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Disruption of Latent Inhibition by Acute Administration of Low Doses of Amphetamine

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WEINER, I., R. E. LUBOW AND J. FELDON. *Disruption of latent inhibition by acute administration of low doses of amphetamine*. PHARMACOL BIOCHEM BEHAV **30**(4) 871–878, 1988.—In the latent inhibition (LI) paradigm, nonreinforced preexposure to a stimulus retards subsequent conditioning to that stimulus. Three experiments investigated the effects of acute amphetamine administration on LI in rats. Experiments 1 and 3 used a conditioned emotional response (CER) procedure and Experiment 2 used two-way active avoidance procedure. Experiments 1 and 2 showed that, in both the CER and avoidance procedures, 1.5 mg/kg dl-amphetamine administered either in the preexposure or the conditioning stage alone did not disrupt LI. In contrast, amphetamine administered in both of the stages abolished LI. Experiment 3 showed that the abolition of LI was obtained when the preexposure and conditioning were given 24 hr apart but not when the two stages were given in one session.

Amphetamine Latent inhibition Conditioned suppression Conditioned avoidance
Animal model of schizophrenia Rat

AMPHETAMINE-INDUCED behavioral changes in animals have been repeatedly suggested as a model of human psychosis (e.g., [10, 21, 22]). In spite of the considerable progress in the understanding of the neurochemical and behavioral actions of amphetamine, several questions have remained a matter of debate. One such question concerns the drug administration regime which is most suitable for producing a valid animal analogue of psychosis. As summarized by Robinson and Becker [21], an enormous variety of injection paradigms, differing in drug dosages, number of injections, and the intervals between injections, have been used to investigate the effects of amphetamine. Robinson and Becker [21] argued that the proper injection paradigm for producing the animal analogue of psychosis, i.e., behavioral sensitization, is one which involves intermittent administration (usually by discrete daily injections) of relatively low doses of amphetamine. Furthermore, these authors emphasized that repeated drug administration for prolonged periods is not only unnecessary for producing behavioral sensitization but that, in fact, behavioral sensitization can be produced by a single injection of a relatively low dose of amphetamine.

Recently, an animal attentional model of amphetamine psychosis has been developed by Solomon and his colleagues [5, 23, 26] and ourselves [28–30]. This model is based on the well-documented fact that schizophrenia is characterized by an attentional deficit, or more specifically, an inability to ignore irrelevant stimuli, and on the contention that if the animal model is indeed analogous to the schizophrenic syndrome, then one should be able to demonstrate a similar attentional deficit in amphetamine-treated animals. This rationale has led both laboratories to investigate the effects of amphetamine on the phenomenon of latent inhibition (LI). In the LI paradigm, repeated nonreinforced preexposure to a stimulus retards subsequent conditioning to that stimulus [13]. For example, if an animal is preexposed to a series of tones, these tones acquire a reduced capacity to enter into new associations with other stimuli, such as food or shock, or responses such as shuttle avoidance. The development of LI has been considered by many authors to reflect a process of learning not to attend, to ignore, or to tune out irrelevant stimuli [14–17, 24]. Solomon *et al.* [23] and Weiner *et al.* [29,30] reasoned that amphetamine-treated animals should be retarded in their ability to develop LI. This expectation was supported by Solomon and his colleagues [5,23] using a conditioned avoidance response test (CAR), and Weiner *et al.* [28–30] using a conditioned emotional response test (CER). However, an inconsistency has emerged between the above two sets of studies regarding the appropriate injection paradigm. Solomon *et al.* [23] used 5 daily injections of 4 mg/kg d-amphetamine. They reported that LI was not disrupted by either acute administration of 4 mg/kg d-amphetamine or chronic administration (5 daily injections) of 1 mg/kg d-amphetamine. The latter result was also obtained by Hellman *et al.* [5]. It was concluded from these studies that chronic administration and a high dose of the drug were required for the abolition of LI. In contrast, we found that LI was abolished by 15 daily injections of 1.5 mg/kg dl-amphetamine. In addition, we showed that chronic

