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The Abolition of the Partial Reinforcement Extinction Effect (PREE) by Amphetamine: Disruption of Control by Nonreinforcement

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WEINER, I., J. FELDON AND H. BERCOVITZ. *The abolition of the partial reinforcement extinction effect (PREE) by amphetamine: Disruption of control by nonreinforcement.* PHARMACOL BIOCHEM BEHAV 27(2) 205–210, 1987.—Two groups of rats were trained to run in a straight alley. The continuously reinforced (CRF) group received a food reward on every trial. The partially reinforced (PRF) group was rewarded on a quasi-random 50% schedule. d-Amphetamine 1 mg/kg was administered to PRF animals in acquisition in a 2×2 design, i.e., drug-no drug on reinforced trials and drug-no drug on nonreinforced trials. In four CRF groups, the drug was administered in the same sequence as in the PRF groups. Following acquisition, all animals were given 4 days of CRF retraining and tested in extinction. No drug was given in retraining and extinction. The PREE, i.e., increased resistance to extinction exhibited by PRF animals as compared to CRF animals, was obtained in groups which received placebo on all acquisition trials or amphetamine on rewarded trials and placebo on nonrewarded trials. The PREE was abolished when amphetamine was administered throughout the acquisition trials or on nonrewarded trials, irrespective of drug treatment on rewarded trials.

d-Amphetamine Continuous reinforcement Partial reinforcement Nonrewarded trials
Rewarded trials Resistance to extinction Rat

IN the partial reinforcement extinction effect (PREE) paradigm animals are trained in the first (acquisition) stage to run down an alley for food reward. One group (the continuous reinforcement or CRF group) receives a reward on every trial. The second group (the partial reinforcement or PRF group) receives a reward only on a certain proportion (typically random 50%) of the trials. In the second stage of the experiment the two groups are tested in extinction, i.e., no rewards are delivered on any trial. The PREE refers to the fact that the PRF animals show increased resistance to extinction as compared to the CRF animals [19].

In a recent experiment [33] we showed that the PREE was abolished by amphetamine. This abolition was entirely due to decreased resistance to extinction of the drug injected PRF animals, while the performance of the drug injected CRF controls was unaffected. Increased resistance to extinction that is normally produced by partial as compared to continuous reinforcement is assumed to reflect the fact that partially reinforced animals learn to respond in the presence of stimuli produced on nonreinforced trials [10,19]. Our result implied that under amphetamine, this process was disrupted. We suggested two possible explanations for this effect of amphetamine: One, that the drug impairs the control of stimuli associated with nonreinforcement, since amphetamine has been shown to disrupt behavior under weak internal control (e.g., [12, 16, 18]). Two, that it selectively enhances the effectiveness of reinforcement or of responding controlled by reinforcement [13, 25, 31]. The present experiment was designed to test these two possibilities. Using a 1 trial/day procedure, we administered amphetamine to PRF animals on only the reinforced trials or on only the nonreinforced trials, as well as throughout the training. In order to control for the possible effects of trial-to-trial transitions from drug to no-drug in the PRF groups, we included comparable drug-injected CRF groups, in which the drug was administered in the same sequence as in the PRF groups. Since in our previous experiment, the abolition of the PREE by amphetamine was obtained irrespective of the drug treatment in extinction (amphetamine or saline), in the present experiment, extinction was carried out under placebo.

METHOD

Subjects

The subjects were 80 male Wistar rats (Tel-Aviv University Medical School, Israel) approximately 4 months old. They were fed for 1 hr a day, commencing at least 1 hr after the last animal had been run that day. Water was freely available.

