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Stressor Invoked Exacerbation of Amphetamine-Elicited Perseveration[1]

HYMIE ANISMAN, BRENDA HAHN, DAVID HOFFMAN AND ROBERT M. ZACHARKO

Unit for Behavioral Medicine and Pharmacology, Department of Psychology, Carleton University Ottawa, Ontario K1S 5B6, Canada

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ANISMAN, H., B. HAHN, D. HOFFMAN AND R. M. ZACHARKO. *Stressor invoked exacerbation of amphetamine-elicited perseveration.* PHARMACOL BIOCHEM BEHAV **23**(2) 173–183, 1985.—The provocation of stimulus perseveration induced by amphetamine in a Y-maze was appreciably enhanced in animals that had been exposed to uncontrollable shock, whereas controllable shock did not influence performance. The enhancement of the stimulus perseveration was evident irrespective of whether the stressor was applied immediately or 72 hr prior to the perseveration test, provided that the stimulus complex in which shock was delivered was similar to that in which the perseveration test was conducted. When the two environments were distinctively different from one another the enhancement of stimulus perseveration was evident immediately after shock exposure, but not 72 hr after shock. It is suggested that stressors may have long-term effects of amphetamine-elicited perseveration, but the expression of such an effect is dependent upon the stimulus context in which the behavior is examined. Moreover, it is suggested that evaluation of amphetamine-induced behavioral changes, and possibly amphetamine-elicited and idiopathic psychosis, should consider the stress history of the organism.

Stress Amphetamine Perseveration

EXPOSURE to aversive stimulation may induce neurochemical alterations which are fundamental to the induction or exacerbation of various forms of behavioral and physical pathology [3,28]. Although the central neurochemical changes provoked by stressors of moderate severity are fairly transient, it seems that traumatic aversive events may result in the sensitization or conditioning of neurochemical changes. In particular, presentation of cues that had previously been paired with uncontrollable footshock will result in a marked increase in the utilization of norepinephrine (NE) [13] and in some brain regions dopamine (DA) neuronal activity will be increased as well [17]. Likewise, it has been demonstrated that among mice exposed to traumatic shock which reduces brain NE concentrations, subsequent reexposure to even a limited amount of shock will result in a rapid reinduction of the amine reduction [2]. As in the case of stressors, it has been demonstrated that sensitization effects may occur in response to catecholamine stimulants such as amphetamine. In particular, among animals treated with amphetamine, subsequent administration of the drug provoked increased DA release from striatal tissue ([26,27], see also [8]), as well as increased unilateral circling [27], stereotypy and polydipsia [8].

Not only will amphetamine and stress exposure result in an enhanced response to subsequent treatment of a similar nature, but cross-treatment sensitization effects have been reported as well. Exposure to a stressor may result in a subsequent enhancement of the stereotyped response patterns ordinarily exerted by amphetamine [8, 9, 22] and vice versa [8,9]. The finding that catecholamine stimulants and amphetamine have additive effects may be related to the fact that the two treatments induce similar neurochemical consequences. Stressors, like amphetamine, are known to provoke increased turnover of NE and in some regions DA (see [4]). Indeed, it has been demonstrated that the neurochemical consequences of a stressor may be augmented among amphetamine treated animals [4,34]. Thus, it has been suggested that administration of amphetamine or a stressor results in the sensitization of the substrate for the neurochemical change, thereby enhancing the subsequent behavioral response to the same or to the alternative treatment [8].

Inasmuch as the stereotypy elicited by amphetamine has been assumed to represent an animal model of amphetamine-induced as well as idiopathic psychosis in humans [19], these findings were taken to suggest that stressful events may be a fundamental variable in provoking or exacerbating psychotic behaviors [8]. Stereotypy, however, is largely influenced by motoric factors, and likely does not tap changes of attentional processes or the response to environmental stimuli, which may be essential factors in psychotic disorders. Accordingly, it was suggested that in evaluating the effects of amphetamine and in drawing parallels to human idiopathic disorders, it would be propitious to assess behaviors in addition to stereotypy, particularly those which involve the response to environmental stimuli [19].

The purpose of the present investigation was to determine whether stressful events would enhance the effects of amphetamine on stimulus perseveration in a Y-maze spontaneous alternation task, a behavior thought to involve variations

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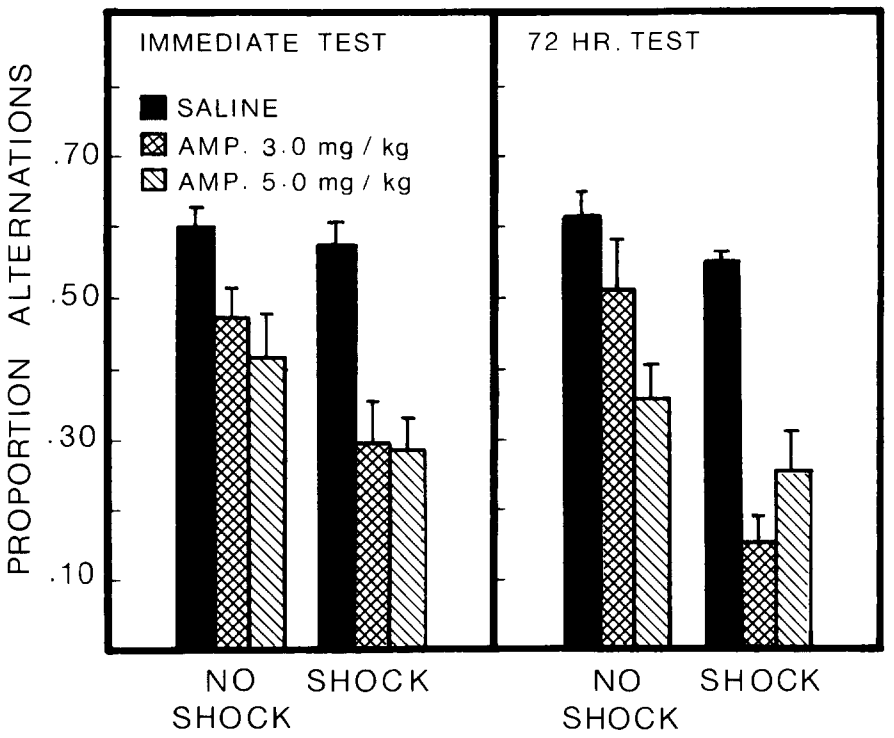

FIG. 1. Mean (±S.E.M.) proportion alternation responses among animals that received saline or d-amphetamine (3.0 or 5.0 mg/kg). Mice were tested in the Y-maze either immediately (left hand panel: Experiment 1) or 72 hr (right hand panel: Experiment 2) after exposure to footshock in an environment similar to that in which the alternation test was conducted.

of attentional processes [19]. Since stimulus perseveration is influenced by the stimulus array of the test environment, as well as the animal's previous experience (habituation) with that environment, it was also determined whether the long-term consequences of stressful events on later amphetamine-elicited perseveration were dependent upon the stimulus array associated with the stressful situation and the subsequent test environment.

