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The Effects of Chronic Amphetamine Administration on the Acquisition and Extinction of an Active and Passive Avoidance Response in Mice

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KOKKINIDIS, L. *The effects of chronic amphetamine administration on the acquisition and extinction of an active and passive avoidance response in mice.* PHARMACOL BIOCHEM BEHAV **19**(4) 593–598, 1983.—Long-term amphetamine treatment had no effect on the acquisition or retention of an active or passive avoidance response. In both tasks, however, mice withdrawn from chronic amphetamine administration showed a resistance to extinction relative to control animals. These findings were related to the effects of long-term amphetamine administration on attentional processes. Possible neurochemical mechanisms governing the attentional deficits induced by chronic exposure to amphetamine were discussed.

Active avoidance Passive avoidance Extinction Chronic Amphetamine treatment Selective attention Norepinephrine Dopamine

CHRONIC amphetamine treatment has pronounced effects on behaviour. For example, rats trained to bar press for electrical brain stimulation and then exposed to a chronic regimen of amphetamine, exhibit depressed rates of self-stimulation responding upon drug withdrawal [15,17]. Despite the finding that amphetamine abstinence results in anhedonia, long-term amphetamine administration potentiates many of the behavioural consequences of the drug (for review see [8,28]). Behaviours that are exacerbated after chronic amphetamine treatment include drug-induced locomotor activity [27,29], facilitation of acoustic startle [12], stereotypic behaviours [28,30], and facilitation of responding for electrical brain stimulation [14,16].

Considerable effort has been expended on delineating the neurochemical consequences of long-term amphetamine treatment (for review see[7,8]). One robust neurochemical effect of chronic amphetamine administration is norepinephrine depletion [3,25,28]. Although the role of norepinephrine depletion in modulating the behavioural effects of long-term amphetamine administration is not well understood, it has been demonstrated, repeatedly, that depletion of this amine results in a resistance to extinction in a variety of learning tasks (for review see [21]). It should be noted, however, that the reliability of some of these findings have been questioned recently [24]. These reports notwithstanding, there is considerable evidence from a number of independent laboratories demonstrating the importance of norepinephrine in the extinction of a conditioned response. For example, although lesions of the locus coeruleus did not impair the acquisition of a classically conditioned nicitating membrane response, there was an extinction deficit; the magnitude of which correlated highly with norepinephrine depletion induced by the lesion [23]. Further to this point, withdrawal from long-term tricyclic antidepressant treatment resulted in a resistance to extinction in both a runway and lever press task [33]. It was suggested that the extinction deficit resulted from a decreased efficacy of norepinephrine neurotransmission induced by long-term exposure to desmethylimipramine [33]. Consistent with the argument that resistance to extinction after norepinephrine depletion involves attentional deficits [21], was the finding that rats depleted of norepinephrine were unable to ignore redundant stimulus information [19].

Recently, it was suggested that in contrast to acute amphetamine administration which facilitated selective attention to environmental stimuli, i.e., stimulus preservation [7], chronic amphetamine treatment had a disruptive effect on attentional process [8]. Attentional deficits after long-term amphetamine administration have been observed in a Y-maze exploratory task [7,8], and in a latent inhibition paradigm [31,32]. Moreover, it was argued that norepinephrine depletion induced by long-term amphetamine treatment was important in subserving these deficits [7,8]. Since long-term amphetamine treatment has pronounced affects on attentional processes, it was of interest to assess the effects of chronic amphetamine treatment on the extinction of an acquired active and passive avoidance response.

EXPERIMENT 1

In Experiment 1, the effects of chronic amphetamine

administration on the acquisition and extinction of a jump-up avoidance response were evaluated.

METHOD

Subjects

Twenty-four naive male Swiss mice procured from the Animal Resources Centre at the University of Saskatchewan served as subjects in Experiment 1. Mice weighed approximately 25–30 g at the initiation of the experiment and were housed individually in standard polypropylene cages with free access to food and water.

Apparatus

Two white Plexiglas chambers, 14.0 cm long × 10.0 cm wide × 13.0 cm high were used in the jump-up avoidance task. The grid floor of the chambers consisted of 0.32 cm stainless steel bars spaced 1.0 cm apart. A metal platform (9.0 cm wide and 0.03 cm thick) attached to a small motor outside one wall of each chamber, protruded 3.0 cm into the chamber (2.0 cm above the grid floor) when activated by the onset of an avoidance trial. When deactivated either by a jump-up response or termination of the trial the platform was withdrawn from the chamber through a slit in the wall. A light source served as the CS and was situated above the platform 10.0 cm above the grid floor. Footshock (300 μA, scrambled) was administered by a Grason-Stadler Shock Generator (E6070B, West Concord, Massachusetts).

