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Sensitization of Stereotyped Behavior to Amphetamine Is Context and Response Dependent

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BATTISTI, J. J., C.-H. CHANG, N. J. URETSKY AND L. J. WALLACE. *Sensitization of stereotyped behavior to amphetamine is context and response dependent.* PHARMACOL BIOCHEM BEHAV **63**(2) 263–269, 1999.—The present study was designed to determine whether the environmental context in which amphetamine is administered plays a role in the development of sensitization to the stereotyped behavioral effects of amphetamine in mice. In male CF-1 mice, the dose–response curve for stereotyped behavior elicited by amphetamine was shifted 1.9-fold to the left 48 h after pretreatment with 14 mg/kg amphetamine. Behavioral sensitization only developed in mice that were pretreated in the same or a similar environment as that of the test environment. In addition, when mice were placed in an environment that attenuated the acute expression of stereotyped behavior elicited by the pretreatment dose of amphetamine, sensitization never developed. A further experiment showed that 96% of the mice that expressed stereotypy after the ED_{50} pretreatment dose of 10 mg/kg amphetamine showed a stereotyped behavioral response to the lesser dose of 7 mg/kg 48 h later, indicating sensitization. In contrast, mice that did not express stereotypy after the ED_{50} dose of amphetamine failed to show a significant stereotyped behavioral response to amphetamine challenge compared to vehicle-pretreated controls. Therefore, the results indicate that preexposure to a single high dose of amphetamine produces context- and response-dependent sensitization to amphetamine-induced stereotyped behavior. © 1999 Elsevier Science Inc.

Sensitization Amphetamine Stereotypy Mice

THE administration of amphetamine to rodents produces two qualitatively different effects on psychomotor behavior. Amphetamine administered in low doses produces primarily locomotor stimulation, while higher doses produce a repetitive stereotyped behavioral response that interferes with locomotion (29,30). This stereotyped behavioral response is expressed in rodents as focused and continuous repetitive head and forelimb movements. Both amphetamine-induced locomotor stimulation and stereotyped behavior are mediated by an increase in dopamine neurotransmission, but these effects are due to an action of amphetamine at different brain sites. The locomotor stimulatory effects of amphetamine are mediated primarily by its action in the nucleus accumbens, while the stereotyped behavioral response appears to be related to an action of amphetamine in the striatum (7,17,31).

The repeated administration of amphetamine can produce a persistent sensitization to both locomotor activity and stereotyped behavior (15,27,29). Recent studies have shown that the development of sensitization to the locomotor stimulant effects of amphetamine is strongly influenced by the environmental context in which amphetamine is administered (1,4, 8,14). Sensitization to locomotor activity will not develop or will be reduced when the environment used for the testing of sensitization is different from that in which rats are pretreated. In contrast to studies on locomotor activity, there is relatively little information on the importance of the environment in the development of sensitization to the stereotyped behavioral effects of amphetamine. Therefore, it is unclear whether the development of sensitization to stereotyped behavior induced by amphetamine, like the locomotor stimulant effects, is subject to environmental control. Because context-dependent sensitization has been postulated to play an important role in psychostimulant craving and relapse, a greater understanding of context and conditioning effects may provide

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insight into factors and neurobiological mechanisms important in drug abuse (28).

The purpose of this study was to determine whether the environmental context in which amphetamine is administered plays a role in the development of sensitization to the stereotyped behavioral effects of amphetamine in mice. To accomplish this goal, mice were pretreated with amphetamine and then placed in an environment that was the same as or different from that used for evaluating the stereotyped behavioral response to amphetamine in testing for sensitization. The results show that the environment is important in the development of sensitization to stereotyped behavior induced by amphetamine. In addition, our results provide evidence that the acute expression of stereotyped behavior after amphetamine pretreatment is also important for the subsequent development of sensitization to the stereotyped behavioral effects of amphetamine.

TABLE 1
EXPERIMENTAL GROUPS FOR SENSITIZATION STUDIES

Paradigm Name	Pretreatment Cage			Test Cage	
	Novelty*	Size	Shape	Size	Shape
test:test	Y	28 x 17 x 11	□	28 x 17 x 11	□
large:test	Y	42 x 41 x 20	□	28 x 17 x 11	□
diff:test	Y	50 x 25 x 30	▨	28 x 17 x 11	□
home:test	N	29 x 21 x 14	□	28 x 17 x 11	□

*A "Y" indicates that the pretreatment cage was different from the home cage, while a "N" indicates that pretreatment was in the home cage.