EXPERIMENTS 1 AND 2

When permitted to explore a symmetrical Y-maze, mice tend to enter successively the least frequently visited arms of the maze (spontaneous alternation). In contrast, following moderate doses of d-amphetamine (3.0–5.0 mg/kg) a stimulus perseveration tendency is evident wherein mice emit successive visits between two arms of the maze (e.g., [20]). It should be emphasized that the perseveration induced by amphetamine is distinct from the stereotyped behaviors elicited by the drug. As indicated earlier, the perseverative tendency is greatly influenced by stimulus factors [19]. Moreover, unlike the stereotyped response patterns provoked by amphetamine, the stimulus perseveration tendency tends to diminish following repeated treatment with amphetamine [19,20]. Furthermore, reduction of brain NE activity tends to reduce the amphetamine-induced perseverative tendency, although a role for DA in subserving the behavior cannot be dismissed [21]. Experiments 1 and 2 determined whether the perseverative tendency, like the stereotypy provoked by amphetamine, would be influenced by aversive stimulation, and whether stressors would have both short and long term effects in this respect.

METHOD

Subjects

Experiments 1 and 2 involved 79 and 80 naive, male CD1 mice obtained from the Canadian Breeding Laboratory, Laprairie, Quebec. Mice were obtained at 55–60 days of age and were acclimatized to the laboratory for 10–14 days prior to being used as experimental subjects. The mice were housed in groups of 5 in standard polypropylene cages and permitted ad lib access to food and water.

Apparatus

Shock was delivered in 30×14×15 cm black Plexiglas chambers covered by red Plexiglas lids to reduce illumination. The floor of each chamber consisted of 0.32 cm stainless steel rods spaced 1.0 cm apart (center to center), connected in series by neon bulbs. The end walls of each chamber were lined with stainless steel plates connected in

series with the grid floor. Footshock (150 μA) could be delivered to the grid floor through a 3000 V source, thus providing relatively constant current. The timing of shock presentations was controlled by a microcomputer system.

Spontaneous alternation/perseveration was evaluated in four symmetrical black Plexiglas Y-mazes, the arms of which measured 22.0×9.0×15.0 cm. Within each arm, situated 3.0 cm from the triangular choice area was a stainless steel horizontally movable gate. Two sets of photocells were mounted 1.0 cm on each side of the gate at heights of 2.0 and 4.0 cm above the grid floor. The photodetectors were wired such that crossing the infrared beams on both sides of the gate simultaneously would not trigger the cells. Only when the mouse crossed the beam further into the arm was the cell triggered. Accordingly, small back and forth movements, head bobbing or tail rattling did not result in the multiple photodetector counts.

The floor of each arm consisted of 0.32 cm stainless steel rods spaced 1.0 cm apart, and the end wall of each arm was lined with a stainless steel plate. The roof of the mazes were composed of red Plexiglas in order to reduce illumination. Thus, the characteristics of the Y-mazes were in most respects identical to those of the shock chambers (same color, floor, roof lighting).

TABLE 1

MEAN (±S.E.M.) ARM ENTRIES AS A FUNCTION OF THE SHOCK AND DRUG TREATMENTS UPON TESTING IMMEDIATELY (EXPERIMENT 1) OR 72 HR (EXPERIMENT 2) AFTER FOOT-SHOCK

Drug Treatment	No Shock	Shock
	Immediate test	
Saline	39.18 ± 4.28 (11)	39.00 ± 5.80 (12)
Amphetamine (3.0 mg/kg)	80.07 ± 14.33 (14)	74.85 ± 11.74 (14)
Amphetamine (5.0 mg/kg)	142.33 ± 15.31 (12)	147.50 ± 21.33 (16)
	72 hr test	
Saline	67.23 ± 4.63 (13)	44.76 ± 5.32 (13)
Amphetamine (3.0 mg/kg)	124.33 ± 20.54 (12)	57.60 ± 19.63 (15)
Amphetamine (5.0 mg/kg)	138.33 ± 22.68 (15)	78.25 ± 22.84 (12)

Numbers in parentheses denote n/group.

Procedure

Mice were placed individually in the shock chambers for a 1.1 hr period and exposed to either 360 shocks of 2 sec duration at intervals of 9 sec, or were not shocked. Mice of Experiment 1 were then placed in the Y-mazes for a 6 min period and the sequence of arm entries were recorded. Mice were then removed from the mazes and injected intraperitoneally with either d-amphetamine sulfate (3.0 or 5.0 mg/kg in a volume of 10 ml/kg) or saline, and placed in individual holding cages for a 15 min period. Following the 15 min period mice were again placed in the Y-mazes and the sequence and number of arm entries were again recorded. The procedure of Experiment 2 differed from that of Experiment 1 in only one respect. After the stress session mice were housed individually and were not tested in the alternation task until 72 hr afterward. At that time mice were preexposed to the Y-mazes, injected with the d-amphetamine sulfate (3.0 or 5.0 mg/kg) or saline and subsequently tested in the alternation task as described in Experiment 1. It will be noted that mice were preexposed to the Y-mazes prior to amphetamine treatment, since this procedure ordinarily enhances the perseverative effects of the drug [19].

Spontaneous alternation (the tendency to enter the least recently visited arm of the maze) was calculated as a proportion of alternation responses divided by the total number of alternation plus nonalternation responses. Thus a sequence of arm entries consisting of 1, 2, *3*, *1*, 3, 1, *2*, *3* received a score of 4 alternation responses and 2 nonalternation responses (alternation score=0.66). Perseveration scores were defined as the probability of entering the most recently visited arm. Thus in the preceding example the nonalternation responses and perseveration responses were synonymous. In addition to this index of perseveration, the number of reentries into the arm the animal had just left were recorded. Separate analyses were conducted in which perseveration was considered the probability of reentering the arm the animal had just left (i.e., reentries divided by all entries), and the probability of emitting a reentry or entering the arm the animal had left on the preceding visit divided by the total number of perseveration and alternation responses. Thus a sequence of arm entries consisting of 1, 2, *2*, *2*, 3, *2*, *2*, *3*, 1, 2 would consist of 3 perseveration responses involving reentry into the arm just left, one perseverative response in which the animal returned to the arm visited on the preceding visit, plus 3 alternation responses. Alternation and perseveration scores were only calculated among animals that exhibited 5 or more responses of one type or another (i.e., a minimum of 7 arm entries). Among animals that exhibited fewer than the required number of alternation/perseveration responses, the number of arm entries emitted was employed in the analysis of locomotor activity.

RESULTS AND DISCUSSION

The mean proportion of alternation responses (i.e., where low alternation scores designate high perseveration) in both Experiments 1 and 2 are shown in Fig. 1. Analysis of variance of the alternation/perseveration scores of Experiment 1 revealed that the shock treatment reduced the alternation tendency, i.e., enhanced perseveration, $F(1,73)=8.03$ and 8.29, p's<0.01 (for perseveration calculated with and without returns to the same arm, respectively), as did the Drug treatment, $F(2,73)=13.98$ and 16.92, p's<0.01, respectively. Newman-Keuls multiple comparisons ($\alpha=0.05$) indicated that both doses of amphetamine increased the frequency of the perseverative tendency. Although the interaction between the Shock × Drug Treatment was not statistically significant, Newman-Keuls multiple comparisons ($\alpha=0.05$) were conducted on the simple effects since an *a priori* prediction had been made concerning this interaction. These comparisons confirmed that in the absence of the drug treatment shock did not influence perseveration. While amphetamine induced the perseverative tendency among both the shocked and nonshocked mice, the extent of the perseveration was appreciably more pronounced in the former case (see Fig. 1, left hand panel). Pairwise comparisons confirmed that the perseveration tendency was significantly greater in

amphetamine treated mice (3.0 and 5.0 mg/kg), that had been exposed to shock than among similarly drug treated animals that had not been shocked.