Procedure

Mice were injected daily with two intraperitoneal injections (10:00 a.m. and 4:00 p.m.) of either saline or 5.0 mg/kg of d-amphetamine sulfate for 10 consecutive days. On day 11, mice in each group (N = 12 per group) were placed in one of the test chambers and presented with the CS for 10 sec. The platform was activated with the onset of the CS. If subjects did not make the required jump-up response during CS interval and thus terminate the trial, electric footshock was introduced and was terminated after the animal jumped up onto the platform or after 10 sec elapsed. At the termination of the trial the platform was withdrawn. Avoidance training for the two groups of mice was carried out in a single session of 120 trials with an intertrial interval of 30 sec. Subjects not reaching the required acquisition criterion of 80% avoidances during the last 20 acquisition trials were dropped from the study. Twenty-four hours after acquisition training mice were placed in the chambers and received 120 extinction trials. Each trial was initiated with the onset of the CS and no shock was presented. The trials were 20 sec in duration and the intertrial interval was 30 sec. Extinction sessions were conducted daily for 12 days. The number of jump-up responses and the latency to respond after CS onset were recorded.

RESULTS

Four mice from the saline group and three mice from the amphetamine group failed to reach the acquisition criterion and were dropped from the experiment. Long-term amphetamine treatment had no effect on the acquisition of the jump-up avoidance response. The mean number of avoidances made by mice in the chronic saline group (90.1 ± 11.3) was not different from that made by mice in the chronic amphetamine group (96.7 ± 13.4, $t = 0.87$, $p > 0.05$). Similarly, no differences between groups were observed when response latencies were considered (4.1 ± 0.84 sec and 3.6 ± 1.7 sec for chronic saline and chronic amphetamine groups, respectively; $t = 0.87$, $p > 0.05$).

The extinction data were analyzed by a two-factor analysis of variance repeated measures design. This analysis yielded significant Drug × Block interactions, $F(5,75) = 2.78$, $p < 0.05$ and $F(5,75) = 2.66$, $p < 0.05$, for jump-up and latency data, respectively. Subsequent Newman-Keuls multiple comparisons ($\alpha = 0.05$) of the simple main effects involved in these interactions revealed that amphetamine administration had no effect on the retention of the learned jump-up response. As depicted in Fig. 1 (Block 1), chronic saline and amphetamine groups performed comparably in terms of number of jump-up avoidance responses, and as shown in Fig. 2 (Block 1), response latencies for the two groups were not different from one another. Whereas mice exposed to chronic saline treatment showed significantly fewer jump-up responses and longer response latencies as a function of repeated exposure to the CS in the absence of shock, performance of mice in the chronic amphetamine group remained consistent over days. Mice in the chronic saline group made fewer jump-up responses (Fig. 1), and had slower response latencies (Fig. 2), than mice in the chronic amphetamine group during blocks 2–6 of the extinction phase of the experiment.

EXPERIMENT 2

The results of Experiment 1 demonstrated that exposure to long-term amphetamine treatment resulted in a resistance to extinction of an acquired jump-up avoidance response. Experiment 2 was designed to examine the effects of long-term amphetamine administration on the acquisition and extinction of a passive avoidance response.

METHOD

Subjects

Twenty naive male Swiss mice served as subjects in Experiment 2. All other particulars concerning subjects were similar to those described in Experiment 1.

Apparatus

The apparatus consisted of a white Plexiglas chamber 18.0 cm long, 10.0 cm wide and 13.0 cm high with a grid floor. A 7.5 cm square wooden platform was situated at the end of the chamber, 4.0 cm above the grid floor. The grid floor consisted of 0.32 cm stainless steel bars spaced 1.0 cm apart and was electrified by a Grason-Stadler Shock Generator (see Experiment 1).