TABLE 1
THE DESIGNS OF EXPERIMENTS 1, 2, 3

Experiment	Days 1–5	6		7		8
1 (CER)	Baseline, no injection	PE	Cond	Test		
		Saline		Saline		Saline
		Saline		Saline		Amph
		Saline		Amph		Saline
		Saline		Amph		Amph
		Amph		Amph		Amph
		Amph		Amph		Saline
		Amph		Saline		Amph
		Amph		Saline		Saline
2 (CAR)	Apparatus familiarization, no injection	PE	Cond			
		Saline		Saline		
		Saline		Amph		
		Amph		Saline		
		Amph		Amph		
		PE	Cond	Test		
		Saline		Saline		No inj
		Amph		Amph		No inj
3 (CER)	Baseline, no injection	PE and Cond	Test			
		Saline		No inj		—
		Amph		No inj		—

administration per se did not disrupt LI unless both the preexposure *and* the conditioning stages were conducted under the drug [30]. Moreover, Weiner *et al.* [28] showed that 6 mg/kg dl-amphetamine, administered either acutely or chronically (8 days), did not disrupt LI. In the same study, LI was abolished by 1.5 mg/kg dl-amphetamine administered prior to preexposure and prior to the conditioning stage. To account for the discrepancy between the results of Solomon *et al.* [23] and Hellman *et al.* [5] as opposed to Weiner *et al.* [28,30], we [28] pointed to a critical difference in the time intervals separating drug injection and the initiation of the LI procedure. We injected the drug 15 min before the start of preexposure and 15 min before the start of conditioning (the two stages were separated by 24 hr), whereas Solomon *et al.* [23] administered one injection of the drug 50 min before the preexposure-conditioning session (65 min prior to conditioning). Brain levels of amphetamine rise substantially within the first 10 minutes following systemic administration, peak in 20–30 min, and then rapidly decline [3, 4, 11, 12]. The levels of the drug in the brain 1 hr after 5 mg/kg d-amphetamine (Solomon *et al.* used a 4 mg/kg dose) are closer to the maximal levels (30 min postinjection) of the drug following 1 mg/kg administration than the maximal level of 5 mg/kg [3,4]. Thus, because of the long injection-conditioning session interval, Solomon *et al.* [23], in fact, examined the effects of a functionally low dose of amphetamine which indeed would be expected to abolish LI. Consequently, we concluded [28] that the discrepancy between our results and those of Solomon and his colleagues was apparent rather than real, and that, indeed, low but not high doses of amphetamine disrupt LI. In the present experiments, we show that LI is disrupted by two injections of 1.5 mg/kg dl-amphetamine given 24 hr apart, in both the CER (Experiments 1 and 3) and the CAR (Experiment 2) procedures.

EXPERIMENT 1

METHOD

Subjects

Subjects were 64 male Charles River rats (Tel-Aviv University Medical School, Israel) approximately 4 months old, housed one to a cage under reversed cycle lighting. Upon delivery, subjects were maintained on ad lib food and water for one week. On the eighth day all animals were weighed and placed on a 23-hr water deprivation schedule which continued throughout the experiment.

Apparatus

The conditioned emotional response (CER) apparatus consisted of two plastic test chambers set in a ventilated sound-insulated Grason-Stadler Research Chest (Model 1101). The internal dimensions of each chamber were 15×20×17 cm, as measured from the raised grid floor. The chambers were flat grey, with small holes drilled in the side for ventilation. A drinking bottle could be inserted into the chamber through a 2-cm diameter hole which was 1.2 cm above the grid floor and 3 cm from the right side of the chamber. When the bottle was not present, the hole was covered by a plastic lid. Licks were detected by a drinkometer circuit. The preexposed to-be-conditioned stimulus was a 5 sec, 2.8 kHz tone produced by a Sonalert module (Model SC 628). The shock grid was made from stainless steel bars 0.25 cm in diameter set at 1.5 cm intervals. Shock was supplied by a Grason-Stadler scrambled shock source (Model E 1064 GS) set at 1 mA, 1 sec duration. A Rockwell AIM-65 microprocessor was used for equipment programming and data recording.