Apparatus

The apparatus consisted of a straight alley made out of

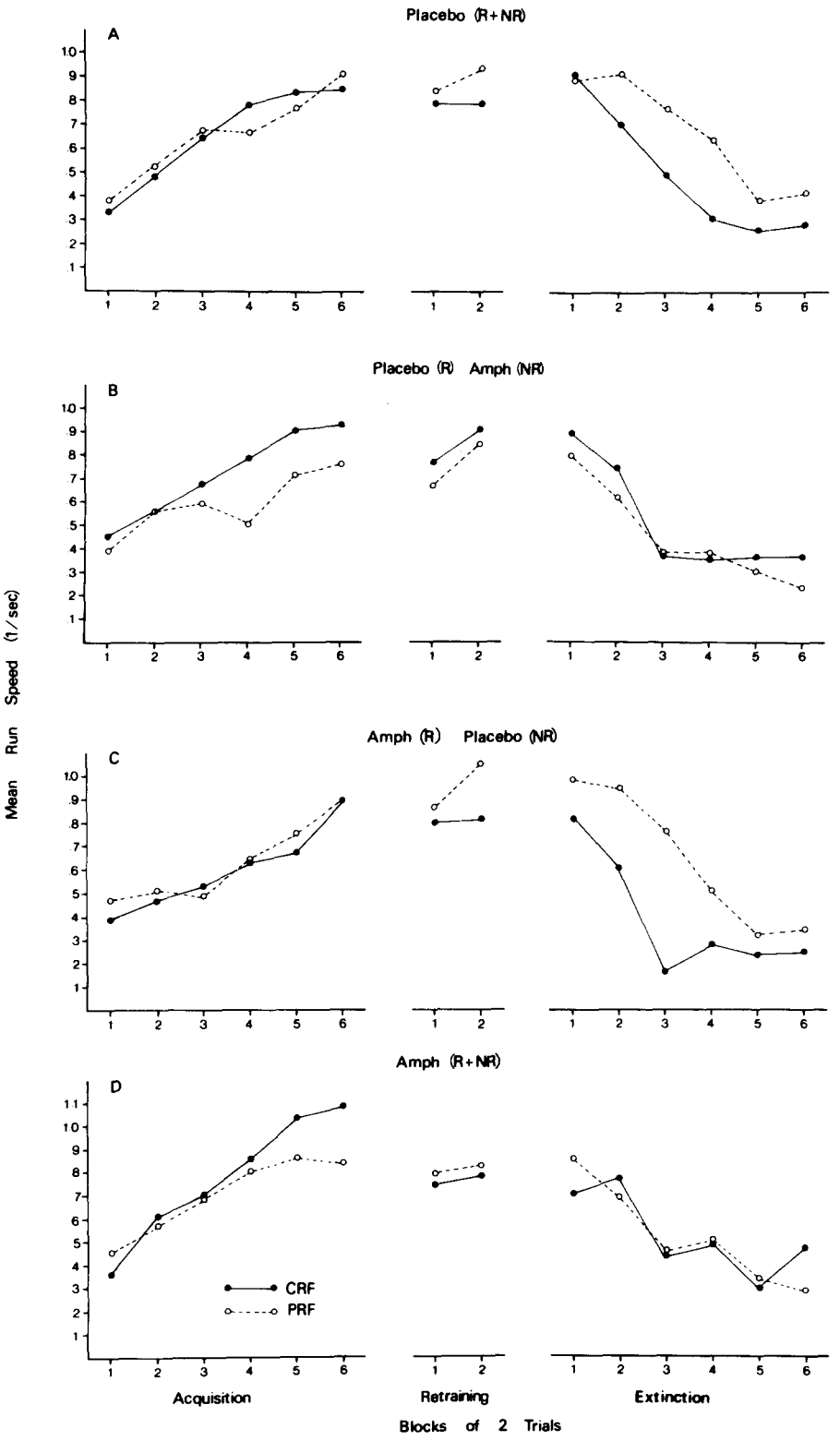

FIG. 1. The course of acquisition, retraining and extinction expressed as means of 2 daily trials in the Run section as a function of reinforcement schedule (continuous, CRF and partial, PRF) for the four drug conditions in acquisition: (A) placebo on rewarded (R) and nonrewarded (NR) trials; (B) placebo on rewarded (R) and amphetamine on nonrewarded trials (NR); (C) amphetamine on rewarded (R) and placebo on nonrewarded (NR) trials, and (D) amphetamine on rewarded (R) and nonrewarded (NR) trials.

