the present study appear to add to the complexity of results in this area. Thus, isolated rats have been shown to be more sensitive to the reinforcing effects of cocaine (7,35) and morphine (1,25) in self-administration tests. Similarly, they are more sensitive to the effects of *d*-amphetamine in drug discrimination (14) locomotor activity (22,42), and conditioned reward paradigms (21,42), although isolated rats have been shown to be either equally (36) or less (29) willing to self-administer *d*-amphetamine compared with socially reared rats. Therefore, isolation rearing appears to induce an enhancement in sensitivity to the reinforcing effects of morphine and amphetamine, but a reduction in sensitivity to the aversive effects of these drugs.

These results contradict the suggestion that CTA and the reinforcing effects of drugs are mediated by the same neurochemical mechanisms, but rather suggest that they may be mediated by opposing mechanisms or at anatomically distinct locations. From the data presented here, it is not possible to draw conclusions about the nature of the differential conditioned aversive and reinforcing effects of these compounds in isolated and enriched rats. Thus, further studies are required

to determine the neuroanatomical location of the CTA induced by drugs such as *d*-amphetamine in isolation-reared rats. It has been suggested that individual vulnerability to the effects of drugs of abuse may depend on a balance between the sensitivity to the aversive and the reinforcing effects of such drugs (10). In this context, results of the present study indicate that isolation-reared rats show an enhanced sensitivity to the reinforcing effects of drugs of abuse such as *d*-amphetamine and morphine, perhaps partly due to a reduced sensitivity to the aversive effects of such drugs.

In comparison with the relative consistency of results with *d*-amphetamine, isolated rats have previously been shown to be both more and less sensitive to the reinforcing effects of cocaine [see (42) for a more detailed discussion of this issue]. However, no differences in sensitivity to the aversive effects of cocaine were observed in the present study. Although this may be a dose-specific phenomenon, it seems more likely that the effects of isolation rearing on sensitivity to cocaine are less consistent and more test specific than the effects of *d*-amphetamine. However, it is important to point out that the lack of influence of rearing conditions on the CTA induced by cocaine, LiCl, nicotine, and alcohol could be a result of the dose used. Thus, if the dose tested produced a maximal effect in both groups, then enriched rats could not have shown an enhanced CTA due to a ceiling effect. Similarly, the drugs where an effect of housing was observed could have been tested at doses producing a submaximal effect. Indeed, without carrying out a dose–response study, it is difficult to properly address this issue. However, this may be an unlikely explanation, as the doses of *d*-amphetamine (2 mg/kg) and caffeine (30 mg/kg) used in the present study were high in comparison with a number of previous studies, whereas a CTA has been observed at doses of cocaine higher than that used in the present work. Therefore another explanation must be found to account for the differential effect of housing conditions on the various drug induced CTAs.

A similar lack of influence of housing conditions on sensitivity to the aversive effects of alcohol in the present study are in agreement with previous studies in our laboratory that have demonstrated a lack of effect of isolation rearing on the acquisition of alcohol self-administration in an operant paradigm (27), although further work suggested that socially reared rats were more sensitive to ethanol's reinforcing effects. The results of studies that have investigated the effects of isolation rearing on alcohol drinking in home cage choice tests have been rather inconclusive. Thus, one study showed no effect of housing conditions (23), another demonstrated an increase in ethanol ingestion in rats reared in an enriched environment (34), while another showed that isolation rearing enhanced ethanol preference (37). Therefore, as with cocaine, the influence of isolation rearing on the effects of ethanol may be inconsistent and dependent on the test conditions.

Isolation rearing led to a reduction in sensitivity to the aversive effects of caffeine, but not nicotine, in the CTA test. Because this is the first study to examine the influence of isolation rearing on sensitivity to the effects of nicotine and caffeine, it is not possible to draw comparisons between the present study and previous work. However, if the results with *d*-amphetamine and morphine are taken into consideration, it may be predicted that isolates will be more sensitive to the reinforcing properties of caffeine, but that isolation rearing will lead to a test specific effect on the sensitivity to nicotine. There is evidence to suggest that the reinforcing and aversive properties of caffeine are mediated by separate mechanisms (9); therefore, an enhanced sensitivity of isolated rats to the reinforcing effects would lend further support to the idea that sensitivity to the aversive effects of drugs in isolation-reared rats is inversely related to sensitivity to their reinforcing effects.

As a result of the necessitated reuse of animals, rats were repeatedly exposed to nondrug-paired presentations of the saccharin solution during the test procedure. Thus, differences observed in the present study may reflect alterations in latent inhibition rather than differences in sensitivity to the aversive effects of drugs. However, this explanation seems unlikely in view of previous research demonstrating that isolated animals show no differences in the development of latent inhibition, although conditioned suppression was retarded in isolated rats (45).

Drugs of abuse increase dopamine transmission in the nucleus accumbens (12), although nicotine, caffeine, and morphine do not release dopamine to the same extent as cocaine and *d*-amphetamine (2). Acute stressors such as foot shock and restraint stress also increase dopamine release in the nucleus accumbens (20), while conditioned stimuli predictive of aversive events have been shown to exert the opposite effect, i.e., to reduce extracellular levels of dopamine in the nucleus accumbens (24). Thus, alterations in mesolimbic dopamine activity appear to be involved in the response to both aversive and appetitive stimuli. The dopaminergic system is also involved in drug induced CTA, and a number of studies have shown that dopaminergic manipulations disrupt the CTA developed following administration of psychoactive drugs (3,19,41). Postweaning social isolation has been shown to enhance mesolimbic dopaminergic function (22) and isolated rats exhibit behavioral changes consistent with enhanced mesolimbic dopaminergic function (42). Therefore, it is possible that the altered mesolimbic dopamine function demonstrated in isolated animals is involved in the mediation of the sensitivity of rats to the aversive effects of certain psychoactive agents. However, if altered mesolimbic dopamine function in isolated rats is the sole reason for the differential sensitivity to drugs of abuse, it is unclear why sensitivity to the effects of *d*-amphetamine often differ from cocaine, because these two psychostimulant agents have very similar effects on dopamine release in the nucleus accumbens (2). Thus, although it seems likely that the mesolimbic dopamine system is involved in the reduced sensitivity of isolated rats to the aversive effects of morphine, *d*-amphetamine, and caffeine, the exact nature of this relationship is unclear from the present results, and further work is needed to investigate this issue more specifically.

In conclusion, results of the present study indicate that postweaning social isolation can reduce the sensitivity of rats to the aversive effects of some psychoactive agents. Thus, while isolated and enriched rats showed no differences in sensitivity to alcohol, nicotine, and cocaine, enriched rats were more sensitive to the aversive effects of *d*-amphetamine, morphine, and caffeine. Further investigation into the relationship between rearing conditions and sensitivity to the aversive and reinforcing effects of psychoactive drugs is likely to enhance our understanding of the role of environmental factors in predisposition to drug addiction.

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