METHOD

Animals and Drugs

Male CF-1 mice (Charles River Laboratories), weighing 28–32 g at the time of experimentation, were housed five per cage (except the home:test group, which were housed one per cage) in a temperature- and humidity-controlled vivarium with a 12 L:12 D cycle. Food and water were provided ad lib. All animal use procedures were performed in strict 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 was obtained from Sigma Chemicals Co. (St. Louis, MO) and was prepared in normal saline solution immediately prior to administration. Dosages were calculated as milligrams of amphetamine sulfate/kg body weight, and were given intraperitoneally in a volume of 0.1 ml/20 g of body weight.

Experimental Procedures

Drug-associated environmental conditions. All experiments consisted of a pretreatment phase in which the environment associated with the administration of amphetamine was varied, followed 48 h later by a test phase in which the environment was held constant. In the pretreatment phase, animals were transported from the vivarium to the laboratory (except for the home:test group, in which animals were pretreated in the vivarium), administered amphetamine, or vehicle (normal saline), and placed individually into one of four different cages. Animals were monitored for 2 h and then returned to the vivarium. On the test day, all animals were transported from the vivarium to the laboratory, administered amphetamine, and placed individually into identical test cages whose dimensions were $28 \times 17 \times 11$ cm, and which contained 1/4″ tan corncob bedding (Harlan Teklad, Madison, WI). The differences between pretreatment and test environments are shown in Table 1. Thus, for the test:test group, there were no differences between the pretreatment and the test environment. For the large:test group, the only difference between the pretreatment and the test environment was the size of the cages. For the diff:test group, the pretreatment and test environments differed both in size of the cage and in the color and texture of the bedding (black Cellu-Dri [Shepherd Specialty Papers, Kalamazoo, MI] in the pretreatment environment vs. tan corncob bedding in the test environment). For the home:test group, the pretreatment and test phases were performed in different rooms: animals were pretreated in their home cages in the vivarium during the pretreatment phase and were treated in the laboratory and placed in the test cages for the first time during the test phase. In one series of experiments, an additional difference between pretreatment and test environments was introduced by placing two animals simultaneously in the pretreatment environment.

Evaluation of Stereotyped Behavior

All animals were evaluated for stereotyped behavior after amphetamine or vehicle pretreatment and after amphetamine challenge. Stereotyped behavior of CF-1 mice was measured according to the procedure described by Karler et al. (16) by an observer who was unaware of the treatment design. These mice respond to low doses of amphetamine by producing an increase in locomotor behavior that is occasionally interrupted by grooming. However, at doses of 12 mg/kg or greater, the mice remain stationary and display rapid and repetitive head and/or forelimb movements, including licking, chewing, and gnawing stereotypies. Such behaviors are easily identified and correspond to a score of 8 on a graded score of 9 in the behaviors described earlier by Ellinwood and Balster (11). This behavior was used as a quantal end point for the measurement of stereotypy. Animals were rated for this behavior over 1 min at 10-min intervals for 120 min after drug injection. The percent of animals exhibiting the stereotyped behavior in each group was determined, and the highest value of this percent among the 30-, 40-, 50-, and 60-min observation points was taken as the response to amphetamine. All studies were conducted between 1000 and 1600 h in a temperature and humidity controlled room.

Statistics

Differences between groups in the percent of animals exhibiting the stereotyped behavioral were 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. Relative potencies from dose–response curves were compared by using the method of Litchfield and Wilcoxon (23). For all tests, $p < 0.05$ was considered significant.

