Pharmacology Biochemistry & Behavior, Vol. 19, pp. 497–504, 1983. Ankho International Inc. Printed in the U.S.A.

Attenuation of Perseverative Behavior after Repeated Amphetamine Treatment: Tolerance or Attentional Deficits?[1]

VENERA BRUTO,* LARRY KOKKINIDIS† AND HYMIE ANISMAN*

Department of Psychology, Carleton University, Ottawa, Ontario, K1S 5B6, Canada*
and Department of Psychology, University of Saskatchewan,† Saskatoon, Saskatchewan, Canada

Received 23 June 1981

BRUTO, V., L. KOKKINIDIS AND H. ANISMAN. *Attenuation of perseverative behavior after repeated amphetamine treatment: Tolerance or attentional deficits?* PHARMACOL BIOCHEM BEHAV 19(3) 497–504, 1983.—When permitted to explore an 8-arm radial maze, animals exhibited a systematic pattern of exploration characterized by preference for the most novel arms (spontaneous alternation) and entry into immediately adjacent arms (adjacent alternation). Acute treatment with moderate dosages of amphetamine reduced the proportion of both types of alternation responses and induced marked stimulus perseveration, i.e., consecutive entries between pairs of arms. Prior exposure to the apparatus enhanced the degree of perseveration ordinarily observed, and provoked perseveration after low doses of the drug. In contrast to acute drug treatment, perseveration was reduced after chronic amphetamine administration. However, chronic amphetamine treatment did not appear simply to reduce the potency of the drug. In contrast to the effects of apparatus pre-exposure on the degree of perseveration induced by acute amphetamine treatment, the degree of perseveration was not enhanced by pre-exposure to the maze in mice with a history of chronic amphetamine administration. Moreover, the exploratory pattern evident in chronically treated animals differed from that of control animals even when tested in the nondrug state. That is, animals chronically treated with amphetamine and tested with saline exhibited alternation scores which did not deviate from chance. These data suggest that chronic amphetamine treatment alters the way in which organisms attend, or respond, to environmental stimuli.

Amphetamine Perseveration Exploration Alternation

WHEN permitted to explore a Y-maze [1, 5, 6] or 8-arm radial maze [3], mice show a pattern of exploration characterized by the tendency to enter the least recently visited arm (spontaneous alternation). Acute treatment with low doses of d-amphetamine has been shown to provoke chance levels of alternation behavior, whereas higher doses induce a perseverative tendency such that animals successively visit two arms of the maze [3, 5, 6]. Following repeated treatment with amphetamine the perseverative effect of the drug is reduced, and chance level responding predominates [3, 7, 8]. Indeed, even when tested with saline, the alternation behavior ordinarily observed is absent among mice that had previously been chronically treated with amphetamine [3]. A relatively detailed analysis of response patterns in the 8-arm radial maze among mice chronically treated with amphetamine revealed an absence of any systematic pattern of exploration. The behavior of these animals was best characterized as a haphazard sequence of visits to the various arms of the maze [3].

It was recently proposed that the elimination of perseveration following repeated amphetamine treatment is not due to drug tolerance. Rather, such treatment may provoke a deficit in the animals' ability to attend to or filter environmental stimuli [9]. Consequently, after chronic amphetamine exposure, the exploratory patterns typically seen among mice tested with saline is disrupted, as is the response pattern of animals tested in the amphetamine condition. The purpose of the present investigation was to determine more directly whether chronic amphetamine treatment disrupts normal behavior patterns by altering the way organisms attend to, or utilize, environmental stimuli.

EXPERIMENT 1

It has been demonstrated that the perseverative behavior induced by amphetamine is influenced by stimulus factors. For example, increasing the heterogeneity of the maze, which retards the course of habituation, decreased the extent of the perseveration provoked by amphetamine [7]. Conversely, prior exposure (habituation) to a Y-maze maximized the perseverative effects of amphetamine [5,6]. It was suggested that among amphetamine treated mice two antagonistic tendencies exist: the inherent tendency to alternate and the perseverative tendency provoked by the drug. Accordingly, prior habituation to the maze which reduced the alternation tendency permitted the expression of the per-

[1]Supported by Grant A9845 from the Natural Sciences and Engineering Research Council to Hymie Anisman.

severation even after low doses of the drug. Experiment 1 was undertaken to ensure that the apparatus pre-exposure effects on amphetamine-induced perseveration previously seen in the Y-maze would also be evident in the 8-arm radial maze. In addition, this experiment assessed the effects of apparatus pre-exposure on the effects of amphetamine on various forms of alternation performance.