transparent perspex with black rubber curtains covering the sides. The runway was 140 cm long, 15 cm wide and 35 cm high, with a startbox (20 cm long) and a goalbox (20 cm long) separated by a run section (100 cm long). The floor consisted of a metal grid composed of equally spaced rods. The startbox door was made of transparent Plexiglas and opened vertically downwards. The door was operated by a solenoid controlled by a pushbutton. The goalbox door was of metal and could be raised and lowered manually. The food pellets were placed in a recessed compartment 4 cm wide and 2.5 cm deep at the far side of the goalbox. There were three light photobeams and photocells, the first one 2 cm beyond the startbox, the second 2 cm before the goal section and the third inside the goalbox. The latter was interrupted when the rat contacted the food compartment. The photobeams operated three electronic timers, accurate to 0.01 sec. The first timer timed the start section (from the opening of the start door to the first photobeam); the second timed the run section (from the first to the second photobeam) and the third, the goal section (from the second to the third photobeam). Prior to each trial, the goalbox door was raised and, on rewarded trials, food was manually placed in the food compartment. Each reward consisted of ten 45 mg Campden Instruments food pellets. Once the animal interrupted the goalbox photobeam, the goalbox door was lowered. A Rockwell-AIM 65 microprocessor was used for equipment programming and data recording.

Procedure

All animals were handled for 2 weeks and given 2 days of pretraining. On day 1 of pretraining, animals were introduced into the alley in groups of four for 20 min. All alley doors were open and food pellets were available in the goalbox compartment. On the second day, animals were placed in the alley in pairs for 10 min, again with food pellets available. The experimenter ensured that all animals reached the goalbox and ate from the food compartment. On the following day, acquisition, consisting of one trial/day for 12 days, was initiated. On each day, the animal was placed in the start section and the three time measurements for the start, run and goal sections were obtained. The CRF groups received a reward on every trial throughout the 12 acquisition days. The PRF groups were rewarded on a quasi-random 50% schedule of RRRNRNNRNNRN, where R is a rewarded trial and N is a nonrewarded trial. The experimenter ensured, on rewarded trials, that the animal consumed all the food pellets. There were no observable differences in consumption times between the drug-injected and placebo animals. Following acquisition, animals were given 5 days rest in their home-cages. Then all animals were given 4 days of CRF retraining with 1 trial/day. Twenty-four hr later, extinction started and continued for 12 days. In extinction animals were run as in acquisition but no rewards were given. The confinement time on nonrewarded trials during acquisition and all extinction trials was 30 sec.

The rest period and CRF retraining served to prevent a drop in running speeds when animals are switched from drug in acquisition to placebo in extinction. In our previous study [33], we overcame this problem by adding 3 days of reinforced trials to acquisition and gradually "tailing off" the drug dose. In the present design, this procedure could not be used in the PRF group which received amphetamine on only the nonreinforced trials. Since we found previously that a period of 3 weeks rest followed by 7 days of CRF retraining did not affect the PREE [29], we used a similar procedure here to prevent performance deficit in extinction resulting from drug-placebo transition.

The animals were randomly assigned to one of eight groups: 4 CRF groups and 4 PRF groups. Each of the PRF groups received one of four drug treatments: placebo on both rewarded and nonrewarded trials (12 days of acquisition); placebo on the rewarded trials (days 1, 2, 3, 5, 8, 11) and amphetamine on the nonrewarded trials (days 4, 6, 7, 9, 10, 12); amphetamine on the rewarded trials and placebo on the nonrewarded trials; amphetamine on both the rewarded and the nonrewarded trials (12 days of acquisition). Each of the PRF groups had a CRF control group which received the same sequence of drug injections during the 12 acquisition days. The eight groups comprised a 2×2×2 factorial design consisting of reinforcement schedule (CRF or PRF), drug (amphetamine or saline) on rewarded trials, and drug (amphetamine or saline) on nonrewarded trials.

Drug Injections

The appropriate drug, either 1 mg/kg d-amphetamine sulfate dissolved in 1 ml saline, or an equivalent volume of saline, was administered IP 15 min prior to the designated trials of acquisition. In the PRF groups, the drug was administered prior to only R trials (Amphetamine R), only N trials (Amphetamine NR) or both (Amphetamine R+NR). The CRF groups received the drug in the same sequence as the comparable PRF groups. CRF retraining and extinction were conducted without drugs.