Thus it appears that exposure to shock effectively augmented the amphetamine induced perseverative tendency. It will be noted that we previously reported that uncontrollable shock may subtly, but significantly, influence alternation performance in an 8-arm radial maze [12]. That is, although shock treatment did not reliably influence alternation and perseveration, it was found to disrupt adjacent alternation performance (i.e., the tendency to visit successively immediately adjacent arms of the 8-arm maze). The fact that the shock itself was without effect on alternation performance in the present investigation is consistent with our previous finding indicating that alternation in a Y-maze was not altered by shock treatment.

The frequency of arm entries was modified by amphetamine treatment, $F(2,73)=25.98$, $p<0.01$. As shown in Table 1 and confirmed by Newman-Keuls multiple comparisons ($\alpha=0.05$), the 3.0 mg/kg dose increased arm entries relative to the saline treatment, and the 5.0 mg/kg dose in turn enhanced arm entries relative to the 3.0 mg/kg dose. In contrast to the effects of the drug treatment, neither the main effect of Shock nor the Shock × Drug treatment interaction approached statistical significance. Thus it seems that the enhancement of the amphetamine-induced perseverative tendency induced by the shock was unrelated to variations of motor activity (see also [20,21]). Although it has been reported that inescapable shock will influence the level of locomotor activity exhibited by animals [33], we have not observed such an effect in a maze when testing was conducted soon after the stress session (e.g., [12]). However, given that arm entries is a crude index of locomotor activity (i.e., activity within an arm of the maze may differ as a function of the shock treatment) these results should not necessarily be taken as being contradictory with previous reports.

Analysis of variance of the alternations scores of Experiment 2 revealed that the perseverative tendency (with and without inclusion of arm reentries) varied as a function of the Shock × Drug Treatment interaction, $F(2,63$ and $2,71)=5.60$ and 5.42, p's<0.01. Newman-Keuls multiple comparisons of the simple effects comprising these interactions ($\alpha=0.05$) confirmed that in saline treated mice the shock treatment was without effect on the perseverative tendency (see Fig. 1, right-hand panel). Among nonshocked mice, however, the 3.0 mg/kg dose produced a small reduction of alternation relative to saline treated animals, while the 5.0 mg/kg dose provoked a significant perseveration tendency. Among shocked animals the perseveration was marked at both doses relative to saline treated animals. Furthermore, at the 3.0 mg/kg dose the perseverative effects of amphetamine were significantly greater among shocked than among nonshocked mice. The difference between shocked and non-shocked mice that received the 5.0 mg/kg dose did not reach statistical significance. It appears that the effectiveness of the shock treatment in enhancing amphetamine-induced perseveration was evident even when the shock treatment had been applied three days earlier.

The frequency of arm entries as a function of the experimental manipulations in Experiment 2 was found to differ substantially from those of Experiment 1. In particular, the analysis of variance revealed that amphetamine treatment significantly enhanced the number of arm entries, $F(2,74)=4.32$, $p<0.05$, while the shock treatment reduced the frequency of arm entries, $F(1,74)=11.31$, $p<0.01$. As seen in Table 1 the reduced frequency of arm entries in shocked animals was evident at each level of the drug treatment. The fact that shock had an effect on locomotor activity in Experiment 2 and not in Experiment 1 may be due to the fact that 3 days intervened between the shock and subsequent test in the second experiment, while in the first experiment testing was conducted immediately after the shock treatment. Indeed, it has been reported on several occasions that the effectiveness of inescapable shock in disrupting subsequent escape behavior may be less pronounced at short intervals after shock of moderate severity than at longer intervals [6, 15, 16]. It is conceivable that the emotional reactivity induced by the shock treatment may prevent expression of the locomotor changes that would be evident in shocked animals once the initial emotional response has subsided. Upon testing animals 3 days after inescapable shock, when the initial emotional reponses induced by the stressor have subsided, the presentation of cues associated with shock may provoke variations of general activity.

Summarizing, it appears that exposure to shock will subsequently enhance the amphetamine-induced perseveration. This effect was evident as long as 72 hr after shock termination, a time when the initial neurochemical consequences of this stress severity have subsided (see [7]). Thus, the data of Experiments 1 and 2 are consistent with the suggestion that stressful events may increase vulnerability to subsequent drug effects owing either to conditioning or sensitization of neurochemical processes [9,22].

EXPERIMENT 3

Many of the behavioral and physiological consequences of stressors have been shown to be dependent on the organism's ability to cope with the stressor through behavioral means. For instance, although escapable shock does not lead to reductions of brain NE, an equivalent amount of inescapable shock applied in a yoked paradigm leads to reductions of this amine [5,32]. Likewise, the yoked inescapable shock treatment is more likely to induce gastric ulceration [31], exacerbate the growth of transplanted tumors [29], disrupt subsequent escape performance [4, 23, 32], and engender an antinociceptive effect [18]. More recently, it was demonstrated that the enhancement of amphetamine and cocaine-induced stereotypy was elicited by uncontrollable stressors, but not by controllable stressors [22]. It was the purpose of Experiment 3 to determine whether stress controllability was fundamental in enhancing the perseveration elicited by amphetamine treatment.

METHOD

Subjects

A total of 69 naive, male CD-1 mice served as subjects. The subject characteristics were the same as those of Experiment 1.

Apparatus

Shock treatments were applied in three black Plexiglas shuttle-boxes that measured 29.2×8.9×16.5 cm (see [1] for a detailed description). The roof, grid floor and wiring were the same as those of the shock boxes described in Experiment 1. Each shuttle box was divided into two equal sized compartments by a horizontally movable stainless steel gate, which was controlled by a solenoid. When the gate was open

a 5.2×6.1 cm space permitted access into the adjacent compartment. Photodetectors mounted on either side of the gate determined the position of the animal. Crossing the detector on the nonshock side of the chamber resulted in the gate closing and the trial terminating. One of the shuttle-boxes was employed to administer escapable shock; a second shuttlebox was connected in series with the first box, such that shock onset and offset occurred concurrently in the two shuttleboxes. Shock was not delivered to the third box which was used for nonstressed animals. The shuttle boxes were controlled by a microcomputer system and were housed in sound attenuated chambers.

Procedure

Mice of one group were placed individually in one of the shuttleboxes, 30 sec after which training commenced. On each trial shock was presented continuously until an escape response was emitted. During the initial 1.5 sec of each trial the gate separating the compartments remained closed. The gate was then opened permitting access to the adjacent shock free chamber. When the mouse crossed into the shock free chamber the trial terminated and the gate closed. Mice received 360 trials at 9 sec intervals between trials, hence the amount of shock approximated that of Experiment 1. Mice in the second chamber served as yoked controls. Shock onset for these animals occurred at the same time as it did for mice in the escape group; however, shock offset was independent of the animal's responses. Rather, shock terminated when mice in the former group successfully escaped. Thus, mice in both groups received the same amount of shock, but only mice in the escape group could determine shock offset by their responses. Mice in the third group were placed in the shuttleboxes, but shock was not delivered. Immediately after the shock session the amphetamine-perseveration test commenced. The procedure employed was exactly the same as that of Experiment 1, except that all mice received injection of the 3.0 mg/kg dosage of d-amphetamine.

