Pharmacology Biochemistry and Behavior, Vol. 66, No. 2, pp. 435–441, 2000

0091-3057/00/$–see front matter

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PII S0091-3057(00)00244-6

Importance of Environmental Context in the Development of Amphetamine- or Apomorphine-Induced Stereotyped Behavior After Single and Multiple Doses

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Received 09 July 1999; Revised 04 November 1999; Accepted 28 November 1999

BATTISTI, J. J., N. J. URETSKY AND L. J. WALLACE. *Importance of environmental context in the development of amphetamine- or apomorphine-induced stereotyped behavior after single and multiple doses.* PHARMACOL BIOCHEM BEHAV **66**(2) 435–441, 2000.—The present study was designed to determine whether single and repeated pretreatment regimens with amphetamine or apomorphine differ in the context-dependency of sensitization of stereotyped behavior. Male CF-1 mice that were pretreated with a single high dose of amphetamine (14 mg/kg intraperitoneally [IP]) or apomorphine (40 mg/kg subcutaneously [SC]) only became sensitized to a lower test dose of amphetamine (7 mg/kg IP) or apomorphine (3 mg/kg SC) when placed in an environment that was the same as the pretreatment environment. However, animals pretreated with 3 high doses (24-h apart) of amphetamine (14 mg/kg IP) or apomorphine (40 mg/kg SC) did demonstrate sensitization to a lower test dose of amphetamine (7 mg/kg IP) or apomorphine (3 mg/kg SC) when placed in an environment that was different from the pretreatment environment. Context-dependent sensitization, but not context-independent sensitization, was extinguished by pairing the test environment with saline injections instead of drug injections. In addition, it was determined that neither sensitization model could be related to pharmacokinetic factors. Therefore, the results indicate that repeated exposure to amphetamine or apomorphine overcomes the context-dependent component of sensitization of amphetamine- or apomorphine-induced stereotyped behavior. © 2000 Elsevier Science Inc.

Amphetamine Apomorphine Stereotyped behavior

THE INTENSITY of locomotor activity and stereotyped behavior elicited by psychostimulant drugs, such as amphetamine and cocaine, and their potency in stimulating these effects can be augmented following exposure to one high dose or repeated administration of a drug, a phenomenon termed sensitization (4,6,14). Sensitization has been studied using a wide variety of paradigms including pretreatment with many low doses of drug, pretreatment with a single high dose of drug, varying the time intervals between pretreatment and testing, and varying the environmental settings (4,6,10,13,15,16,21). Comparisons of different experimental paradigms suggest that sensitization is influenced by a complex interplay of many factors, which may vary depending on the particular paradigm employed (18).

Several studies have addressed the role of environmental setting on sensitization. One question regarding the role of environment is whether multiple exposures to drug in a particular setting engenders an association between the drug and the environment that becomes capable of producing a conditioned response in the absence of drug. Taken together, these studies suggest that conditioning generally occurs and contributes to the sensitized response (17,18). Another question

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This study was supported by NIH grant DA10469. J.J.B. was supported in part by a predoctoral fellowship from the American Foundation for Pharmaceutical Education and NIH Training Grant MH19936.

is whether novelty influences the development and expression of sensitization. The general conclusion from these studies appears to be that drug administration in a novel environment enhances the development of sensitization (18). Thus the optimum condition for development of sensitization is drug experience in an environment different from the "home" setting, whereas optimum condition for the expression of sensitization is drug test in the same environment in which drug has previously been experienced. In addition, a theme that seems to be developing from a variety of studies is that the role of environment is greatest with protocols involving low doses of drugs or few drug administrations and is least with protocols involving high doses of drugs or many drug administrations (2).