RESULTS

The first set of experiments established conditions for development of sensitization in the control (test:test) group. Sensitization was induced by pretreatment with a single high dose of amphetamine, as described previously (5). A prelimi-

nary dose–response study showed that with our laboratory conditions, a single dose of 14 mg/kg, IP, elicited the desired stereotyped behavioral end point in at least 80% of mice without lethality. Higher doses were not used because of lethality: 16 mg/kg amphetamine produced lethality in 10% of the mice. The test for sensitization was performed 48 h after pretreatment. To select a dose of amphetamine to study the expression of sensitization, a dose–response relationship for the effect of amphetamine on stereotyped behavior was determined in mice pretreated with vehicle or 14 mg/kg amphetamine (Fig. 1). For vehicle-pretreated animals, the ED_{50} for stereotyped behavior induced by amphetamine was 9.8 mg/kg (95% CI = 8.1–12). Pretreatment with amphetamine resulted in a 1.9-fold shift to the left of the dose–response curve with an ED_{50} of 5.1 mg/kg (95% CI = 4.0–6.4), indicating that sensitization had developed. For subsequent studies, the dose of 7 mg/kg amphetamine was utilized for the measurement of sensitization in the test phase, as this dose produced stereotyped behavior in 20% of mice pretreated with vehicle and in at least 80% of mice pretreated with 14 mg/kg amphetamine (Fig. 1). The percent of mice showing stereotyped behavior at various times after the administration of 7 mg/kg amphetamine to animals pretreated with 14 mg/kg amphetamine or vehicle is shown in Fig. 2. The peak effect occurred between 30 and 60 min after injection. Therefore, in subsequent experiments, the highest value of this percent among the 30-, 40-, 50-, and 60-min observation points was taken as the response to amphetamine.

To determine the importance of environmental context in the development of sensitization to the stereotyped behavioral effects of amphetamine, amphetamine and vehicle pretreatments were associated with environments that were identical to, similar to, or markedly different from the test environment (Table 1). When the only difference between pretreatment and test conditions was cage size (large:test group: surface area of the pretreatment cage 3.7 times larger than that of the test cage), mice manifested sensitization equivalent to that of the control (test:test) group (Fig. 3). In contrast, when the pretreatment and test environments differed in terms of physical characteristics, such as the color and

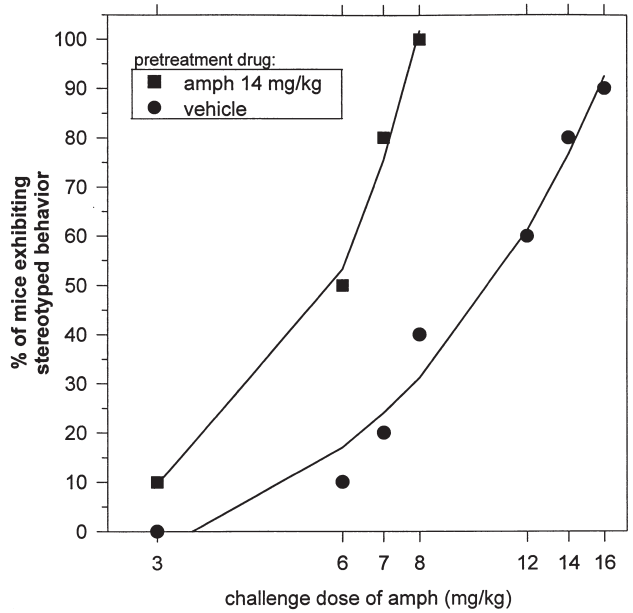

FIG. 1. Dose–response curves for amphetamine (amph)-induced stereotyped behavior in mice pretreated with amphetamine or vehicle. Each point represents a group of 10 animals. The challenge dose of amphetamine was administered 48 h after drug pretreatment. The ED_{50} values and their 95% confidence intervals are 5.1 mg/kg (4.0–6.4) for amphetamine-pretreated animals and 9.8 mg/kg (8.1–12) for vehicle-pretreated animals. A relative potency test shows that these two curves are significantly different ($p < 0.05$) (23). The treatment paradigm used was test:test.