RESULTS AND DISCUSSION

As shown in Fig. 2 (left), alternation/perseveration performance induced by amphetamine varied as a function of the Shock Treatment mice received, $F(2,65)=3.59$, $p<0.05$. Newman-Keuls multiple comparisons ($\alpha=0.05$) confirmed that relative to the nonstressed animals exposure to escapable shock did not influence performance. In contrast, the perseverative tendency was pronounced in mice that received exposure to inescapable shock. Precisely, the same pattern was evident with respect to the proportion of perseveration responses emitted when returns to the same arm were included in the analysis.

As in Experiment 1, the frequency of arm entries did not differ as a function of the shock treatment mice received, $F(2,66)=1.12$, $p>0.10$. As seen in Fig. 2 (right) there was a trend towards lower levels of activity being evident among mice that received the inescapable shock treatment, but this difference did not reach statistical significance.

It would appear that the stress-induced enhancement of the perseverative tendency was more evident in mice that received inescapable shock than in mice that received escapable shock. Although both treatments are known to increase the utilization of brain NE (see [4]), the inescapable shock treatment is thought to produce greater amine utilization than escapable shock, ultimately resulting in reductions in

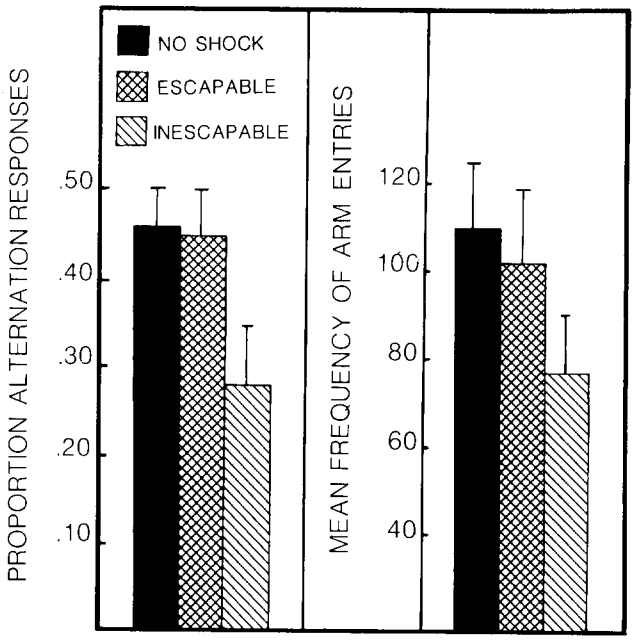

FIG. 2. Mean (±S.E.M.) proportion alternation responses and the mean frequency of arm entries among mice that received d-amphetamine (3.0 mg/kg) following exposure to either escapable shock, yoked inescapable shock or no shock.

the concentration of this amine. While we previously reported that NE neuronal activity may account for the variations of amphetamine-induced perseveration [19], a role for other transmitters should not be discounted for the combined effects of stress and amphetamine on perseverative response styles. Stressors have been shown to influence DA activity in some brain regions (e.g., [11, 17, 30]), and uncontrollable shock has more pronounced effects on DA receptor density than does escape shock [14]. Likewise, there is reason to believe that 5-HT concentrations in some brain regions may be influenced by stress controllability [25], and alterations of endogenous opioids may likewise be differentially influenced by controllable and uncontrollable shock (see [18,23]). Although there are limited data concerning the contribution of these transmitters to amphetamine-induced perseveration, it is premature to dismiss the possibility that they contribute to the shock × amphetamine interaction on perseverative behavior.

EXPERIMENTS 4 AND 5

Although exposure to inescapable shock was found to enhance the effects of subsequent amphetamine treatment applied three days afterward, it is not clear whether this reflected a stress-induced sensitization of neurochemical systems, the conditioning of an emotional response to apparatus cues which subsequently enhanced the drug effect, or both these processes. In particular, the shock chambers of Experiments 1 and 2 were similar in several ways to the Y-maze in which mice were subsequently tested. Experiments 4 and 5 were undertaken to determine whether the short and long term effects of stress on subsequent amphetamine-induced perseveration would be evident under conditions where the apparatus used during shock was dis-

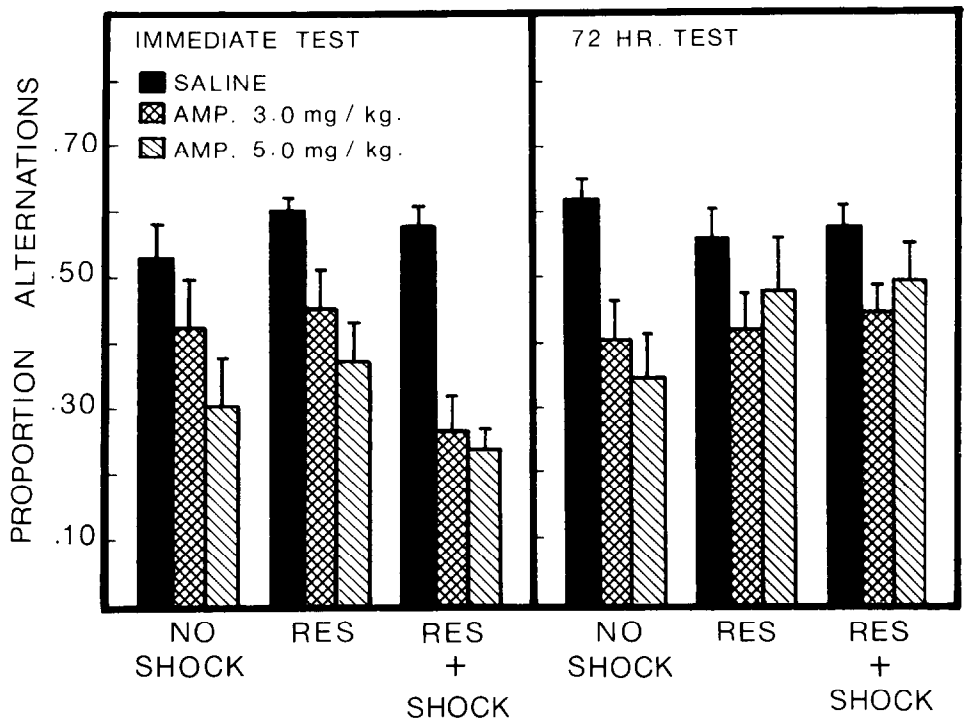

FIG. 3. Mean (±S.E.M.) proportion alternation responses among animals that received either saline or d-amphetamine (3.0 or 5.0 mg/kg). The alternation test was conducted either immediately (left-hand panel: Experiment 4) or 72 hr (right hand panel: Experiment 5) after exposure to tail-shock. The test environment was distinctively different from that in which shock was delivered.

similar from that in which perseveration was subsequently monitored.

METHOD

Subjects and Apparatus

A total of 119 and 86 naive male CD-1 mice were obtained from the Canadian Breeding Laboratory at 55–60 days of age. The subject characteristics were the same as those of Experiment 1. For the purpose of shock stress mice were placed individually in clear Plexiglas semicircular restraining tubes that measured 4.9 cm in length. Once the mouse was placed in the restraining tube, a Plexiglas insert was placed behind the mouse, and the tail which protruded through the insert was fastened to a Plexiglas plate. Thus the mouse was kept relatively immobile. Two aluminum foil electrodes, measuring approximately 0.5 cm in width, were wrapped about the base and midsection of the mouse's tail, and these were in turn attached to a shock source, through which shock of 150 μA could be delivered (as described in Experiment 1). Perseveration was monitored in the Y-mazes described earlier. Thus, the shock apparatus and lighting conditions were distinctively different from that in which mice were subsequently tested.