The majority of papers addressing the questions mentioned above have studied sensitization of drug-induced locomotor activity responses. We have recently addressed the role of environmental setting on sensitization using a protocol in which sensitization of stereotyped behavior elicited by either amphetamine or apomorphine was developed using a single high-dose pretreatment of drug (4,5). This sensitization was documented to be context-dependent in that the sensitized response was only observed when the test was performed using an environment similar to that used for the pretreatment. In the present study, we address the question of whether the role of environment on sensitization of drug-induced stereotyped behavior is lessened when multiple doses of amphetamine or apomorphine are used in the pretreatment. The results support this concept. With both a context-dependent and a context-independent model of sensitization established, we evaluated the role of environmental conditioning in each sensitization model by determining whether sensitization can be extinguished by pairing the test environment with saline injections instead of drug injections. In addition, studies were performed to determine whether sensitization in each model was persistent as well as whether the expression of sensitization could be related to pharmacokinetic factors. Both amphetamine, which acts presynaptically to increase dopamine transmission, and apomorphine, which directly activates dopamine receptors, were studied to determine whether the sensitization models were mediated by a presynaptic or postsynaptic mechanism.

METHOD

Animals and Drugs

Male CF-1 mice (Charles River Laboratories), weighing 28 to 32 g at the time of experimentation, were housed 5 per cage in a temperature (24° ± 1°C) and humidity (55% to 65%) controlled vivarium with a 12-h light/dark cycle. Food and water were provided ad libitum. All animal use procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Laboratory Animal Care and Use Committee. D-amphetamine sulfate and R(-)-apomorphine HCl were obtained from Sigma Chemicals Co. (St. Louis, MO, USA) and were prepared in normal saline (amphetamine) or distilled water with 0.1% ascorbic acid (apomorphine) immediately prior to administration. Dosages were calculated as mg of amphetamine sulfate or apomorphine HCl/kg body weight and were given intraperitoneally (IP) amphetamine or subcutaneously (SC) apomorphine in a volume of 0.1 ml/20 g of body weight.

Evaluation of Stereotyped Behavior

All animals were evaluated for stereotyped behavior after amphetamine, apomorphine, or vehicle pretreatment and after amphetamine or apomorphine challenge during the test phase. The individual who evaluated the behavior was unaware of which mice received amphetamine, apomorphine, or vehicle. As described previously (6,11), the stereotyped behavioral response of the CF-1 mouse is well-defined with the mouse remaining stationary and exhibiting rapid, repetitive head and/or fore-limb movements. This behavior corresponds to a score of 8 on a graded score of 9 in the behaviors described by Ellinwood and Balster (8). After drug injection, mice were then placed one per cage (amphetamine) or three per cage (apomorphine) and were observed for 1-min at 10-min intervals. Mice were scored positive for stereotyped behavior when this behavior was exhibited for greater than 30 sec of a 1-min observation period. Group data are expressed as the percentage of mice rated as positive for stereotyped behavior. It was previously shown that amphetamine produces a peak stereotyped behavioral effect between 30 to 50 min after administration (4) and apomorphine between 20 to 40 min after administration (5). The percentage of mice exhibiting stereotyped behavior at the peak effect was used as the measure of the stereotyped behavioral response to drug. All studies were conducted between 10.00 and 16.00 h in a temperature (24 ± 1°C) and humidity (55% to 65%) controlled room. Animals were used in only one experiment.

Design and Procedures

Effect of Varying the Number of Amphetamine or Apomorphine Pretreatments on the Role of Environmental Context in Sensitization. For both amphetamine and apomorphine, 120 mice were divided into two groups called test:test (40 mice) and diff:test (80 mice). The diff:test group was further subdivided such that one group received 1 pretreatment injection (for amphetamine experiment: vehicle or 14 mg/kg amphetamine; for apomorphine experiment: vehicle or 40 mg/kg apomorphine), whereas the second group received 3 pretreatment injections (for amphetamine experiment: vehicle or 14 mg/kg amphetamine daily for 3 days; for apomorphine experiment: vehicle or 40 mg/kg apomorphine daily for 3 days). Mice in the test:test and diff:test groups were transported from the vivarium to the laboratory; administered amphetamine, apomorphine, or vehicle; and placed into either the test cages (test:test group) or cages that were different from the test cages (diff:test group). The test cages measured 28 × 17 × 11 cm and contained tan corncob bedding (Harlan Teklad, Madison, WI, USA), whereas the "diff" cages were larger in size than the test cages (50 × 25 × 30 cm) and contained black colored bedding (black Cellu-Dri-Shepherd Specialty Papers, Kalamazoo, MI, USA) with a different texture than the tan corncob bedding of the test cages. The differences between pretreatment and test environments are shown in Table 1. After 120 min (amphetamine and vehicle) or 90 min (apomorphine and vehicle), all mice were returned to their home cages in the vivarium. The test phase of the experiment was performed 3 and 14 days after pretreatment. All mice were transported from the vivarium to the laboratory, administered amphetamine (7 mg/kg) or apomorphine (3 mg/kg), placed into the test cages containing the tan corncob bedding, and evaluated for stereotyped behavior.