The data were transformed into reciprocals to allow the use of analysis of variance. ANOVAs were performed for the acquisition, retraining and extinction phases. For each phase, start, run and goal data were analyzed separately. Each analysis included three main factors: drug on rewarded trials, drug on nonrewarded trials, and reinforcement schedule, and a repeated measurements factor of trials (days). Six subjects (one from Placebo PRF; two from Amphetamine R-PRF; two from Amphetamine R+NR CRF; and one from Amphetamine R+NR PRF) were dropped from the experiment because they failed to acquire the running response during the first three days of acquisition. Thus, the final analysis was performed on 74 subjects.

RESULTS

Figure 1 presents the course of acquisition, CRF retraining and extinction, expressed in mean running speeds (1/sec), in the Run section of the alley for Placebo (panel A), Amphetamine NR (panel B), Amphetamine R (panel C) and Amphetamine R+NR (panel D) conditions.

Acquisition

The only significant outcome in the Run section was the interaction of Reinforcement × Trials, $F(11,726)=2.77$, $p<0.002$, which reflected an overall tendency of the PRF animals to have slightly faster speeds at the beginning of acquisition and slightly slower speeds towards its end. A similar pattern appeared in the Start, $F(11,726)=1.81$, $p<0.05$, and the Goal, $F(11,726)=4.92$, $p<0.001$, sections of the alley.

CRF Retraining

No significant main effects or interactions were found in retraining in any of the alley sections.

Extinction

In the Run section of the alley, there was a significant Reinforcement × Trials interaction, $F(11,726)=2.43$, $p<0.01$, indicating the overall existence of the PREE effect, i.e., slower extinction of PRF as compared with CRF animals. However, the significant interaction of Drug NR × Reinforcement, $F(1,66)=5.38$, $p<0.03$, and the interaction of these factors with Trials which approached significance, $F(11,726)=1.64$, $p<0.09$, points to the existence of the PREE in those groups which were administered placebo on NR trials (see panels A and C in Fig. 1), whereas the groups which received amphetamine on NR trials, irrespective of the drug injected on R trials (amphetamine or placebo) showed no PREE (see panels B and D in Fig. 1). A similar picture was obtained in the Goal section of the alley as reflected in the significant interaction of Drug NR × Reinforcement, $F(1,66)=4.12$, $p<0.05$. No other significant effects or interactions were obtained in any of the alley sections.

DISCUSSION

The administration of amphetamine throughout the acquisition trials of the CRF and PRF conditions abolished the PREE. This abolition was due to a reduction in running speeds in extinction of the drug injected PRF animals, while the performance of drug injected CRF animals was unaffected. This result provides a replication of our previous findings [33]. Administration of the drug only on rewarded trials left the PREE intact. In contrast, the PREE was abolished when the drug was administered only on nonrewarded trials, irrespective of drug treatment on rewarded trials. Moreover, the effect of amphetamine administration on NR trials mimicked that produced by drug administration on both R and NR trials, i.e., decreased resistance to extinction in the PRF animals without influencing the CRF animals.

Increased resistance to extinction of PRF animals is assumed to reflect the fact that these animals learn to respond in the presence of stimuli associated with nonreinforcement [19]. In other words, PRF animals' responding comes under the control of stimuli produced on nonreinforced trials. The present results indicate that such stimulus control is disrupted if the nonreinforced trials are experienced under amphetamine.

It should be pointed out that there are two actions of amphetamine other than impaired control by stimuli associated with nonreinforcement which could potentially lead to the abolition of the PREE in the Amphetamine NR condition: The administration of the drug on NR trials only could serve as a discriminative stimulus (e.g., [4,17]), signalling the absence of reinforcement or, the drug could serve as a reinforcer (e.g., [30,32]), making the NR trials functionally equivalent to R trials, thus transforming the PRF into a CRF condition. Both possibilities are unlikely. Although amphetamine can acquire the capacity to act as a discriminative stimulus, the development of such a discrimination requires extensive training [3, 4, 17, 27, 28]. For example, in Kuhn *et al.*'s [17] study, which also used 1 mg/kg d-amphetamine, animals required 40 days of 1/2 hr daily sessions of discrimination training to develop drug discrimination. Since in our experiment, animals were given altogether 12 acquisition trials, with an ITI of 24 hr, drug discrimination could not develop under these conditions. It is of interest to note that there was a trend towards slower running speeds on Amphetamine-NR trials as compared to R trials (without the drug), which would be expected if the drug acted as a discriminative cue signalling the absence of reinforcement. However, exactly the same trend was evident in the Amphetamine (NR+R) condition, indicating that the slowed down running was, if anything, *not* a result of amphetamine acting as a discriminative stimulus. Additional support for the fact that amphetamine in the present procedure does not acquire stimulus properties comes from our previous PREE experiment [33] which showed, using exactly the same procedure and the same drug dose, that amphetamine did not produce state-dependent learning: The PREE was abolished in animals trained under amphetamine and switched to saline in extinction as well as in animals trained and extinguished under the drug, but not in animals trained under saline and extinguished under the drug.