METHOD

Subjects

Eighty naive, male Swiss-Webster mice between 50 and 65 days of age were obtained from BioBreeding Laboratory, Ottawa. Animals were housed in groups of five in polypropylene cages and permitted ad lib access to food and water. Mice were acclimatized to the laboratory for seven days prior to behavioral testing.

Apparatus

An 8-arm wooden radial maze, described by Bruto and Anisman [3], was constructed such that each of the arms (55.9×11.4 cm) radiated from a central octagonal area (25.4 cm in diameter).

Procedure

Half of the mice were individually placed in the central area of the radial maze and allowed to explore the maze freely for a 15 minute period. The remaining mice were placed in individual holding cages for an equivalent period of time. Immediately following pre-exposure, mice received an intraperitoneal (IP) injection of either physiological saline (10.0 ml/kg) or d-amphetamine sulfate (1.0, 3.0 or 5.0 mg/kg salt weight, in a volume of 10.0 ml/kg) and placed in individual holding cages to await behavioral testing. Fifteen minutes after injection, mice were individually placed in the central area of the apparatus and allowed to explore the maze for 15 minutes. The sequence and number of arm entries was recorded.

Behavioral Assessment

The patterns of exploration were assessed in terms of: (a) locomotor activity: the total number of arm entries. (b) 2-Arm alternation: the proportion of visits made to one of the two least recently entered arms. The probability of occurrence of a 2-arm alternation response was 0.25. (c) 4-Arm alternation: the proportion of entries to one of the four least recently visited arms. The probability of such a response would be 0.50, and this measure would, in essence, be a more lax index of the alternation tendency than the 2-arm alternation measure. Moreover, a nonalternation in this context would constitute a 4-arm perseveration, the probability of which would also be 0.50, and would thus be analogous to the alternation/perseveration observed in the Y-maze task. (d) Perseveration: the proportion of entries to the most recently visited arms. The probability of such a perseveration response would be 0.125, and would thus represent a more stringent measure of the perseveration tendency than the 4-arm perseveration measure. (e) Adjacent alternation: the proportion of sequential entries to immediately adjacent novel arms. In this context, each arm entry was considered in the context of the previous two arm entries and considered an adjacent alternation if it was at least the third entry in an unidirectional sequence of adjacent arm entries.

TABLE 1

MEAN NUMBER OF ARM ENTRIES (±S.E.M.) AS A FUNCTION OF DRUG TREATMENT AND PRE-EXPOSURE TO THE APPARATUS

	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Naive to apparatus	50.3 ±7.2	78.2 ±10.4	99.5 ±8.4	102.6 ±20.8
Pre-exposed to apparatus	42.2 ±8.7	77.4 ±5.3	91.4 ±17.7	106.1 ±18.6

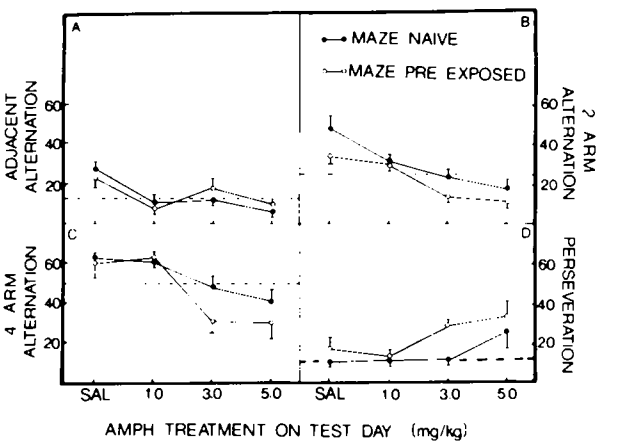

FIG. 1. Mean proportion (%) ±S.E.M. of adjacent alternation, 2-arm and 4-arm alternation and perseveration responses as a function of Prior Experience in the Apparatus, and Drug Treatment on Test Day (10.0 ml/kg saline, 1.0, 3.0 or 5.0 mg/kg d-amphetamine). The dotted lines designate chance levels of responding.

RESULTS AND DISCUSSION

Locomotor Activity

Analysis of variance indicated that Amphetamine Treatment modified locomotor activity, $F(3,72)=7.37$, $p<0.05$ (see Table 1). Newman-Keuls multiple comparisons ($\alpha=0.05$) revealed that 1.0, 3.0 and 5.0 mg/kg produced a significant increase in activity compared with saline-treated controls. Pre-exposure to the maze did not influence activity at any of the dosages.