Procedure

In Experiments 4 and 5 mice were assigned to three treatment conditions. Mice of one group were placed into the restraining tubes and the aluminum foil electrodes were fastened to their tails. Over a period of 11 minutes mice received 60 shocks of 2 sec duration at intervals of 9 sec. A second group of mice were restrained for an equivalent amount of time, but were not shocked, while mice of a third group were handled and placed in a clear Plexiglas cage without being stressed by either shock or restraint. Mice of Experiment 4 were tested immediately after the test session using the procedures of Experiment 1, while mice of Experiment 5 were tested 72 hr after the stress session as described in Experiment 2. It will be noted that Experiments 4 and 5 differed from the preceding experiments in that only 60 shocks were administered. Preliminary studies indicated that the combination of restraint and 360 shocks was particularly stressful, and frequently mice did not make any movements in the Y-maze. As will be seen in the results, the immediate effects of 60 tail shocks applied to restrained mice actually had behavioral effects comparable to those of 360 shocks applied to freely moving mice.

TABLE 2

MEAN (±S.E.M.) ARM ENTRIES AS A FUNCTION OF SHOCK AND DRUG TREATMENTS UPON TESTING IMMEDIATELY (EXPERIMENT 4) OR 72 HR (EXPERIMENT 5) AFTER TAIL-SHOCK

Drug Treatment	No Shock	Restraint	Restraint + Shock
	Immediate test		
Saline	58.70 ± 3.09 (10)	60.69 ± 3.71 (13)	50.55 ± 8.85 (12)
Amphetamine (3.0 mg/kg)	98.85 ± 20.80 (14)	92.92 ± 14.45 (14)	120.06 ± 19.46 (15)
Amphetamine (5.0 mg/kg)	136.71 ± 13.55 (14)	150.72 ± 35.21 (11)	159.93 ± 17.08 (16)
	72 hr test		
Saline	68.33 ± 7.43 (6)	83.50 ± 15.30 (6)	68.00 ± 12.86 (6)
Amphetamine (3.0 mg/kg)	143.18 ± 27.17 (11)	96.15 ± 12.86 (13)	147.45 ± 19.60 (11)
Amphetamine (5.0 mg/kg)	178.63 ± 22.83 (11)	163.00 ± 21.71 (11)	171.00 ± 23.55 (11)

Numbers in parentheses denote n/group.

RESULTS AND DISCUSSION

The performance of mice of Experiments 4 and 5 are shown in Fig. 3. Administration of 60 tail shocks followed immediately by the perseveration test resulted in behavioral changes remarkably similar to those provoked by 360 foot-shocks in Experiment 1. In particular, analyses of variance revealed that the proportion of perseveration responses (both when returns to the arm just left were or were not included in the analysis) varied as a function of the Drug treatment, $F(2,103 \text{ and } 2,107)=16.82, 18.50$, p's<0.01, and the Shock condition, F's $(2,103 \text{ and } 2,107)=3.12, 4.28$, p's<0.05. Newman-Keuls multiple comparisons ($\alpha=0.05$) indicated that for both measures treatment with amphetamine induced an increase in the perseverative tendency relative to saline treated mice, and that the shock treatment provoked a greater amount of perseveration than did either the restraint or no stress treatment. The interaction between the Shock and Drug treatments were not significant. Nevertheless, since specific comparisons were predicted on the basis of Experiment 1, Newman-Keuls multiple comparisons were conducted on the simple effects. These comparisons revealed that in the absence of the drug treatment exposure to shock did not provoke a greater perseverative tendency. Indeed, animals that received shock treatment exhibited slightly more alternation than did nonstressed animals (see Fig. 3, left). Administration of amphetamine at both the 3.0 and 5.0 mg/kg doses induced a perseverative tendency. Moreover, the perseverative tendency induced by the low dose of amphetamine was more pronounced among mice that received shock than among the remaining two groups. With the 5.0 mg/kg dosage the shock treatment was not found to enhance the perseveration probably owing to a ceiling effect (see Fig. 3, left). Taken together, it appears that if mice were tested immediately after exposure to tail-shcok the perseverative tendency induced by a low dose of amphetamine was enhanced just as it was in Experiment 1 in mice that had received foot-shock.

As seen in Table 2, the frequency of arm entries varied as a function of the Drug Treatment mice received, $F(2,110)=16.41$, $p<0.05$. Newman-Keuls multiple comparisons confirmed that the number of arm entries emitted was greater among mice that received 5.0 mg/kg of amphetamine than among mice that received the 3.0 mg/kg dosage. The number of arm entries emitted by the latter group, was in turn greater than that seen in saline treated mice. Neither the Shock nor Restraint treatment reduced the frequency of arm entries. Indeed, a small nonsignficant increase in the arm entries was evident among the drug treated animals that received the shock treatment.

When mice were tested in the Y-maze 72 hr after shock exposure in a distinctively different environment (Experiment 5) performance differed markedly from that seen when mice were tested immediately after the shock treatment (Experiments 1 and 3) or 72 after foot-shock applied in an apparatus similar to that in which testing was conducted (Experiment 2). Administration of amphetamine was found to induce a perseverative tendency both when arm reentries were included or not included in the analyses, $F(2,75)=4.66, 3.59$, $p<0.05$. The Shock treatment, however, was found not to influence performance (see Fig. 3, right). The number of arm entries emitted was increased by amphetamine treatment, $F(1,77)=14.61$, $p<0.01$. Newman-Keuls multiple comparisons revealed that although both doses of amphetamine enhanced the frequency of arm entries, the 3.0 mg/kg dose was more effective in this respect. Contrary to the results of Experiment 2, when mice were tested in a distinctively different environment the previous shock treatment was found not to influence the number of arm entries emitted. Neither the main effect of Shock nor the Shock × Drug interaction approached statistical significance (F's<1).

EXPERIMENT 6

Although administration of amphetamine to animals that received 60 tail-shocks while being restrained led to behavioral effects comparable to those of mice that received 360 foot-shocks, such an effect was evident only when the amphetamine test followed immediately after the stress session. When 3 days elapsed between the stress and amphetamine sessions the enhanced perseveration was evident only among mice that had received the foot-shock test. Inasmuch as the apparatus cues in the chambers used to administer foot-shock were similar to those of the Y-mazes, the possibility exists that the enhanced perseveration was elicited by these cues. Yet, the possibility cannot be dismissed that 60 tail-shocks was not sufficient to permit expression of a sensitization effect 3 days later, despite the fact that such a

TABLE 3

MEAN (±S.E.M.) PROPORTION OF ALTERNATION RESPONSES AND ARM ENTRIES AS A FUNCTION OF DRUG AND TAIL-SHOCK TREATMENTS

Drug Treatments	No shock	60 shocks	180 shocks	360 shocks
		Proportion of Alternation Responses		
Saline	0.55 ± 0.04	0.58 ± 0.03	0.54 ± 0.03	0.61 ± 0.02
Amphetamine (3.0 mg/kg)	0.30 ± 0.05	0.29 ± 0.06	0.36 ± 0.06	0.42 ± 0.07
Amphetamine (5.0 mg/kg)	0.40 ± 0.09	0.37 ± 0.10	0.54 ± 0.09	0.59 ± 0.06
		Arm Entries		
Saline	68.71 ± 8.10 (07)	69.28 ± 2.40 (07)	60.85 ± 4.17 (07)	61.00 ± 4.97 (07)
Amphetamine (3.0 mg/kg)	143.92 ± 23.31 (13)	129.14 ± 29.17 (14)	130.53 ± 18.44 (13)	167.35 ± 21.04 (14)
Amphetamine (5.0 mg/kg)	106.25 ± 30.81 (08)	151.00 ± 23.83 (07)	159.62 ± 41.67 (08)	169.00 ± 25.37 (07)

Numbers in parentheses denote the n/group.

treatment exacerbated the effects of amphetamine when the perseveration test was conducted immediately after the shock session. Accordingly, an additional experiment was conducted to evaluate the effects of amphetamine following a greater number of tail-shocks.