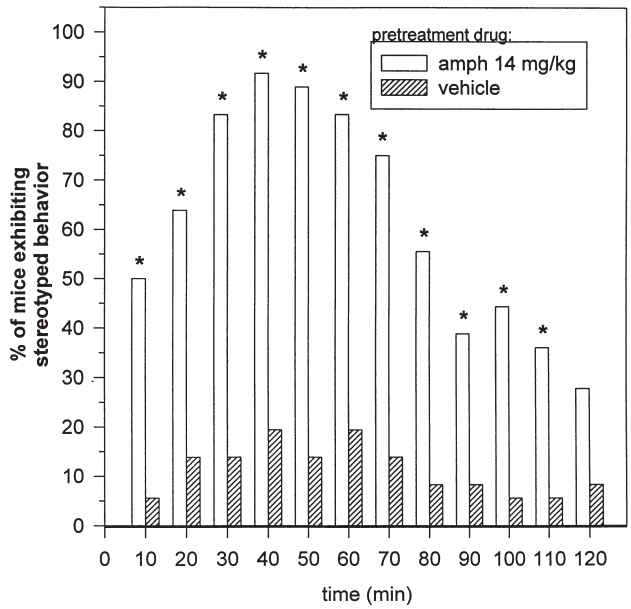

FIG. 2. Time course for the stereotyped behavioral effect of 7 mg/kg amphetamine (amph) challenge when administered 48 h after pretreatment with 14 mg/kg amphetamine or vehicle. Each bar represents a group of 15 animals. *Significantly different from vehicle control, as determined by chi-square analysis ($p < 0.05$). The treatment paradigm used was test:test.

TABLE 2

EFFECT OF PRETREATMENT ENVIRONMENT ON THE ACUTE STEREOTYPED BEHAVIORAL RESPONSE TO 14 mg/kg AMPHETAMINE

Pretreatment Environment	Percent of Mice Exhibiting Stereotyped Behavior
Test	87 (13/15)*
Large	93 (14/15)*
Diff	80 (12/15)*
Home	47 (7/15)*†

Mice were pretreated with amphetamine or vehicle in one of four different pretreatment environments (see Table 1) and were evaluated for the presence of stereotyped behavior. Vehicle control data are not shown, because none of the animals expressed stereotyped behavior.

*Significantly different from vehicle control, as determined by chi-square analysis ($p < 0.05$).

†Significantly different from the average percentage value of the other three groups (87%), as determined by chi-square analysis ($p < 0.05$).

texture of animal bedding (diff:test group) or the location and novelty of the cages (home:test group), mice did not become sensitized to amphetamine. It was also observed in this experiment that varying the pretreatment environment affected the initial or acute stereotyped behavioral response to 14 mg/kg amphetamine. In the control (test:test) group, the large:test group, and the diff:test group, an average of 87% of animals expressed the acute stereotyped behavioral response. In contrast, only 47% of the animals in the home:test group expressed stereotyped behavior acutely (Table 2).

The environmental context of the initial amphetamine pretreatment was also changed by the addition of a second mouse to the pretreatment environment. The results (Fig. 4) show that sensitization did not develop when there were two animals present in the pretreatment phase and one animal present in the test phase. The results of this experiment also showed that the addition of a second mouse to the pretreatment cage inhibited the acute expression of stereotypy, because only 40% of mice placed two to a cage after the high pretreatment dose (14 mg/kg) of amphetamine showed the acute stereotyped behavioral response (Table 3).

In experiments done to this point, sensitization to amphetamine never developed when the pretreatment condition diminished the acute stereotyped behavioral response to amphetamine. This suggested the possibility that the initial expression of stereotyped behavior in response to amphetamine pretreatment could be important for the subsequent development of sensitization. This hypothesis was evaluated in two ways. The first evaluation used a retrospective analysis of the data shown in Figs. 3 and 4 and Tables 2 and 3. In these experiments, only 9% of mice (3 out of 33) became sensitized to amphetamine without first expressing stereotyped behavior after amphetamine pretreatment. In contrast, 88% of mice (59 out of 67) that initially expressed a stereotyped behavioral response to amphetamine became sensitized.

TABLE 3

THE EFFECT OF NUMBER OF MICE PER CAGE DURING PRETREATMENT ON THE ACUTE STEREOTYPIC RESPONSE TO 14 mg/kg AMPHETAMINE

Pretreatment Environment	Percent of Mice Exhibiting Stereotyped Behavior
1 / cage	79 (55/70)*
2 / cage	40 (12/30)*†

Data were pooled from experiments in which mice were pretreated with amphetamine or vehicle and placed one or two per cage and evaluated for stereotyped behavior. Vehicle control data are not shown because none of the animals expressed stereotyped behavior.