Spontaneous Alternation

The data were analysed through Analysis of Variance of the individual alternation scores. In addition, χ^2 analyses of each of the group scores were conducted to determine whether performance deviated from chance. As predicted, the degree of preference which animals exhibited for the least recently visited arms of the maze was influenced by both the Amphetamine Treatment F's$(3,72)=18.70$, 15.87, p's<0.05 and Prior Exposure to the apparatus, F's$(1,72)=7.47$, 6.18, p's<0.05 for the 2-arm and 4-arm alternation measures, respectively (see Panels B and C of Fig. 1). Although the interaction between these two factors failed

TABLE 2

χ^2 ANALYSIS OF TOTAL GROUP PROPORTION OF RESPONSE TYPES

Treatments	Adjacent Alternation	2-arm Alternation	4-arm Alternation	Perseveration
Mice Naive to Apparatus				
saline	21.97*	30.72*	6.76*	0.21
1.0 mg/kg Amph	0.21	1.92	5.76*	0.23
3.0 mg/kg Amph	0.02	0.05	0.16	0.11
5.0 mg/kg Amph	3.86*	2.61	3.24	19.22*
Mice Pre-exposed to Apparatus				
saline	10.1*	4.32*	3.24	1.85
1.0 mg/kg Amph	1.85	1.92	6.76*	0.02
3.0 mg/kg Amph	2.77	6.47*	14.4*	22.0*
5.0 mg/kg Amph	0.57	9.01*	16.0*	38.4*

In each case, $df = 1$, χ^2 value necessary for $p<0.05 = 3.86$.
*Deviates from chance performance.

to reach statistical significance, multiple comparisons of the simple main effects were justified since an a priori prediction concerning this interaction had been made [13]. These comparisons confirmed previous findings [3] that among mice naive to the maze, 3.0 and 5.0 mg/kg of d-amphetamine reduced the proportion of alternation responses (2- and 4-arm) relative to saline-treated controls, whereas acute injection of 1.0 mg/kg of the drug was without effect. Pre-exposure to the test environment did not significantly reduce the intensity of the alternation tendency (as indexed by either the 4- or 2-arm alternation measures) among animals tested after injection with either saline or 1.0 mg/kg of amphetamine. However, prior exposure to the maze did reduce the alternation scores of mice treated with the 3.0 mg/kg dose of amphetamine. Indeed, whereas 3.0 mg/kg produced chance levels of alternation in the apparatus-naive group, alternation scores which fell significantly below chance were seen in the 3.0 mg/kg group that had been pre-exposed to the maze (see Table 2). Finally, although apparatus pre-exposure appeared not to influence overall alternation scores after 5.0 mg/kg, some subtle effect of pre-exposure may be detected. If the most stringent/sensitive measure of the alternation tendency is considered (i.e., 2-arm alternation) the maze pre-exposed and maze-naive 5.0 mg/kg groups may be distinguished from one another. Whereas mice naive to the apparatus displayed levels of 2-arm alternation which did not deviate from chance after injection of 5.0 mg/kg, their pre-exposed counterparts exhibited scores which fell significantly below chance. It may be that 5.0 mg/kg elicits such marked reductions in alternation that further decrements among mice pre-exposed to the maze become difficult to detect.

Not unexpectedly, the proportion of adjacent alternation responses was also influenced by the Drug Treatment, $F(3,72) = 10.75$, $p<0.05$ (see Panel A of Fig. 1). Newman-Keuls multiple comparisons ($\alpha = 0.05$) indicated that amphetamine treatment, at all dosages, decreased adjacent alternation relative to saline-treated controls; the drug groups did not differ significantly from one another.

Perseveration

Consistent with the observations of Kokkinidis and Anisman [5,6] perseveration was influenced by both the Drug Treatment, $F(3,72) = 5.16$, $p<0.05$, and Prior Exposure to the Maze, $F(1,72) = 4.27$, $p<0.05$. Newman-Keuls multiple comparisons ($\alpha = 0.05$) were conducted for the simple main effects comprising the factorial design since a priori predictions had been made on the basis of earlier experiments [5]. As previously reported [3], among mice that had not been pre-exposed to the maze treatment with the 5.0 mg/kg dose of amphetamine significantly increased the proportion of perseveration responses relative to saline treated controls (see Panel D of Fig. 1). Treatment with lower doses was without effect. Prior exposure to the apparatus did not significantly alter the degree of perseveration observed after injection of saline or 1.0 mg/kg of the drug. In contrast, however, pre-exposure to the maze significantly increased the degree of perseveration produced by 3.0 mg/kg of amphetamine. Indeed, whereas 3.0 mg/kg administered to mice naive to the apparatus produced perseveration scores which did not deviate from chance, the same dosage elicited perseverative responding which exceeded chance among mice pre-exposed to the maze (see Table 2). Finally, pre-exposure to the apparatus produced a small nonsignificant increase in perseverative responding in mice treated with 5.0 mg/kg of the drug. At this dosage mice that had been pre-exposed or naive to the maze exhibited perseverative responding which exceeded chance (see Table 2).