Subjects and Apparatus

A total of 112 naive, male CD-1 mice served as subjects. The subject and apparatus specifications were the same as those of Experiment 4.

Procedure

Independent groups of mice were placed in the restraining chambers and exposed to either 60, 180 or 360 tail-shocks of 2 sec duration at 9 sec intervals as described in the procedure of Experiment 4. An additional group was handled and housed individually for 1.1 hr, but were neither restrained nor shocked. Mice were then housed individually, and 3 days later tested in the Y-maze perseveration task. The testing procedure was the same as that of Experiment 1 insofar as the apparatus preexposure and drug dosages were concerned. A relatively large number of mice were tested with the 3.0 mg/kg dosage, since the preceding experiments revealed that behavior of stressed mice was most affected at this drug dosage.

RESULTS AND DISCUSSION

The analysis of variance of the alternation scores revealed that performance varied as a function of the Drug treatment, $F(2,93)=10.42$, $p<0.01$. Subsequent Newman-Keuls multiple comparisons ($\alpha=0.05$) revealed that both doses of amphetamine reduced the alternation tendency relative to saline treated animals. Moreover, the extent of the perseverative tendency was greater following the 3.0 mg/kg dosage than after the 5.0 mg/kg dosage. Neither the main effect of the drug treatment nor the Drug × Shock Treatment interaction approached statistical significance. Indeed, as seen in Table 3, the extent of the perseveration was somewhat less pronounced among mice that had received 180 or 360 shocks, although this effect was not statistically significant. With respect to the number of arm entries emitted, the analysis of variance revealed that the Drug treatment influenced performance, $F(2,100)=12.50$, $p<0.01$, but neither the shock nor Shock × Drug interaction reached statistical significance ($F's<1$).

It appears that exposure to tail-shock was without effect on amphetamine-induced perseveration evaluated 3 days after the stress session, irrespective of whether mice received 60, 180 or 360 shock trials. As such, it seems that the effectiveness of foot-shock in enhancing amphetamine provoked perseveration 72 hr afterward (Experiment 2) might have been related to the similarity of the apparatus cues in the shock and test situations rather than to the differences in the shock procedures employed.

EXPERIMENT 7

Although the data of the preceding experiments are certainly consistent with the suggestion that stimulus factors are important in determining the long-term effects of stressors on amphetamine elicited perseveration, these experiments did not directly test this assumption. Accordingly, an additional experiment was necessary to determine whether, in fact, the stimulus context in which shock was delivered was fundamental in determining the perseverative response tendency elicited by amphetamine.

METHOD

Subjects and Apparatus

A total of 159 naive male CD-1 mice were employed. The subject characteristics were the same as those described in Experiment 1. The apparatus used to administer footshock, as well as the Y-mazes used for alternation testing were the same as those of Experiment 1. Additionally, however, white inserts could be placed on the floor and walls of the Y-mazes, thereby changing their color, and texture of the floor (i.e., elimination of the grid floor).

Procedure

Mice were placed individually in the black preshock boxes for a 1.1 hr period, during which half the mice were exposed to 360 shocks (2 sec duration, 150 μA) at 9 sec intervals, while the remaining mice were not shocked. Following the shock treatment mice were returned to their home cages until testing which was conducted 72 hr afterward. On the day of test mice were placed in the Y-mazes for a 6-min

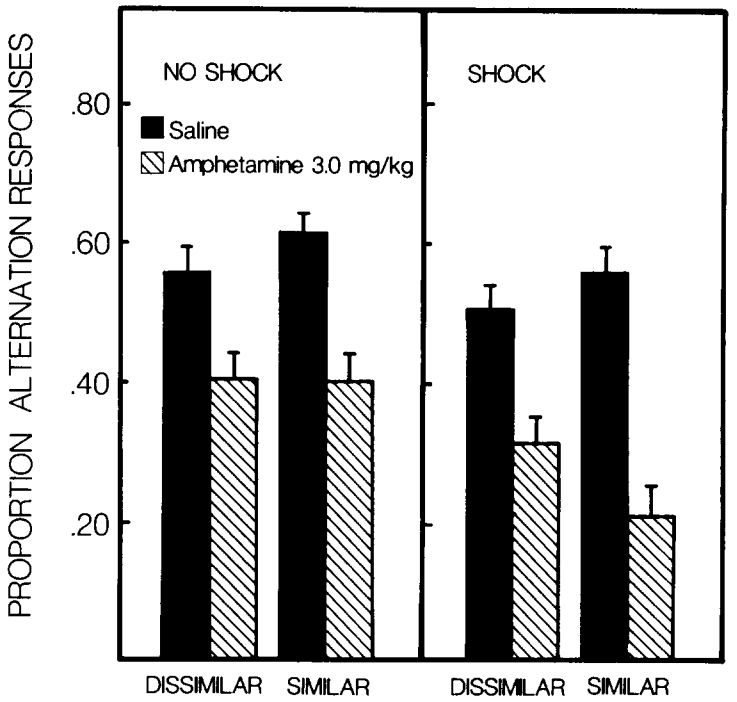

FIG. 4. Mean (±S.E.M.) proportion alternation responses in animals that received saline or d-amphetamine (3.0 mg/kg). Mice had been exposed to either inescapable shock or no shock 72 hr earlier, and were tested in Y-mazes either similar or dissimilar to the shock chambers.

acclimatization period. For half the mice of the shock and non-shocked groups the Y-maze was black and contained the grid floor. Thus, the apparatus was similar to the chambers in which shock had previously been delivered. For the remaining mice the walls and floor of the Y-mazes were covered by white inserts, making them distinctively different from the shock chambers. Following the 6 min acclimatization period mice were further subdivided and given either IP injection of amphetamine sulfate (3.0 mg/kg) or saline. Mice were returned to the Y-mazes 15 min afterward and perseveration performance determined as in the preceding experiments.

RESULTS AND DISCUSSION

The mean proportion of perseveration responses for each of the groups is shown in Fig. 4. Analysis of variance revealed that performance varied as a function of the interaction between Apparatus color and Drug treatment, $F(1,151)=3.86$, $p=0.051$. In vehicle treated mice alternation levels were somewhat higher when animals were tested in the black maze than in the white maze. The drug treatment provoked a reduction of alternation regardless of the maze in which mice were tested, but the perseverative (nonalternation) tendency was more pronounced in the black maze than in the white maze. In addition, the analysis of variance revealed that shock reduced the alternation tendency, $F(1,151)=13.99$, $p<0.01$.