*Significantly different from vehicle control, as determined by chi-square analysis ($p < 0.05$).

†Significantly different from 1 / cage, as determined by chi-square analysis ($p < 0.05$).

In the second evaluation of the hypothesis, we experimentally determined the frequency of the stereotyped behavioral response to 7 mg/kg amphetamine in mice that expressed and did not express stereotyped behavior during the pretreatment phase (Fig. 5). In this experiment, the pretreatment environment was identical to the test environment. The experimental design used the approximate ED_{50} dose (10 mg/kg; see Fig. 1) of amphetamine as the pretreatment dose, resulting in 60% of the animals (24 out of 40) expressing stereotyped behavior acutely. The standard test dose of amphetamine (7 mg/kg) was given to all animals 48 h later. The results show that 96%

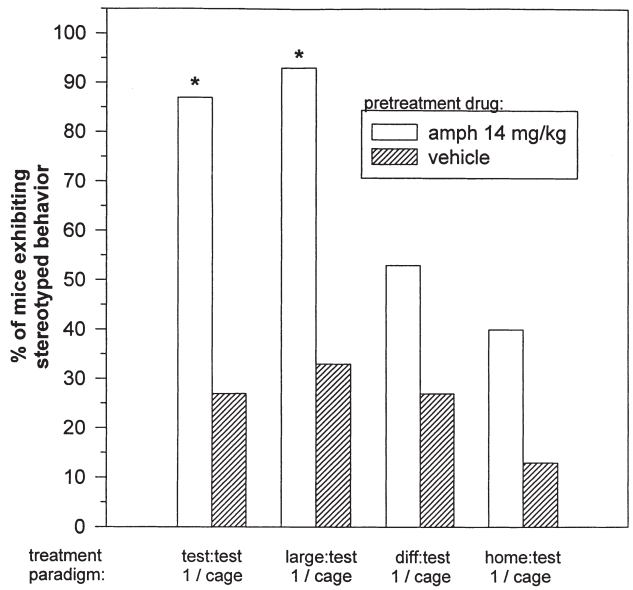

FIG. 3. The effect of varying the pretreatment environment on the development of sensitization. Mice were pretreated with 14 mg/kg amphetamine (amph) or vehicle in one of four different pretreatment environments (see Table 1) and challenged 48 h later with amphetamine 7 mg/kg in the test cage to test for sensitization. Each bar represents a group of 15 animals. *Significantly different from vehicle control, as determined by chi-square analysis ($p < 0.05$).

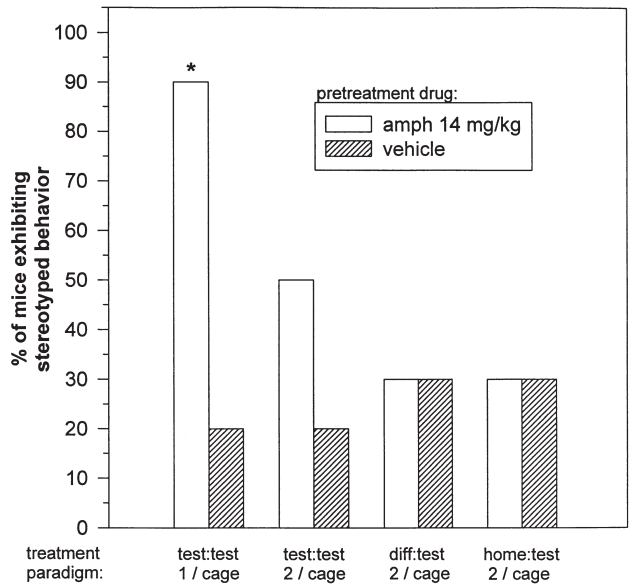

FIG. 4. The effect of varying the pretreatment environment and the number of mice per cage during pretreatment on the development of sensitization. Mice were pretreated with 14 mg/kg amphetamine (amph) or vehicle in one of four different pretreatment environments (see Table 1) and challenged 48 h later with amphetamine 7 mg/kg in the test cage (one animal/cage) to test for sensitization. Each bar represents a group of 10 animals. *Significantly different from vehicle control, as determined by chi-square analysis ($p < 0.05$).