To summarize, prior exposure to the maze did not influence the degree of perseveration observed after injection with either saline or 1.0 mg/kg of amphetamine. Minimal perseveration was ordinarily observed in these groups and no significant enhancement was provided by 15 minutes of pre-exposure to the apparatus. In contrast, prior exposure to the maze significantly increased the proportion of perseverative responses induced by the 3.0 mg/kg dose of amphetamine. Whereas maze-naive mice that received 3.0 mg/kg of amphetamine exhibited levels of perseveration which did not differ significantly from those of saline-treated animals, the same drug dosage administered to mice previously exposed to the maze provoked a pronounced perseverative tendency. When marked perseveration was induced by the drug in maze-naive mice, as in the case of the 5.0 mg/kg dosage, a further enhancement of perseveration was not detectable after prior exposure to the apparatus.

TABLE 3

MEAN NUMBER OF ARM ENTRIES (±S.E.M.) AS A FUNCTION OF DRUG HISTORY, DRUG TREATMENT ON DAY OF TESTING AND APPARATUS PRE-EXPOSURE

	Naive to Apparatus				Pre-exposed to Apparatus			
	Drug Treatment on Day of Testing							
Chronic Drug History	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Saline	67 ± 4	70 ± 9	117 ± 13	75 ± 12	48 ± 3	62 ± 8	98 ± 15	100 ± 18
Amphetamine (10.0 mg/kg/day)	73 ± 7	89 ± 6	140 ± 19	98 ± 24	58 ± 4	68 ± 4	170 ± 11	159 ± 15

EXPERIMENT 2

As indicated earlier, following chronic treatment with amphetamine the perseverative effects ordinarily induced by acute administration of moderate doses of amphetamine are eliminated. However, the behavior of chronically treated mice does not resemble that of mice that received saline. Even after a fairly lengthy amphetamine treatment regimen, the high levels of alternation ordinarily seen among saline treated animals are not observed. Rather, chance levels of alternation are evident. On the one hand it might be argued that following repeated amphetamine treatment partial tolerance develops to the drug, such that the perseverative tendency is reduced but emergence of the alternation tendency is prevented. Alternatively, it is possible that chronic amphetamine treatment results in disturbances of attentional processes or stimulus filtering, thereby provoking a haphazard pattern of responding.

It was demonstrated in Experiment 1 that prior exposure to the maze enhanced the perseverative effects of low doses of amphetamine. Presumably, pre-exposure to the maze resulted in the reduction of the alternation tendency, thereby permitting manifestation of the perseverative effects of the drug. If chronic amphetamine treatment disrupts the animal's ability to filter or respond to environmental stimuli, it might be expected that pre-exposure to the maze would not enhance the perseverative tendency induced by amphetamine among mice that had previously received chronic treatment with the drug. In contrast, if the chance levels of alternation and perseveration seen in animals with a history of repeated amphetamine treatment reflects a reduction in the potency of the drug, then it should be possible to enhance perseveration by exposing mice to the apparatus cues prior to testing. That is, treatment with a moderate dose of amphetamine (5.0 mg/kg) following a repeated drug regimen ordinarily induces alternation and perseveration scores comparable to those of mice that received acute treatment with a lower dose of the drug (1.0–3.0 mg/kg). If chronic treatment with amphetamine results in a reduction of drug potency, then prior habituation to the maze should effectively enhance the perseverative effects of a moderate dose of amphetamine, just as prior apparatus habituation induces such effects among otherwise naive animals acutely treated with lower doses of the drug.

METHOD

Subjects and Apparatus

A total of 128 naive, male Swiss-Webster mice served as subjects. All particulars concerning the subjects and apparatus were the same as those outlined in Experiment 1, with the qualification that animals were housed individually from the commencement of the chronic drug or saline regime.

Procedure

Mice were injected daily with either amphetamine sulfate (10.0 mg/kg in a 10.0 ml/kg volume) or physiological saline (10.0 ml/kg) for ten consecutive days. On the eleventh day, half the mice of each group were individually placed in the maze for 15 minutes while the remaining mice spent an equivalent period of time in individual holding cages. Immediately thereafter, mice (n=8/group) received IP injection of either saline or amphetamine (1.0, 3.0 or 5.0 mg/kg) and were placed in individual holding cages to await behavioral testing. Fifteen minutes after injection, animals were placed in the maze and behavior was observed and scored as described in Experiment 1.