Procedure

Mice were randomly assigned to one of two groups (N = 10 per group) and were treated with two intraperitoneal injections (10:00 a.m. and 4:00 p.m.) of 5.0 mg/kg of d-amphetamine sulfate, or saline daily for 10 consecutive days. On day 11, mice were placed on the platform and the latency to step down onto the grid floor was recorded. A step-down response was defined as subjects placing all four feet on the grid floor. When mice stepped down off the platform they received footshock (300 μA, scrambled) until they escaped back onto the platform or 10 sec elapsed. If escape had not occurred successfully after 10 sec, footshock was

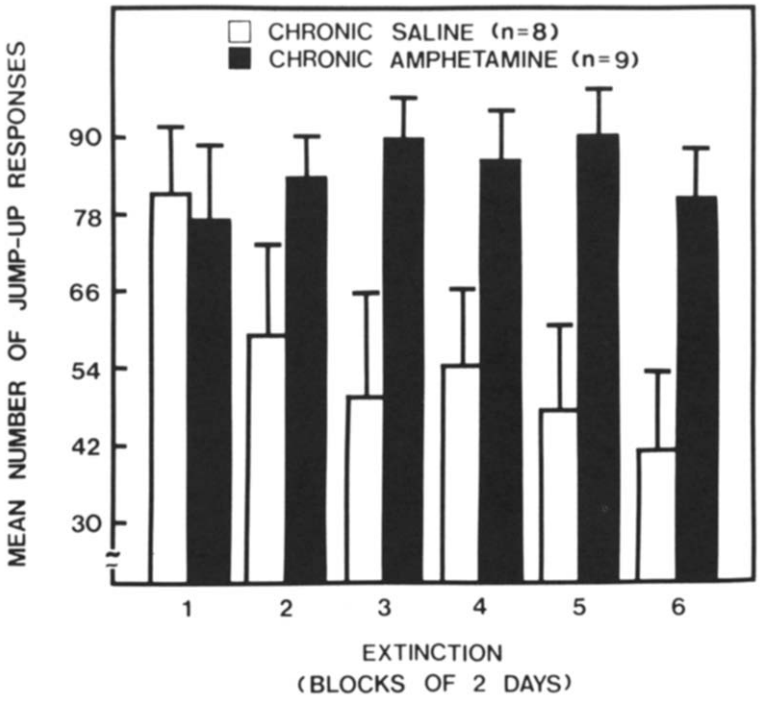

FIG. 1. Mean number of jump-up responses (+S.E.M.) during 12 successive days of extinction testing as a function of long-term exposure to amphetamine or saline.

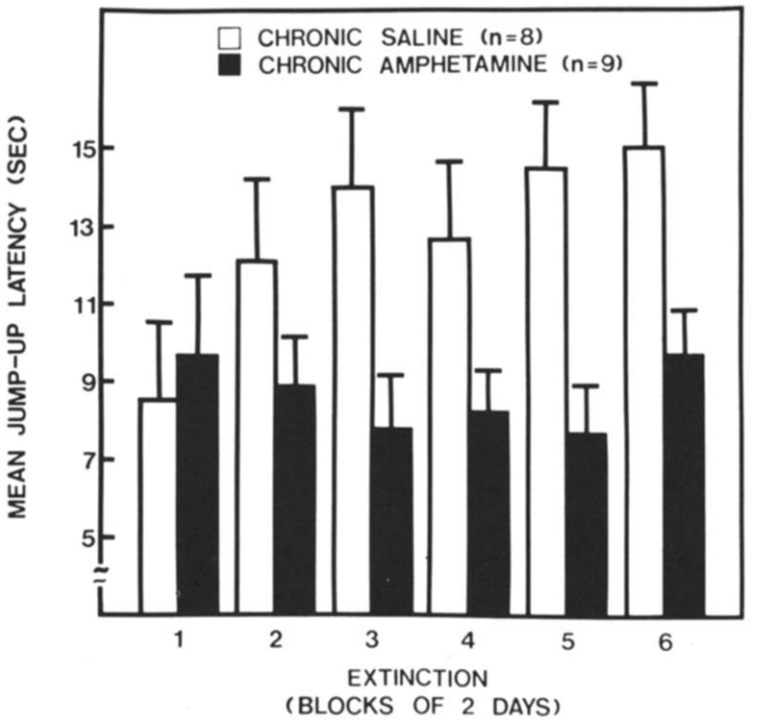

FIG. 2. Mean jump-up response latencies (+S.E.M.) during 12 successive days of extinction testing as a function of long-term exposure to amphetamine or saline.