of those animals that exhibited an acute stereotyped behavioral response after 10 mg/kg amphetamine pretreatment manifested this same response after the lower dose of 7 mg/kg amphetamine was given in the test phase. In contrast, only 38% of mice that did not exhibit the stereotyped behavioral response in the pretreatment phase showed the stereotyped behavioral response in the test phase. This latter value was not significantly different from the 25% of animals that expressed the stereotyped behavioral response to amphetamine, 7 mg/kg, in the vehicle-pretreated group (Fig. 5). These results are consistent with the hypothesis that the initial expression of stereotyped behavior in response to amphetamine pretreatment is important for the subsequent development of sensitization. However, the possibility cannot be excluded that those animals that did not initially express stereotypy may be simply less sensitive to all effects of amphetamine.

DISCUSSION

These results show that the administration of a single high dose of amphetamine can increase the percent of mice exhibiting a stereotyped behavioral response to a smaller challenge dose of amphetamine, confirming the previous observation of Bedingfield et al. (5). In the present study, the dose–response curve to amphetamine was shifted 1.9-fold to the left 48 h after pretreatment with 14 mg/kg amphetamine, indicating that sensitization to amphetamine had developed. Furthermore, the present results indicate that certain requirements must be met for sensitization to occur. The environment in which the animals are placed during the amphetamine test phase must be the same as or very similar to the environment used during the pretreatment phase, suggesting that the sensitization developed under these conditions is context dependent. In addition, it is important that mice express stereotyped behavior after the amphetamine pretreatment in order for sensitization of the stereotyped behavior to develop.

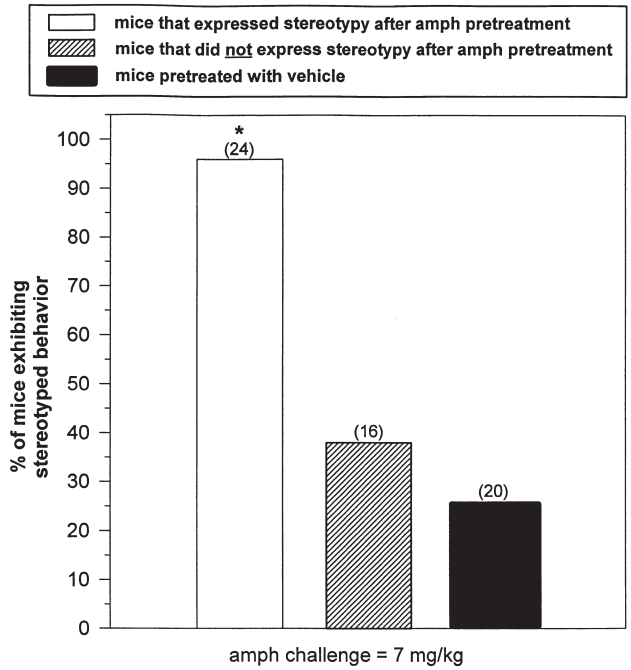

FIG. 5. The effect of acute expression of stereotyped behavior after amphetamine (amph) or vehicle pretreatment on the development of sensitization. Mice were pretreated with amphetamine (10 mg/kg) or vehicle 48 h prior to challenge with 7 mg/kg amphetamine. Sample size for each group is displayed in parentheses above the corresponding bar. *Significantly different from vehicle control, as determined by chi-square analysis ($p < .05$). The treatment paradigm used was test:test.

The present study indicates that the sensitized stereotyped behavioral response to a challenge dose of amphetamine is dependent upon environmental cues. Amphetamine did not produce a significant increase in the frequency of the behavioral response in mice that were pretreated in an environment that represented a change in familiarity (home vs. a novel cage), physical makeup (color and texture of bedding), or social environment (two vs. one mouse per cage), compared to the test environment. An increase in the percent of mice that responded to the challenge dose of amphetamine could only be demonstrated when the pretreatment and test environments were the same or differed only in cage size. These results suggest that the sensitized stereotyped behavioral response to amphetamine in mice pretreated with a single high dose of amphetamine involves a process in which the mice become conditioned to the environment associated with the amphetamine pretreatment. This conditioning appears to involve an interaction between the effects of amphetamine and environmental cues because mice that were placed in testing cages after amphetamine pretreatment did not express a conditioned stereotyped behavior in the testing cages when challenged with vehicle instead of amphetamine (data not shown).