The possibility that amphetamine in the present study acted as a reinforcer is made unlikely by the results obtained in the CRF groups. It will be recalled that we included, in addition to CRF-saline and CRF-amphetamine-throughout groups, two CRF groups which received the drug on the same sequence of trials as the comparable PRF groups which received the drug on either the R or the NR trials only, i.e., on a random 50% of CRF trials. Thus, these CRF animals were exposed to two types of trials, food only vs. food + amphetamine. It is well documented that any variability in the conditions of acquisition increases subsequent resistance to extinction [19]. If amphetamine acted as a reinforcer this would produce some difference between the food alone and food + amphetamine trials and would lead to at least a trend towards increased resistance to extinction in these CRF groups compared with either the saline-throughout or amphetamine-throughout CRF groups. Nothing of this sort appeared in our results. In addition, if amphetamine acted as a reinforcer on NR trials, it would also act as a reinforcer in extinction, leading to increased resistance to extinction in CRF trained animals. We showed in our previous experiment [33] that amphetamine did not affect resistance to extinction in CRF animals. The same result was reported by Dudderidge and Gray [7].

Thus, there is no evidence that amphetamine in the present procedure acts either as a reinforcer or as a discriminative stimulus. Indeed, both of these actions cannot explain the abolition of the PREE when amphetamine is administered on both the R and the NR trials.

Amphetamine is known to disrupt stimulus control in various operant schedules and discrimination tasks. Thus, the drug increases responding during periods of nonreinforcement on FI, DRL and multiple operant schedules [26]. However, this action of amphetamine has been most often interpreted as an instance of the drug's tendency to increase low response rates [6, 18, 26], rather than of disrupted control by nonreinforcement under the drug. Numerous studies have shown that amphetamine disrupts discrimination performance (e.g., [1, 11, 14–16, 20–22]. But also these results pose problems of interpretation. First, the effects of the drug on stimulus control may be confounded with its effects on response rate (in free operant procedures) or response perseveration [12, 14, 21, 23]. Second, decreased accuracy of discrimination produced by amphetamine does not indicate whether the effect of the drug stems from loss of control by reinforcement or nonreinforcement. Since discrimination performance is controlled by both S+ and S− [19], poorer performance may reflect either of these effects or both.

The present procedure enabled us to assess separately the

effects of amphetamine on stimulus control by reinforcement and by nonreinforcement. Moreover, since we used a discrete trial procedure with a single trial per day, such effects could not be confounded with drug effects on response rate or perseveration. The results demonstrate that the drug reduces the control over behavior by stimuli associated with nonreinforcement without affecting the capacity of reinforcement to control behavior. As was elaborated above, the latter conclusion receives additional support from the results of the CRF groups.

However, it is important to note that amphetamine disrupts control by nonreinforcement in partial reinforcement training, but *not* in extinction. Thus, in our previous experiment [33] amphetamine administration in extinction did not affect extinction of the CRF animals. It has been generally assumed that there is a common mechanism underlying animals' responding to nonreinforcement in partial reinforcement training and extinction [2, 5, 10, 19]. On the basis of this assumption, any treatment that disrupts the control of behavior by stimuli associated with nonreinforcement should produce two outcomes: decrease resistance to extinction of PRF animals when administered in acquisition and increase resistance to extinction of the CRF animals when administered in extinction. This was indeed found with hippocampal [24] and septal [8] lesions as well as with anxiolytic drugs [9]. In contrast, under amphetamine, there is a dissociation between the effects of the drug following PRF and CRF training. This suggests firstly that amphetamine affects animals' responding to nonreinforcement only when it occurs in the context of concurrent reinforcement, and secondly, that partial reinforcement and extinction may be governed by different mechanisms.

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