RESULTS AND DISCUSSION

Locomotor Activity

Analysis of variance of the number of arm entries revealed a significant interaction between Drug History and Drug Treatment on Day of Testing, $F(3,112)=2.77$, $p<0.05$. Newman-Keuls multiple comparisons ($\alpha=0.05$) of the simple effects comprising this interaction indicated that locomotor activity was enhanced after acute injection with either 3.0 or 5.0 mg/kg of amphetamine. Moreover, the locomotor excitation typically observed after 3.0 and 5.0 mg/kg was enhanced in amphetamine pre-treated mice (see Table 3). Analysis of Variance of the number of arm entries also yielded a significant interaction between Drug Treatment on Day of Testing and Apparatus Pre-exposure, $F(3,112)=5.55$, $p<0.05$. This interaction reflected the finding that pre-exposure to the apparatus enhanced the degree of locomotor excitation typically observed after injection with 5.0 mg/kg of amphetamine, but did not significantly alter the effects of the other drug doses.

TABLE 4

MEAN PROPORTION OF 2-ARM ALTERNATION RESPONSES AS A FUNCTION OF DRUG HISTORY, DRUG TREATMENT ON TEST DAY AND APPARATUS PRE-EXPOSURE

	Naive to Apparatus				Pre-exposed to Apparatus			
	Drug Treatment on Test Day							
Chronic Drug History	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Saline	0.51 ±0.05	0.38 ±0.04	0.28 ±0.02	0.19 ±0.04	0.43 ±0.05	0.35 ±0.04	0.16 ±0.04	0.15 ±0.03
Amphetamine (10.0 mg/kg/day)	0.39 ±0.05	0.34 ±0.03	0.28 ±0.04	0.17 ±0.03	0.45 ±0.04	0.38 ±0.05	0.25 ±0.03	0.20 ±0.04

TABLE 5

MEAN PROPORTION OF 4-ARM ALTERNATION RESPONSES AS A FUNCTION OF DRUG HISTORY, DRUG TREATMENT ON TEST DAY AND APPARATUS PRE-EXPOSURE

	Naive to Apparatus				Pre-exposed to Apparatus			
	Drug Treatment on Test Day							
Chronic Drug History	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Saline	0.79 ±0.04	0.69 ±0.05	0.64 ±0.04	0.37 ±0.08	0.64 ±0.02	0.68 ±0.05	0.42 ±0.06	0.38 ±0.06
Amphetamine (10.0 mg/kg/day)	0.72 ±0.03	0.67 ±0.04	0.56 ±0.04	0.38 ±0.06	0.74 ±0.02	0.71 ±0.04	0.58 ±0.03	0.54 ±0.08

Spontaneous Alternation

As seen in Tables 4 and 5, the degree of preference animals demonstrate for the more temporally novel arms of the maze, as measured by 2- and 4-arm alternation varied as a function of the Drug Treatment on Day of Testing, $F's(3,112)=40.02$, 38.45, $p<0.05$, respectively. Newman-Keuls multiple comparisons ($\alpha=0.05$) indicated that 3.0 and 5.0 mg/kg of amphetamine significantly reduced the proportion of 2- and 4-arm alternation responses compared with mice that had been tested with saline or 1.0 mg/kg. Although the Drug History × Drug Treatment on Test Day interaction did not reach statistical significance, it may be worth noting that the 2-arm alternation scores of 4 of 8 animals chronically treated with amphetamine and tested in the saline condition did not reach the above chance levels typical of mice treated with saline throughout the experiment.

Of particular interest was the finding that alternation (2- and 4-arm) also varied as a function of the Drug History × Apparatus Pre-exposure condition, $F(1,112)=7.07$, 5.61, $p<0.05$. Newman-Keuls multiple comparisons ($\alpha=0.05$) revealed that, regardless of the drug administered on test day, pre-exposure to the maze reduced the alternation tendency of mice that had been chronically pretreated with saline. In contrast, those mice that had received chronic amphetamine pretreatment were unaffected by prior experience in the test environment.