TABLE 1

EXPERIMENTAL GROUPS FOR STUDIES ON SENSITIZATION INDUCED BY AMPHETAMINE AND APOMORPHINE. SIZES ARE IN cm. SHAPES WITH NO FILL CORRESPOND TO CAGES WITH TAN CORNCOB BEDDING, WHILE SHAPES WITH FILL CORRESPOND TO CAGES WITH BLACK CELLU-DRI BEDDING

	Pretreatment Cage			Test Cage		
Paradigm	Location	Size	Shape	Location	Size	Shape
test:test	lab	28 × 17 × 11	□	lab	28 × 17 × 11	□
diff:test	lab	50 × 25 × 30	■■	lab	28 × 17 × 11	□

Effect of Varying the Number of Amphetamine or Apomorphine Pretreatments on the Extinction of Sensitization. For both amphetamine and apomorphine, 80 mice were divided into two groups of 40 mice each. One group received 1 pretreatment injection (for amphetamine experiment: vehicle or 14 mg/kg amphetamine; for apomorphine experiment: vehicle or 40 mg/kg apomorphine) in the test cage and the other group received 3 pretreatment injections (for amphetamine experiment: vehicle or 14 mg/kg amphetamine daily for 3 days; for apomorphine experiment: vehicle or 40 mg/kg apomorphine daily for 3 days) in the "diff" cage. After 120 min (amphetamine) or 90 min (apomorphine), all mice were returned to their home cages in the vivarium. Seventy-two hours after pretreatment, mice were administered the challenge dose of amphetamine (7 mg/kg) or apomorphine (3 mg/kg), placed in the test cage, and evaluated for stereotyped behavior. Animals were then subjected to an extinction schedule. All mice injected with amphetamine on day 3 were injected daily for 6 days with normal saline and placed in the test cage for 2 h after each injection. Similarly, all mice injected with apomorphine on day 3 were injected daily with normal saline for 12 days and placed in the test cage for 1.5 h after each injection. On day 10 (amphetamine) or day 16 (apomorphine), mice were again administered the challenge dose of amphetamine or apomorphine, placed in the test cage, and evaluated for stereotyped behavior.

Brain Concentrations of Apomorphine

In the first study, twenty-four mice were injected with 1 dose (40 mg/kg) or 3 doses of apomorphine (40 mg/kg daily × 3 days), and brain concentrations of apomorphine were determined 1, 2, or 10 h later. In the second study, forty-eight mice were pretreated with 1 dose of either vehicle or apomorphine (40 mg/kg) or 3 doses of either vehicle or apomorphine (40 mg/kg daily × 3 days) and placed in the test cages (1 dose group) or diff cages (3 dose group) for 90 min after each administration before being returned to their home cages. Three days later, all mice were injected with apomorphine, 3 mg/kg, and placed in test cages. The brain apomorphine concentrations were determined at 10, 20 and 30 min after apomorphine administration according to the method of Von Voigtlander et al. (20) with minor modifications. Mice were euthanized, and their brains rapidly removed and homogenized in 2.0 ml 0.4 N perchloric acid. After centrifugation (1600 × g for 15 min) and decantation of the supernatant, 2.0 ml of reagent grade ethyl acetate were added to each tube. Each sample was mixed for 30 sec in a vortex mixer and centrifuged (1600 × g for 15 min). The organic phase was placed in a spectrofluorometer (Aminco-Bowman) with an excitation wavelength of 282 nm and an emission wavelength of 379 nm. When apomorphine was added to a brain homogenate from control mice to test for recovery, 100% of the apomorphine was extracted into the ethyl acetate fraction.