TABLE 1
ACQUISITION OF A PASSIVE STEP-DOWN RESPONSE AS A FUNCTION OF CHRONIC SALINE OR AMPHETAMINE TREATMENT

	Saline	Amphetamine	t-Test
Mean (±S.E.M.) time in apparatus prior to criterion (sec)	304.5 ± 27.3	345.4 ± 61.3	t = 0.60, p > 0.05
Mean (± S.E.M.) number of step-down responses	3.9 ± .46	3.5 ± .55	t = 0.53, p > 0.05
Mean (± S.E.M.) latency to step-down (sec)	79.6 ± 9.7	124.1 ± 30.0	t = 1.38, p > 0.05
Mean (±S.E.M.) initial step-down latency (sec)	29.0 ± 11.8	86.8 ± 37.4	t = 1.46, p > 0.05

terminated and mice were placed back onto the platform. The number of step-down responses, the latency to step-down and the time in the apparatus prior to animals reaching the acquisition criterion were recorded. The acquisition criterion consisted of subjects remaining on the platform for 5 consecutive minutes. Twenty-four hours after acquisition training the extinction phase of the experiment was initiated. Animals were placed on the wooden platform and the latency to step-down on the grid floor was recorded. Footshock was not delivered and animals were allowed to remain on the grid floor for 10 sec prior to removal from the chamber. If mice remained on the platform for 5 min without stepping down they were removed from the chamber for the day. This procedure was followed daily for 14 days.

RESULTS

All measures taken during acquisition training yielded no statistically significant differences between groups (see Table 1). A small non-significant effect was observed, however, when mean step-down latency was considered. Specifically, mice chronically treated with amphetamine tended to have longer step-down latencies than mice in the chronic saline group. As shown in Table 1, much of this marginal difference between groups is accounted for by differences on the initial step-down latency measure. Again, although not statistically significant, mice in the chronic amphetamine group on average took three times longer than saline animals to step down off the platform upon initial exposure to the apparatus. Observation of subjects revealed that mice chronically treated with amphetamine were more active in exploring the platform and surrounding walls than were chronic saline treated mice.

Two factor analysis of variance of the extinction data with repeated measures on one factor yielded a significant Group x Blocks interaction, $F(6,108)=2.61$, $p<0.05$. Subsequent Newman Keuls multiple comparisons ($\alpha=0.05$) of the simple main effects involved in the interaction revealed that there were no significant differences between groups in the retention of the passive avoidance response (see Fig. 3; Block 1), suggesting that 48 hours after acquisition training both groups were performing at the same level. As depicted in Fig. 3, chronic saline treated mice showed decreased step-down latencies as a function of repeated testing, whereas performance of mice in the chronic amphetamine group remained relatively consistent over days. Differences between groups emerged during the last two test blocks (i.e., 4 days). During this time mice in the chronic saline group stepped down off the platform significantly faster than did mice that were chronically exposed to amphetamine.

GENERAL DISCUSSION

There is accumulating evidence suggesting that long-term amphetamine administration has disruptive effects on attentional processes. For example, after acute amphetamine administration mice continuously explore only two arms of a symmetrical Y-maze [9]. After long-term amphetamine administration, however, the perseverative response to amphetamine is attenuated, and the exploratory behaviour of mice in the Y-maze tends to be haphazard and non-directed [10]. Initially, it was thought that the decreased perseverative response to amphetamine reflected the development of tolerance [10]. However, it was later suggested that the random non-directed behavioral patterns observed in the Y-maze after long-term exposure to amphetamine were governed by drug-induced changes in attentional processes [7,8].

Another line of evidence implicating long-term amphetamine treatment to attentional deficits deals with the effects of the drug on latent inhibition. Specifically, after chronic amphetamine administration animals exposed to a series of nonreinforced presentations of a stimulus acquired, with little difficulty, a conditioned avoidance response to that stimulus when it was subsequently paired with shock [31]. This was in marked contrast to the performance of naive undrugged animals, which was characterized by marked deficits in acquisition of the conditioned response following preexposure to the series of nonreinforced presentations of the conditioned stimulus, i.e., latent inhibition [31]. It was suggested that during stimulus preexposure, animals treated chronically with amphetamine were unable