The proportion of adjacent alternation responses as a function of Drug Treatments and Apparatus Pre-exposure condition are presented in Table 6. Analysis of Variance revealed that adjacent alternation varied as a function of Drug History, $F(1,112)=4.32$, $p<0.05$, and Drug Treatment on Day of Testing, $F(3,112)=25.28$, $p<0.05$. As previously observed [3], Newman-Keuls multiple comparisons ($\alpha=0.05$) indicated that, among saline-pretreated mice, acute administration of 3.0 and 5.0 mg/kg reduced the adjacent alternation tendency relative to animals treated with saline or 1.0 mg/kg of the drug. Although the adjacent alternation tendency could not be differentiated on the basis of drug history among mice tested following injection of 1.0, 3.0 or 5.0 mg/kg of amphetamine, drug history was observed to be an important variable when considering animals tested in the nondrug state. Animals chronically treated with amphetamine and tested with saline displayed significantly lower levels of adjacent alternation than did their saline pretreated counterparts.

Perseveration

Analysis of Variance of the perseveration scores yielded a

TABLE 6

MEAN PROPORTION OF ADJACENT ALTERNATION RESPONSES AS A FUNCTION OF DRUG HISTORY, DRUG TREATMENT ON DAY OF TESTING AND APPARATUS PRE-EXPOSURE

	Naive to Apparatus				Pre-exposed to Apparatus			
	Drug Treatment on Test Day							
Chronic Drug History:	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg	Saline	1.0 mg/kg	3.0 mg/kg	5.0 mg/kg
Saline	0.39 ±0.06	0.20 ±0.04	0.11 ±0.03	0.08 ±0.03	0.32 ±0.03	0.15 ±0.04	0.11 ±0.03	0.12 ±0.04
Amphetamine (10.0 mg/kg/day)	0.18 ±0.06	0.22 ±0.07	0.08 ±0.03	0.09 ±0.03	0.29 ±0.03	0.20 ±0.04	0.06 ±0.02	0.03 ±0.01

significant Drug History × Drug Treatment on Test Day × Apparatus Pre-exposure interaction, $F(3,112)=3.70$, $p<0.05$ (see Fig. 2). Newman-Keuls multiple comparisons ($\alpha=0.05$) of the simple main effects comprising this interaction showed that, among saline pre-treated mice, 5.0 mg/kg of d-amphetamine significantly increased the frequency of perseveration responses relative to animals tested with saline. In contrast to the 5.0 mg/kg dosage, the perseveration induced by acute treatment with either 1.0 or 3.0 mg/kg could not be differentiated from that of saline-treated animals. Moreover, χ^2 tests indicated that the perseveration scores of animals tested following administration of saline, 1.0 or 3.0 mg/kg amphetamine did not deviate from chance, whereas the scores of the 5.0 mg/kg group significantly exceeded chance. Consistent with the results of Experiment 1, among mice chronically treated with saline, prior experience in the maze modified perseveration following injection of 3.0 mg/kg but not after administration of either saline, 1.0 or 5.0 mg/kg of amphetamine. It appears that with 1.0 mg/kg of amphetamine the perseverative tendency is weak and its expression is not enhanced by 15 minutes of pre-exposure to the apparatus. As in Experiment 1, following 5.0 mg/kg of amphetamine, perseveration is sufficiently intense to preclude further enhancement of this tendency by apparatus pre-exposure. However, among mice that had been pretreated with saline, pre-exposure to the maze increased the proportion of perseverative responses after 3.0 mg/kg of amphetamine. Indeed, as reported in Experiment 1 and by Kokkinidis and Anisman [5] chance levels of perseveration were apparent among mice naive to the apparatus and tested with 3.0 mg/kg, while perseveration scores which exceeded chance were evident at this dosage among mice previously exposed to the maze (see Table 7).

In agreement with previous observations [3,10] the degree of perseveration ordinarily observed after 5.0 mg/kg was reduced among mice with a history of repeated amphetamine administration. In fact, whereas perseveration exceeded chance levels among mice pretreated with saline and treated with 5.0 mg/kg amphetamine, perseveration scores did not deviate from chance in those animals that had been pretreated with amphetamine. Chronic amphetamine administration did not influence the perseveration observed after saline, 1.0 or 3.0 mg/kg. Each of these groups displayed chance levels of perseveration, and as such no attenuation