Although the Shock treatment was not found to interact significantly with any of the other variables, it is clear from Fig. 4 that the effects of the shock were most discernible in amphetamine treated mice. For instance, in nonshocked mice amphetamine elicited perseveration scores of 0.40, while in shocked mice amphetamine elicited perseveration scores of 0.21 and 0.30. Inasmuch as *a priori* predictions had been made concerning the effects of stressors and stimulus factors in the amphetamine elicited perseveration, Newman-Keuls multiple comparisons were conducted on the means comprising the Shock × Apparatus color × Drug interaction. As predicted, the amphetamine induced perseveration tendency was influenced by the shock treatment mice received, as well as by the similarity between the test environment in which animals had initially been shocked and that in which they were subsequently tested. In particular, relative to saline treated animals administration of amphetamine to nonshocked mice reduced the alternation tendency (and induced a significant perseveration) regardless of the color of the test apparatus. In mice that were shocked and subsequently tested in a dissimilar apparatus the amphetamine-induced perseverative tendency was somewhat enhanced ($0.05<p<0.10$). If, however, the test apparatus was similar to that in which mice had initially been shocked, the amphetamine treatment significantly enhanced perseveration relative to nonshocked mice that received the drug ($p<0.01$). Moreover, the perseverative tendency induced by amphetamine in mice tested in the apparatus similar to that in which they had been shocked was somewhat greater than that of mice tested in an apparatus distinctively different from that in which shock had been applied ($0.05<p<0.10$). Thus it appears that the long-term effects of the shock treatment on amphetamine-induced perseveration may have been related to the stimulus context associated with the shock treatment and that in which mice were tested. The fact that the amphetamine elicited perseveration was

somewhat enhanced even when the shock and test sessions involved different environmental cues suggests that either some of the factors unrelated to stimulus factors accounted for some of the variability attributable to the shock treatment (i.e., a sensitization effect) or that the shock situations were sufficiently similar to permit enhancement of the amphetamine effect (e.g., handling, apparatus roof, etc).

Analysis of the frequency of arm entries revealed that amphetamine treatment significantly enhanced activity, $F(1,151)=50.99$, $p<0.01$. Moreover, as in Experiment 2, the shock treatment applied 3 days earlier was found to reduce locomotor activity, $F(1,151)=3.93$, $p<0.05$. The reduced activity was evident regardless of the similarity between the shock and test apparatus. Once again, these data suggest that either stimulus factors were unimportant in provoking the activity changes, or that there was sufficient similarity between the shock and test situations (even when the color of the apparatus differed) to permit expression of the altered locomotor activity.

GENERAL DISCUSSION

Administration of amphetamine, as previously reported [20,21], induced a marked perseverative tendency in which mice persisted in reentering those arms of the maze that had most recently been visited. Although neither foot-shock nor tail-shock influenced perseveration/alternation performance in the Y-maze, these treatments effectively enhanced the amphetamine-provoked perseverative tendency, provided that testing was conducted soon after application of the stressor. Moreover, it appeared that the organism's ability to contend with the stressor through behavioral means was fundamental in determining whether the enhanced perseveration would be evident. That is, while escapable shock was without effect on amphetamine-elicited perseveration, an identical amount of inescapable shock appreciably enhanced the perseverative tendency.

As indicated earlier, stressor application and amphetamine administration have been shown to induce several neurochemical changes which are similar to one another. Commensurate with the stressor provoked behavioral changes seen in the present investigation, it has been demonstrated that uncontrollable shock will influence neurochemical activity and concentrations to a greater degree than will controllable shock [5, 25, 32]. Accordingly, the differential effects of controllable and uncontrollable shock on amphetamine-induced perseveration may have been due to the increased catecholamine activity exerted by these treatments. This, of course, does not imply that other transmitters are not involved in the conjoint effects of the shock and amphetamine treatments. Stressors have been shown to influence 5-HT and endorphin activity [10,24]. Moreover, these neurochemical variations may depend on the controllability of the stressor [18, 23, 25] and are also subject to conditioning/sensitization processes [18]. Thus, it would be premature at this juncture to dismiss the potential contribution of these transmitters to the long-term consequences of uncontrollable stressors on amphetamine-elicited perseveration.

The effectiveness of stressors in provoking the enhanced amphetamine-induced perseveration was not only evident when animals were tested immediately after the stress session, but were apparent when animals were tested 72 hr after stressor application. The long lasting effect of the shock treatment, however, was evident provided that testing was conducted in a stimulus complex which was similar to that in which inescapable shock had been delivered. When shock and testing involved distinctively different environments (e.g., when stress was applied in the tail-shock apparatus and mice tested in the black Y-maze) enhanced perseveration was evident at the brief test interval, but not when mice were tested 72 hr after the stress session. Likewise, the enhancement of the amphetamine-induced perseveration was most pronounced at the 72 hr interval when the shock and test environments were similar (e.g., both apparatus being black and containing a grid floor). Accordingly, the possibility exists that the enhancement of the amphetamine effect 72 hr after inescapable shock was attributable to the conditioning of neurochemical changes associated with the stressor.

The finding that tail-shock did not influence performance 72 hr later, while foot-shock enhanced amphetamine-induced perseveration at this time could be attributed to factors other than conditioning. For instance, the different types of stress procedures (foot-shock vs. tail-shock) may not have been perceived as being equally aversive or may have lead to qualitative or quantitative differences in neurochemical activity. Additionally, in the tail-shock preparation animals were immobilized, whereas foot-shock was delivered to freely moving animals. As a result different patterns of exploration may have been induced in a subsequent test. Yet, the finding that enhanced perseveration was evident at the brief test interval irrespective of the stress paradigm employed suggests that the failure to detect long-lasting effects following tail-shock was probably not a phenomenon unique to this type of shock procedure or to the particular response styles that such a treatment might have provoked. Nevertheless, the position might still be entertained that tail-shock presented to immobilized animals may simply have produced a weaker, and hence shorter lasting sensitization effect, than did foot-shock applied to freely moving animals. Yet, the finding that foot-shock enhanced amphetamine-elicited perseveration only when the stimulus context in the stress and test situations were similar suggests that conditioning factors were likely determined whether long-term effects of the stress treatment would be evident.

Several investigators demonstrated that cues previously associated with shock will influence subsequent neurochemical activity. For instance, as indicated earlier, stimuli explicitly paired with shock have been shown to increase utilization of whole brain NE [13], and increased DA activity in the nucleus accumbens has been noted upon exposure to apparatus cues that had been associated with shock [17]. Thus it is conceivable that upon reexposure to cues associated with shock, the activity of DA and NE neurons would be increased, thereby leading to the enhancement of the amphetamine effects.

The fact that the long-term effects of shock on perseveration appeared to be dependent on the stimulus conditions in which animals were stressed and tested, should not be taken to imply that sensitization processes are not operative in the elicitation of other behaviors. As indicated earlier, it has been demonstrated repeatedly that stereotypy and locomotor activity provoked by amphetamine are subject to sensitization-like effects by prior stress [22]. Inasmuch as locomotor activity and stereotypy are largely subserved by DA alterations, while perseveration may involve an NE component [19], it is conceivable that these neurochemical systems are differentially influenced by conditioning and sensitization processes. Indeed, there appears to be speci-

ficity for the sensitization effect even when different DA systems are considered. Electrical self-stimulation of the nucleus accumbens or medial frontal cortex has been shown to enhance the stereotypy induced by amphetamine administered 24 hr later, while stimulation of the nigrostriatal DA system did not lead to such an effect [8].