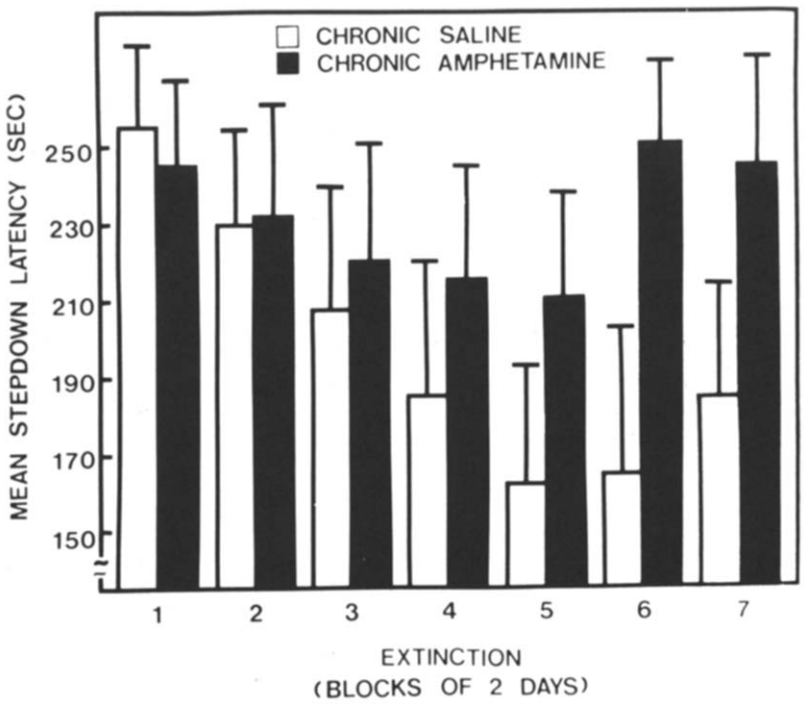

FIG. 3. Mean step-down latencies (± S.E.M.) in a passive avoidance task during 14 successive days of extinction testing as a function of long-term exposure to amphetamine or saline.

to attend selectively to the irrelevant stimulus, resulting in a retarded latent inhibition effect [31].

The results of this investigation are consistent with the position that long-term amphetamine treatment disrupts attentional mechanisms. In Experiment 1, it was found that whereas chronic exposure to amphetamine did not impair the acquisition of a jump-up avoidance response, there was a resistance to extinction of this response. In Experiment 2, long-term amphetamine administration had no effect on the acquisition of a passive avoidance response, although it appeared that after chronic amphetamine treatment mice displayed more exploration of the platform relative to mice chronically treated with saline. As was the case in Experiment 1, a resistance to extinction was observed after long-term amphetamine treatment in the passive avoidance task. Using similar behavioral paradigms, it was demonstrated that norepinephrine depletion induced by lesions to the ascending dorsal noradrenergic bundle resulted in a resistance to extinction [5,22]. It was suggested that attentional deficits induced by norepinephrine depletion were responsible for the observed extinction effects [21]. More specifically, it was argued that decreased noradrenergic activity resulted in increased sampling of the stimulus array during the acquisition of the conditioned response. This in turn allowed for the formation of more stimulus-response associations resulting in a resistance to extinction during extinction testing [21]. Although norepinephrine levels were not measured in the present study, it is noteworthy that injections of 10 mg/kg of d-amphetamine daily for 5 consecutive days to mice of the same strain employed in these experiments, resulted in a 20% depletion of whole brain norepinephrine [11].

Parenthetically, other less direct manipulations of norepinephrine activity also produced deficits in the extinction of well learned responses. For example, exposure to isolation stress, which like long-term amphetamine administration, depletes norepinephrine (for review see [1]), produced a resistance to extinction of an active avoidance response [20]. This is not surprising when it is considered that the behavioral and neurochemical correlates of stress closely parallel those seen after chronic amphetamine treatment. In fact both manipulations appear to sensitize the organism to later amphetamine administration [4,13]. For example, as was observed after long-term amphetamine treatment, exposure to stress potentiated the stereotypic, locomotor and startle responses to amphetamine [6,13,26].

Finally, there is recent evidence indicating that dopamine plays a critical role in the development of attentional deficits observed after chronic amphetamine administration, as well. Solomon and Stranton [32], demonstrated that daily microinjection of d-amphetamine into the nucleus accumbens for 5 consecutive days resulted in a retarded latent inhibition effect. This was not the case, however, when animals received microinjections of d-amphetamine into the caudate-putamen [32]. Thus, in addition to norepinephrine, it appears that mesolimbic dopamine activity is important in governing the attentional deficits seen after long-term amphetamine administration. It is unlikely, however, that changes in norepinephrine and dopamine modify attentional processes in a singular fashion. Rather, as we previously suggested [7], as have others [2], the behavioral consequences of amphetamine treatment are likely subserved by complex interactions between these neurotransmitters.

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