Statistics

The percentage of mice in different experimental groups that exhibited stereotyped behavior was compared by Chi-square analysis. The Fisher Exact test was used whenever 20% of the expected values in a contingency table were less than 5. Brain concentrations of apomorphine were compared using a two way ANOVA with a least significant difference post hoc analysis. For all tests, $p < 0.05$ was considered significant.

RESULTS

Effect of Varying the Number of Amphetamine or Apomorphine Pretreatments on the Role of Environmental Context in Sensitization: One-Dose Models. Mice were pretreated with one dose of vehicle or amphetamine (14 mg/kg) or one dose of vehicle or apomorphine (40 mg/kg), placed in either the test environment (test:test group) or in an environment that was markedly different from the test environment (diff:test group), and evaluated for stereotyped behavior. The difference in the pretreatment environments did not affect the acute stereotyped behavioral response to the 14 mg/kg amphetamine or 40 mg/kg apomorphine pretreatment (data not shown). Three and 14 days later, mice were administered the test dose of amphetamine (7 mg/kg) or apomorphine (3 mg/kg), placed in the test cage, and evaluated for stereotyped behavior. Only mice in the test:test group exhibited a sensitized stereotyped behavioral response (Figs. 1 and 2). When the pretreatment and test environments differed in terms of physical characteristics, such as cage size and the color and texture of animal bedding (diff:test group), mice pretreated with one dose failed to exhibit a sensitized response to either amphetamine or apomorphine (Figs. 1 and 2). Because the environmental context in which amphetamine or apomorphine was administered was critical for sensitization, this one-dose model is termed context-dependent.

Effect of Varying the Number of Amphetamine or Apomorphine Pretreatments on the Role of Environmental Context in Sensitization: Three-Dose Models. Mice were pretreated with 3 doses of vehicle or amphetamine (14 mg/kg daily × 3 days) or 3 doses of vehicle or apomorphine (40 mg/kg daily × 3 days), placed in an environment that was markedly different from the test environment (diff:test group), and evaluated for stereotyped behavior. The variation in the pretreatment environment did not affect the acute stereotyped behavioral response to the 14 mg/kg amphetamine or 40 mg/kg apomor-

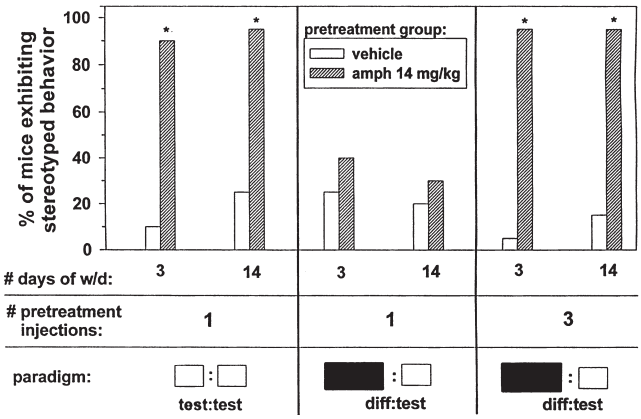

FIG. 1. The effect of varying the number of amphetamine (amph) pretreatments on the role of environmental context in sensitization. Mice were pretreated with 1 dose of vehicle or amphetamine (14 mg/kg) or 3 doses of vehicle or amphetamine (14 mg/kg daily × 3 days) and placed into either the test or diff environment. Three and 14 days later, a challenge dose of amphetamine (7 mg/kg) was administered and the mice were observed in the test environment. Each bar represents a group of 20 mice. *Significantly different from vehicle control as determined by Chi-square analysis ($p < 0.05$). w/d = withdrawal.