The requirement for similar pretreatment and test environments for the development of sensitization to the stereotyped behavioral response induced by amphetamine is also observed for development of sensitization to the locomotor activity elicited by this drug. Thus, the development of sensitization to the locomotor stimulant effects of psychostimulant drugs such as amphetamine (1,4,8,14) and cocaine (12,13,26,33) is context dependent, occurring when the pretreatment environment is the same as or similar to that used for testing for sensitization. It is interesting that the processes of development of sensitization to locomotor activity and stereotyped behavior share this requirement, as these two types of behavior appear to be qualitatively different and have been attributed to the ability of amphetamine to increase dopamine neurotransmission at different brain sites.

One interesting observation of the present study is that the expression of the acute stereotyped behavioral response to 14 mg/kg amphetamine was influenced by the environment. It would appear that novelty augments the ability of amphetamine to elicit this behavior because animals that first received the drug in their home cage in the vivarium showed less stereotyped behavior compared to animals that first received the drug in a new or novel cage in the laboratory. This is consistent with several studies that showed that the acute locomotor response to amphetamine was higher in animals treated in a novel environment vs. their home environment (2–4,8,14).

In the present study, it was documented that mice pretreated with amphetamine did not become sensitized if they did not express stereotyped behavior after the acute 14 mg/kg dose of amphetamine. This observation suggests that the expression of stereotyped behavior in response to the pretreatment dose of amphetamine may be important for the development of sensitization. This hypothesis is consistent with the results of recent studies using locomotor activity as a measure of behavioral sensitization. In these studies, it was found that

rats, repeatedly administered direct-acting dopamine agonists but prevented from expressing the locomotor response to these drugs, did not become sensitized (10,25,34). Similarly, it has been reported that mice, which were repeatedly administered either morphine, methamphetamine, or cocaine but placed in small cages that physically restricted their movements, did not become sensitized to the locomotor stimulant effects of these drugs (18–21). In addition, mice, that received repeated injections of morphine, methamphetamine, or cocaine and then placed in their home cage with 10 other mice, showed only a partial sensitization (18,20). Because under these latter conditions the mice exhibited fighting and vocalization, which interfered with locomotor activity, it was suggested that this interference with the ambulatory effects of these drugs was responsible for the inhibition of sensitization. Based on these and the observations of the present study, it appears that the initial expression of a drug-induced response may be necessary for the development of sensitization to that response.

The hypothesis that the initial expression of behavior is important for the development of sensitization is not consistent with observations on the effect of D_2 antagonists on the development of sensitization in rats. It has been shown that D_2 receptor antagonists, which block the acute expression of locomotor activity induced by amphetamine, apomorphine, or cocaine, do not prevent the development of sensitization to these compounds after their repeated administration (9,24,32). It, therefore, appears that under some conditions, the expression of the behavior to be sensitized may not be necessary for the subsequent development of sensitization. However, the effects of D_2 antagonists appear to be different in rat and mouse models. Thus, in mice like in rats, D_2 receptor antagonists inhibit the acute expression of locomotor activity and stereotyped behavior induced by psychostimulant drugs. However, D_2 receptor antagonists administered concurrently with psychostimulant drugs to mice are able to inhibit the development of sensitization of both the locomotor stimulant and the stereotyped behavioral effects of psychostimulant drugs (6,22). Thus, at least in mice, the effects of D_2 antagonists on sensitization are consistent with the hypothesis that the initial expression of a drug-induced response is necessary for the development of sensitization to that response.

This hypothesis may have implications for studying mechanisms of development of sensitization. For example, information on the neural mechanisms involved in the development of sensitization is frequently derived from the actions of drugs that inhibit both the acute response to psychostimulant drugs and behavioral sensitization. In such experiments, the drug-induced attenuation of sensitization may be due to the inhibition of the acute behavioral response to psychostimulant drugs rather than of neural mechanisms of sensitization.

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