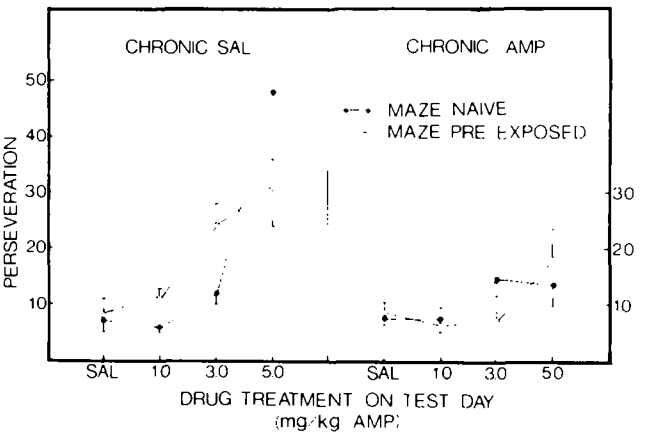

FIG. 2. Mean proportion (%) ±S.E.M. of perseveration responses as a function of Drug History (10.0 ml/kg saline, or 10.0 mg/kg d-amphetamine for 10 consecutive days), Prior Experience in the Maze and Drug Treatment on Test Day (10.0 ml/kg saline, 1.0, 3.0 or 5.0 mg/kg d-amphetamine).

was observed after chronic treatment with the drug. Of particular interest in the present experiment was the finding that unlike mice that received saline pretreatment, pre-exposure to the test environment did not influence the behavior of animals with a history of repeated amphetamine injections. Specifically, pre-exposure to the maze did not alter the perseveration scores of animals chronically treated with amphetamine when tested after injection with 3.0 or 5.0 mg/kg. Regardless of apparatus pre-exposure condition, amphetamine pretreated mice tested with 3.0 or 5.0 mg/kg showed levels of perseveration which did not differ from chance performance.

GENERAL DISCUSSION

As in the free-running Y-maze exploratory task, mice permitted to explore an 8-arm radial maze exhibited a systematic pattern of exploration. That is, mice tended to visit

TABLE 7

χ^2 ANALYSIS OF TOTAL GROUP PROPORTION OF RESPONSE TYPES

	Adjacent Alternation	2-arm Alternation	4-arm Alternation	Perseveration
Chronic Saline				
Maze-naive				
saline	64.2*	36.06*	33.6*	2.77
1.0 mg/kg Amph	5.14*	9.01*	14.4*	3.85
3.0 mg/kg Amph	0.21	0.48	2.56	0.02
5.0 mg/kg Amph	1.85	1.92	6.76*	115.2*
Maze pre-exposed				
saline	34.7*	17.28*	2.56	1.85
1.0 mg/kg Amph	0.57	5.33*	13.0*	0.21
3.0 mg/kg Amph	0.21	4.32*	2.56	12.1*
5.0 mg/kg Amph	0.02	5.33*	5.76*	31.3*
Chronic Amphetamine				
Maze naive				
saline	2.77	10.45*	19.4*	1.85
1.0 mg/kg Amph	8.25*	4.32*	11.6*	1.85
3.0 mg/kg Amph	1.85	0.48	1.44	0.21
5.0 mg/kg Amph	1.12	3.41	5.76*	0.02
Maze pre-exposed				
saline	24.9*	21.33*	23.0*	1.12
1.0 mg/kg Amph	5.14*	9.01*	17.6*	2.77
3.0 mg/kg Amph	3.86*	0	2.56	1.85
5.0 mg/kg Amph	7.83*	1.33	0.64	2.77

In each case, $df = 1$, χ^2 value necessary for $p < 0.05 = 3.86$.
*Deviates from chance performance.

the least recently visited arms of the maze (spontaneous alternation). Moreover, mice often exhibited sequences of three or more arm entries to immediately adjacent arms (adjacent alternation). In accordance with previously reported observations of mice in both the Y- and radial-mazes [1, 3, 5, 6], acute treatment with low doses of amphetamine (3.0 mg/kg) reduced each of these alternation tendencies, where injection of 5.0 mg/kg also elicited marked stimulus perseveration. As reported by Kokkinidis and Anisman [5,6] habituation appears to influence the perseverative tendency. That is to say, prior exposure to the maze (habituation) enhanced the degree of perseveration ordinarily observed after a moderate dosage of amphetamine. Whereas 3.0 mg/kg of amphetamine reduced alternation to chance levels with minimal effects on perseveration, this dosage elicited marked perseveration among mice that had been pre-exposed to the maze.