phine pretreatments (data not shown). Three and 14 days later, the mice were tested for sensitization after the administration of the test dose of amphetamine (7 mg/kg) or apomorphine (3 mg/kg) in the test cage. In contrast to the one-dose model of sensitization, when the pretreatment and test environments differed in terms of physical characteristics, such as cage size and the color and texture of animal bedding (diff:test group), mice exhibited a sensitized response to amphetamine or apomorphine (Figs. 1 and 2). Because the environmental context in which amphetamine or apomorphine

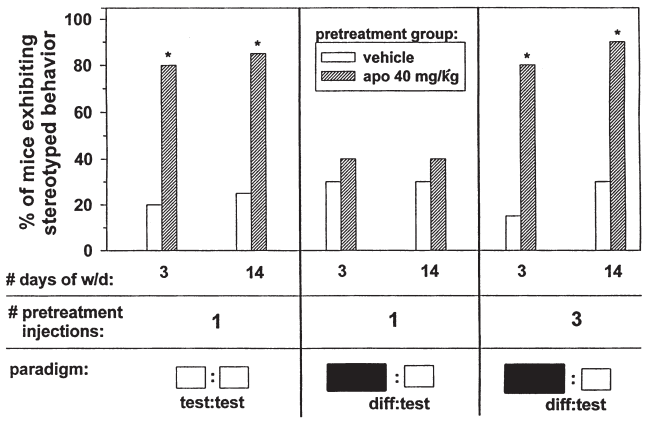

FIG. 2. The effect of varying the number of apomorphine (apo) pretreatments on the role of environmental context in sensitization. Mice were pretreated with 1 dose of vehicle or apomorphine (40 mg/kg) or 3 doses of vehicle or apomorphine (40 mg/kg daily × 3 days) and placed into either the test or diff environment. Three and 14 days later, a challenge dose of apomorphine (3 mg/kg) was administered and the mice were observed in the test environment. Each bar represents a group of 20 mice. *Significantly different from vehicle control as determined by Chi-square analysis ($p < 0.05$). w/d = withdrawal.

was administered was not critical for sensitization, this three-dose model is termed context-independent.

Effect of Varying the Number of Amphetamine or Apomorphine Pretreatments on the Extinction of Sensitization: One- and Three-Dose Models.

Mice, pretreated with one dose of amphetamine (14 mg/kg) or 3 doses of amphetamine (14 mg/kg daily × 3 days), exhibited sensitization after receiving the test dose of amphetamine 3 days after the pretreatment phase. For the extinction phase, mice were injected with normal saline and placed in the testing cages daily for 6 days. On the next day (day 10 of withdrawal), mice were injected with amphetamine (7 mg/kg) and placed in the test cage for evaluation of stereotyped behavior. Mice that were pretreated once with amphetamine in the test environment (context-dependent sensitization) failed to demonstrate a sensitized response to the test dose of amphetamine (Fig. 3). In contrast, mice that were pretreated with three-doses of amphetamine in an environment different from the test environment (context-independent sensitization) were still sensitized (Fig. 3).

Similarly, mice pretreated with one dose of apomorphine (40 mg/kg) or 3 doses of apomorphine (40 mg/kg daily × 3 days) were administered the test dose of apomorphine 3 days after the pretreatment phase and were sensitized. For the extinction phase, all mice were treated with saline and placed in the test cages. In preliminary studies, it was found that after a 6-day extinction phase, both groups of mice exhibited the sensitized response (data not shown). As a result, in the current experiment, the extinction phase was lengthened to 12 days. At the end of the extinction phase (day 16 of withdrawal), the mice that were pretreated once with apomorphine in the test environment (context-dependent sensitization) failed to demonstrate a sensi-