Irrespective of the underlying mechanism, it is clear that aversive events may enhance the behavioral consequences of subsequent amphetamine treatment. Accordingly, in the evaluation of the response profile elicited by amphetamine administration, and in relating these response patterns to psychosis in humans, it would be appropriate not only to consider the organism's previous drug history, but also the backdrop upon which the drug is applied. Likewise, it is conceivable that psychological or physical insults may influence the course of drug-induced or idiopathic psychosis.

REFERENCES

1. Anisman, H. and L. S. Sklar. Social housing conditions influence escape deficits produced by uncontrollable stress: Assessment of the contribution of norepinephrine. *Behav Neural Biol* **32:** 406–427, 1981.
2. Anisman, H. and L. S. Sklar. Catecholamine depletion upon reexposure to stress: Mediation of the escape deficits produced by inescapable shock. *J Comp Physiol Psychol* **93:** 610–625, 1979.
3. Anisman, H. and R. M. Zacharko. Depression: The predisposing influence of stress. *Behav Brain Sci* **5:** 89–137, 1982.
4. Anisman, H., L. Kokkinidis and L. S. Sklar. Contribution of neurochemical change to stress-induced behavioral deficits. In: *Theory in Psychopharmacology*, vol 1, edited by S. J. Cooper. London: Academic Press, 1981.
5. Anisman, H., A. Pizzino and L. S. Sklar. Coping with stress, norepinephrine depletion and escape performance. *Brain Res* **191:** 583–588, 190.
6. Anisman, H., D. deCatanzaro and G. Remington. Escape performance following exposure to inescapable shock: Deficits in motor response maintenance. *J Exp Psychol: Anim Behav Proc* **4:** 197–218, 1978.
7. Anisman, H., J. Irwin, C. Beauchamp and R. M. Zacharko. Cross-stressor immunization against the behavioral deficits introduced by uncontrollable shock. *Behav Neurosci* **97:** 452–461, 1983.
8. Antelman, S. M. and L. A. Chiodo. Amphetamine as a stressor. In: *Stimulants: Neurochemical, Behavioral and Clinical Perspectives*, edited by I. Creese. New york: Raven Press, 1983.
9. Antelman, S. M., A. J. Eichler, C. A. Black and D. Kocan. Interchangeability of stress and amphetamine in sensitization. *Science* **207:** 329-331, 1980.
10. Barta, A. and K. Yashpal. Regional redistribution of β-endorphin in the rat brain: The effects of stress. *Prog Neuropsychopharmacol* **5:** 595–598, 1981.
11. Blanc, G., D. Herve, H. Simon, A. Lipoprawski, J. Glowinski and J. P. Tassin. Response to stress of mesocortico-frontal dopaminergic neurons in rats after long-term isolation. *Nature* **284:** 265–267, 1980.
12. Bruto, V. and H. Anisman. Acute and chronic amphetamine treatment: Differential modification of exploratory behavior in a radial maze. *Pharmacol Biochem Behav* **19:** 1983, in press.
13. Cassens, G., M. Roffman, A. Kuruc, P. J. Orsulak and J. J. Schildkraut. Alterations in brain norepinephrine metabolism induced by environmental stimuli previously paired with inescapable shock. *Science* **209:** 1138–1140, 1980.
14. Cherek, D. R., J. D. Lane, M. E. Freeman and J. E. Smith. Receptor changes following shock avoidance. *Soc Neurosci Abstr* **6:** 543, 1980.
15. Glazer, H. I. and J. M. Weiss. Long-term and transitory interference effects. *J Exp Psychol: Anim Behav Proc* **2:** 191–201, 1976.
16. Glazer, H. I. and J. M. Weiss. Long-term interference effect: An alternative to "Learned Helplessness." *J Exp Psychol: Anim Behav Proc* **2:** 202–213, 1976.
17. Herman, J. P., D. Guillonneau, R. Dantzer, B. Scatton, L. Smerdjian-Rouquier and M. LeMoal. Differential effects of inescapable footshocks and of stimuli previously paired with inescapable footshocks on dopamine turnover in cortical and limbic areas of the rat. *Life Sci* **30:** 2207–2214, 1982.
18. Jackson, R. L., S. F. Maier and D. J. Coon. Long-term analgesic effects of inescapable shock and learned helplessness. *Science* **206:** 91–93, 1979.
19. Kokkinidis, L. and H. Anisman. Amphetamine models of paranoid schizophrenia: An overview and elaboration of animal experimentation. *Psychol Bull* **88:** 551–579, 1980.
20. Kokkinidis, L. and H. Anisman. Amphetamine psychosis and schizophrenia: A dual model. *Neurosci Biobehav Rev* **5:** 449–461, 1981.
21. Kokkinidis, L. and H. Anisman. Interaction between cholinergic and catecholaminergic agents in a spontaneous alternation task. *Psychopharmacology (Berlin)* **48:** 261–270, 1976.
22. MacLennan, A. J. and S. F. Maier. Copine and stress-induced potentiation of stimulant stereotypy in the rat. *Science* **219:** 1091–1093, 1983.
23. Maier, S. F., J. E. Sherman, J. W. Lewis, G. W. Terman and J. C. Liebeskind. The opioid/nonopioid nature of stress-induced analgesia and learned helplessness. *J Exp Psychol Anim Behav Proc* **9:** 80–90, 1983.
24. Palkovits, M., M. Brownstein, J. S. Kizer, J. M. Saavedra and I. J. Kopin. Effects of stress on serotonin and tryptophan hydroxylase activity of brain nuclei. In: *Catecholamines and Stress*, edited by E. Usdin, R. Kvetnansky and I. J. Kopin. New York: Pergamon, 1976.
25. Petty, F. and A. D. Sherman. A neurochemical differentiation between exposure to stress and the development of learned helplessness. *Drug Dev Res* **2:** 43–45, 1982.
26. Robinson, T. E. and J. B. Becker. Behavioral sensitization is accompanied by an enhancement in amphetamine-stimulated dopamine release from striatal tissue in vitro. *Eur J PHarmacol* **85:** 253–254, 1982.
27. Robinson, T. E., J. B. Becker and S. K. Presty. Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: Sex differences. *Brain Res* **253:** 231–241, 1982.
28. Sklar, L. S. and H. Anisman. Stress and cancer. *Psychol Bull* **89:** 369–406, 1981.
29. Sklar, L. S. and H. Anisman. Stress and coping factors influence tumor growth. *Science* **205:** 513–515, 1979.
30. Thierry, A. M., J. P. Tassin, G. Blanc and J. Glowinski. Selective activation of the mesocortical DA system by stress. *Nature* **263:** 242–244, 1976.
31. Weiss, J. M. Effects of coping behavior with and without a feedback signal on stress pathology in rats. *J Comp Physiol Psychol* **77:** 22–30, 1971.
32. Weiss, J. M., H. I. Glazer, L. A. Pohorecky, W. H. Bailey and L. H. Schneider. Copine behavior and stress-induced behavioral depression: Studies of the role of brain catecholamines. In: *The Psychobiology of the Depressive Disorders*, edited by R. A. Depue. New York: Academic Press, 1979.
33. Weiss, J. M., W. H. Bailey, L. A. Pohorecky, D. Korzeniowski and J. Grillone. Stress-induced depression of motor activity correlates with regional changes in brain NE but not DA. *Neurochem Res* **5:** 9–22, 1980.
34. Welch, B. L. and A. S. Welch. Control of brain catecholamines and serotonin during acute stress and after d-amphetamine by natural inhibition of monozmine oxidase: An hypothesis. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970.