The perseverative behavior ordinarily observed after acute administration of amphetamine (5.0 mg/kg) was reduced among mice that had received repeated drug treatment. It did not appear, however, that this was a consequence of a reduction in the potency of the drug effect. In particular, if chronic amphetamine treatment reduced the potency of the drug treatment, then it would reasonably have been expected that the effects of 5.0 mg/kg of amphetamine in chronically treated mice would have been reminiscent of lower doses of the drug acutely applied. However, the effects of the chronic drug treatment on perseveration and alternation behavior could be distinguished from that provoked by acute treatment of lower doses. As in the case of acute administration of 3.0 mg/kg of the drug, treatment with 5.0 mg/kg of amphetamine in chronically treated mice resulted in chance levels of alternation and perseveration. However, whereas prior exposure to the maze enhanced perseveration of mice that received acute drug treatment, performance was unaltered among mice that received the chronic drug regimen. Moreover, the behavior of mice that received the chronic drug treatment and tested with 5.0 mg/kg could be distinguished from that of naive mice tested with saline or 1.0 mg/kg of amphetamine. Whereas mice of the latter groups displayed levels of alternation and adjacent alternation that exceeded chance, mice chronically treated with the drug exhibited chance levels of alternation. Indeed, even when tested in the non-drug state, mice with a history of amphetamine administration did not exhibit the patterns of exploration (alternation and adjacent alternation) characteristic of pharmacologically naive animals. The fact that chronic amphetamine treatment influences behavior when testing was conducted in the non-drug state suggests that the drug regimen had lasting effects on behavior quite apart from tolerance effects that could have developed.

The effects of prior exposure to the maze on the response to amphetamine in the chronic drug group is consistent with the contention that the disruption of normal behavioral pat-

terns after chronic amphetamine treatment may be dependent on variations in the way animals attend to stimuli in their environment [9]. Whether the variations in the behavior of animals with a history of repeated amphetamine administration reflects an inability to filter environmental cues or to attend/respond selectively to environmental cues, owing to specific alterations of norepinephrine and dopamine receptors or in the turnover of these amines, remains to be determined. Finally, these data raise the possibility that the attenuation of other amphetamine-induced behavior after chronic treatment may similarly be dependent on alterations in the way animals attend/respond to environmental stimuli. For instance, the attenuation of amphetamine-induced increases in intracranial self-stimulation response rates [11] and response rates in time-based reinforcement schedules after chronic amphetamine treatment [4,12] may reflect attentional variations rather than a change in drug potency.

REFERENCES

1. Adkins, J., J. W. Packwood and G. L. Marshall, Jr. Spontaneous alternation and d-amphetamine. *Psychon Sci* **17:** 167–168, 1969.
2. Brodie, B. B., A. K. Cho and G. L. Gissa. Possible role of p-hydroxy-norephedrine in the depletion of norepinephrine induced by d-amphetamine. In: *Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970.
3. Bruto, V. and H. Anisman. Acute and chronic amphetamine treatment: Differential modification of exploratory behavior in a radial maze. *Pharmacol Biochem Behav* **19:** 487–496, 1983.
4. Campbell, J. C. and L. S. Seiden. Performance influence on the development of tolerance to amphetamine. *Pharmacol Biochem Behav* **1:** 703–708, 1973.
5. Kokkinidis, L. and H. Anisman. Interaction between cholinergic and catecholaminergic agents in a spontaneous alternation task. *Psychopharmacology (Berlin)* **48:** 261–270, 1976.
6. Kokkinidis, L. and H. Anisman. Dissociation of the effects of scopolamine and d-amphetamine on a spontaneous alternation task. *Pharmacol Biochem Behav* **5:** 293–297, 1976.
7. Kokkinidis, L. and H. Anisman. Abatement of stimulus perseveration following chronic d-amphetamine treatment: Absence of behaviorally augmented tolerance. *Pharmacol Biochem Behav* **8:** 557–563, 1978.
8. Kokkinidis, L. and H. Anisman. Behavior specific tolerance following chronic d- or l-amphetamine treatment: Lack of involvement of p-hydroxynorephedrine. *Neuropharmacology* **17:** 95–102, 1978.
9. Kokkinidis, L. and H. Anisman. Amphetamine models of paranoid schizophrenia: An overview and elaboration of animal experimentation. *Psychol Bull* **88:** 551–579, 1980.
10. Kokkinidis, L., D. Walsh, R. Lahue and H. Anisman. Tolerance to d-amphetamine behavioral specificity. *Life Sci* **18:** 913–918, 1976.
11. Leith, N. J. and R. J. Barrett. Amphetamine and the reward system: Evidence for tolerance and post-drug depression. *Psychopharmacology (Berlin)* **46:** 19–26, 1976.
12. Tilson, H. A. and R. H. Rech. Prior drug experience and effects of amphetamine on schedule controlled behavior. *Pharmacol Biochem Behav* **1:** 129–132, 1973.
13. Winer, B. J. *Statistical Principles in Experimental Design*. New York: McGraw Hill, 1961.