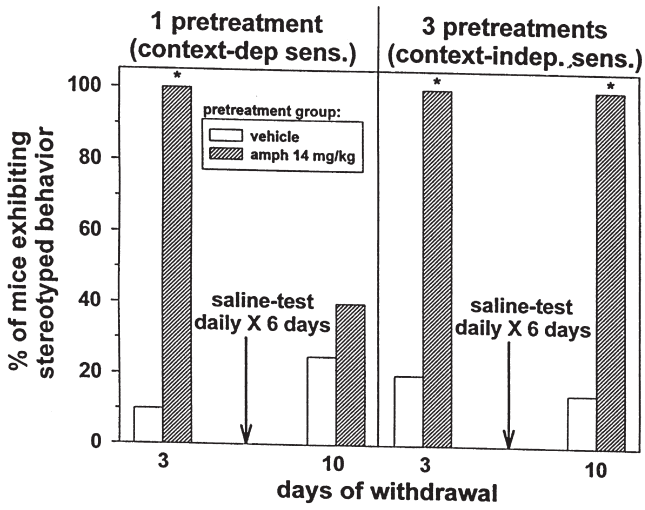

FIG. 3. The effect of varying the number of amphetamine (amph) pretreatments on the extinction of sensitization. Mice were pretreated with 1 dose of vehicle or amphetamine (14 mg/kg) or 3 doses of vehicle or amphetamine (14 mg/kg daily × 3 days). On day 3 of withdrawal, mice were administered a challenge dose of amphetamine (7 mg/kg). Following a 6-day extinction phase, in which mice received daily saline injections in the test cage, mice were again administered a challenge dose of amphetamine (day 10). Each bar represents a group of 20 mice. *Significantly different from vehicle control as determined by Chi-square analysis ($p < 0.05$).

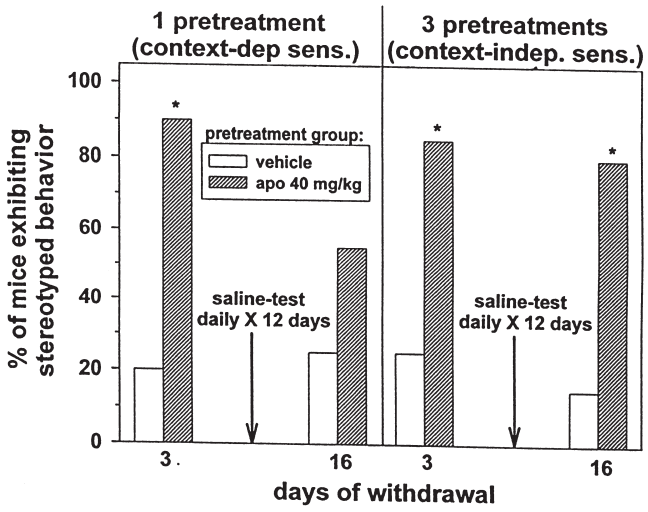

FIG. 4. The effect of varying the number of apomorphine (apo) pretreatments on the extinction of sensitization. Mice were pretreated with 1 dose of vehicle or apomorphine (40 mg/kg) or 3 doses of vehicle or apomorphine (40 mg/kg daily × 3 days). On day 3 of withdrawal, mice were administered a challenge dose of apomorphine (3 mg/kg). Following a 12-day extinction phase, in which mice received daily saline injections in the test cage, mice were again administered a challenge dose of apomorphine (day 16). Each bar represents a group of 20 mice. *Significantly different from vehicle control as determined by Chi-square analysis ($p < 0.05$).

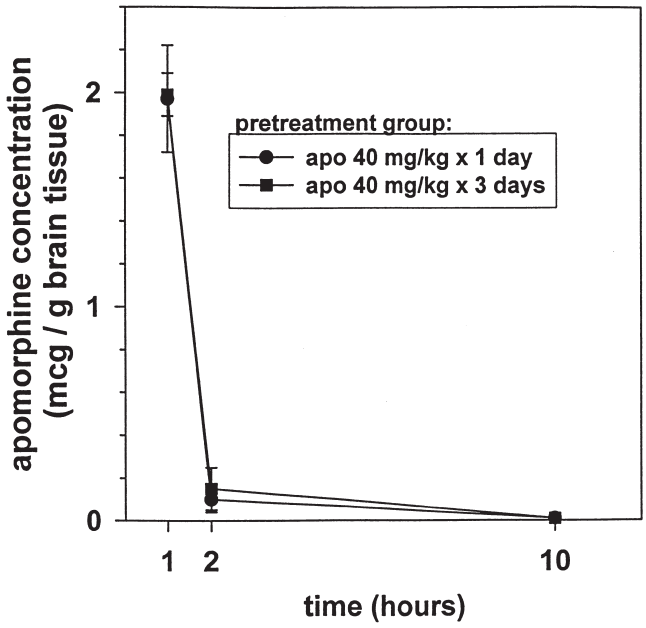

FIG. 5. Mean concentrations of apomorphine (apo) in the mouse brain 1, 2, or 10 h after 1 dose of apomorphine (40 mg/kg) or after the last of 3 doses of apomorphine (40 mg/kg daily × 3 days). Each point represents the mean ± SEM from a group of 4 mice.

tized response, whereas mice that were pretreated with three doses of apomorphine in an environment different from the test environment (context-independent sensitization) maintained their sensitized response (Fig. 4).

Apomorphine Brain Concentrations

In order to determine whether context-dependent or context-independent sensitization can be attributed to pharmacokinetic changes, brain apomorphine concentrations were determined. Only a trace amount of apomorphine could be detected 10 h after the administration of one 40 mg/kg dose of apomorphine (context-dependent sensitization) or after the last administration of 3 doses of apomorphine (40 mg/kg daily × 3 days; context-independent sensitization) (Fig. 5). In addition, the brain concentrations of apomorphine between 10 to 30 min after administration of the test dose of apomorphine (3 mg/kg) were not greater in mice pretreated once with apomorphine (40 mg/kg), once with vehicle, 3 times with apomorphine (40 mg/kg daily × 3 days), or 3 times with vehicle (daily × 3 days) (Fig. 6).

DISCUSSION

The results demonstrate that sensitization of the stereotyped behavioral response elicited by amphetamine or apomorphine is expressed after pretreatment with either one or three doses of these drugs. However, constancy between the pretreatment and test environments is only crucial for the sensitization that develops after a single dose of amphetamine or apomorphine. This study is consistent with the hypothesis that environmental factors are most important in sensitization when the number of exposures is minimal. One other study has directly compared the interaction between environment and the number of pretreatment drug experiences producing sensitization. Post et al. (15) observed that pre-exposure to three high doses of cocaine produced a context-independent sensitization of locomotor activity, whereas sensitization resulting from exposure to a single high dose pretreatment was con-

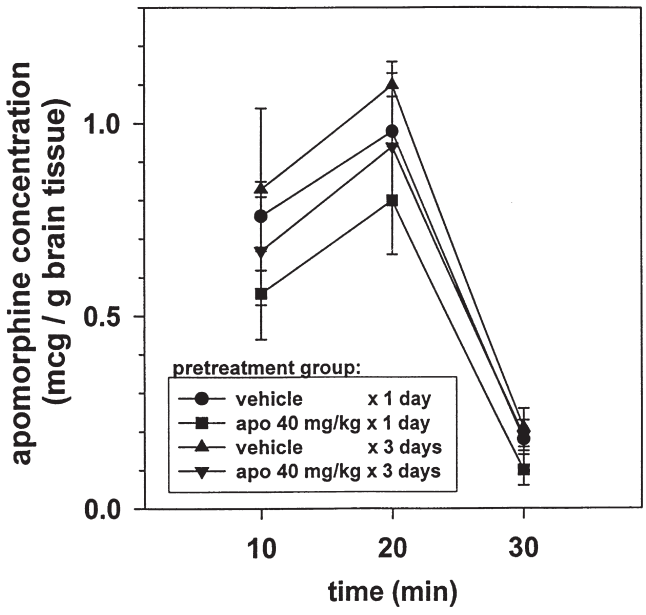

FIG. 6. Mean concentrations of apomorphine (apo) in the mouse brain 10 to 30 min after challenge with 3 mg/kg of apo. Mice were pretreated 3 days earlier with 1 dose of vehicle or apomorphine (40 mg/kg), or after the last of 3 doses of vehicle or apomorphine (40 mg/kg daily × 3 days). Each point represents the mean ± SEM from a group of 4 mice.

text-dependent. Thus the results of this and the present study suggest that the mechanism of development and/or expression of sensitization of the effects of amphetamine and apomorphine are different for the one- and three-dose pretreatment regimens. These observations suggest that a single administration of these drugs induces changes in the brain such that the drugs elicit intensified behavioral responses under appropriate environmental conditions. When an animal then receives subsequent drug administrations, additional brain changes occur such that the intensified behavioral responses can be manifested under less restrictive environmental conditions.

The requirement of constancy between pretreatment and test environments for the manifestation of sensitization after one pretreatment dose suggests that environmental cues are associated with the expression of sensitization. This leads to the hypothesis that pairing of the environmental cues with a saline injection might weaken this association, leading to extinction of sensitization. According to this hypothesis, sensitization exhibited after a single dose of amphetamine or apomorphine, but not after three doses of amphetamine or apomorphine, should be extinguished by repeatedly administering saline in the test cages instead of amphetamine or apomorphine. The results show that sensitization of amphetamine-induced stereotyped behavior that developed after a single injection of amphetamine could be completely extinguished after six daily injections of saline in the test cages. Similarly, sensitization of apomorphine-induced stereotyped behavior that developed after a single injection of apomorphine could be extinguished after 12 daily injections of saline in the test cages. This is in contrast to several extinction studies reported in the sensitization literature. The most robust previously reported extinction of sensitized drug-induced activities appears to be a 60% decrement in the amount of time that sensitized rats spent in stereotypy after cocaine administration (9). Other work measuring locomotor activity or circling behavior showed more modest effects of extinction (1) or no effect at all (2,7,19). All of these studies showing modest or no extinction, along with the experimental group in our study where extinction was not observed, have in common the fact that multiple drug administrations were used in the sensitization paradigm. Thus it would appear that sensitization elicited by a single drug administration can be extinguished. However, multiple drug administrations induce a transition to a state in which sensitization cannot be extinguished.

Neither context-dependent nor context-independent sensitization appeared to be due to pharmacokinetic factors, because 10 h after pretreatment only a trace of apomorphine remains in the brain in either model. Moreover, no pretreatment regimen altered brain levels of apomorphine following a test dose. Both results are in agreement with our previous results on context-dependent sensitization induced by apomorphine (5). Although we did not assay for amphetamine brain concentrations, Badiani et al. (3) showed no differences in plasma or striatal levels of amphetamine in their sensitization paradigms. Also, the half-life for amphetamine is 29 min in the plasma and 53 min in the striatum (12), and the maximum stereotyped behavioral response occurs 30 to 50 min after pretreatment and returns to baseline 110 min after pretreatment. Therefore, the washout of amphetamine after pretreatment should have been completed during our 72-h withdrawal period.

In our experiments, the characteristics of sensitization induced by the indirect acting dopamine agonist, amphetamine, and by the direct acting dopamine agonist, apomorphine, were indistinguishable. Therefore, we hypothesize that postsynaptic mechanisms may be more important than presynaptic mechanisms in mediating both context-dependent and context-independent sensitization of drug-induced stereotyped behavior in mice.

Many studies have demonstrated a relationship between the environmental context of drug administration and the development of sensitization (18). In general, these studies support the conclusion that the environment is most important when the sensitizing paradigm uses few exposures to high doses of drugs. Our results strongly support this concept. Taken further, our results have interesting implications relative to the problem of drug abuse. If the human experience is such that a transition occurs to environmentally independent sensitization that can not be extinguished by classical extinction procedures, this could be an important criterion for drug addiction. Furthermore, this observation would suggest that in these situations the sensitized state could persist for long periods of time. Thus future comparisons of the context-dependent and context-independent models of sensitization, established in this study, may be useful for examining the neurobiologic mechanisms involved in environment-induced drug craving and relapse and for screening possible pharmacological treatments for drug addiction.

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