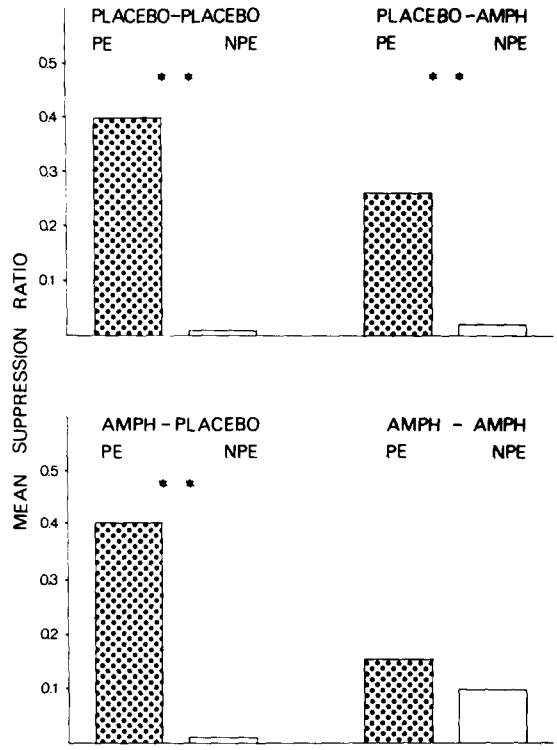

FIG. 1. Mean suppression ratios of the preexposed (PE) and nonpreexposed (NPE) groups under four drug conditions in preexposure and conditioning (placebo-placebo, placebo-amphetamine, amphetamine-placebo, and amphetamine-amphetamine). The ** sign represents a significant difference ($p<0.01$) between the PE and the NPE groups.

Procedure

Baseline. On each of five days, rats were individually placed into the experimental chamber and allowed to make 600 licks. The subject was then returned to its home cage and allowed access to water for 30 minutes.

Preexposure (PE). On day 6, with the bottle removed, each animal was placed in the experimental chamber. The preexposed (PE) animals received 45 3-sec tone presentations with an ITI of 50 seconds. The nonpreexposed (NPE) animals were confined to the chamber for the identical period of time but did not receive the tone.

Conditioning. On day 7, with the bottle removed, each animal was given two tone-shock pairings. Tone parameters were identical to those used in preexposure. The 1 mA, 1-sec shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the conditioning session. Five minutes later the second pairing was administered. After the second pairing, animals were left in the experimental chamber for an additional five minutes.

Test. On day 8, each animal was placed in the chamber and allowed to drink from the bottle. When the subject completed 90 licks the tone was presented. The tone continued until 10 additional licks were completed. If the subject failed to complete the last 10 licks within 300 seconds, the session was terminated and a score of 300 was recorded. The times between licks 80–90 and 90–100 were recorded. The amount of suppression of licking was indexed using a suppression ratio, A/A+B, where A is the time to complete licks 80–90 (pre-CS period) and B is the time to complete licks 90–100 (CS period). A suppression ratio of 0.00 indicates complete suppression (no LI) and a ratio of 0.50 indicates no change in response time from the pre-CS to the CS period (LI).

Drug Injections

The appropriate drug, either 1.5 mg/kg dl-amphetamine sulphate dissolved in 1 ml of isotonic saline or an equivalent volume of saline, was administered IP 15 minutes prior to the start of each stage (preexposure, conditioning and test).

Experimental Design

The animals were randomly assigned to one of 16 experimental groups in a 2×2×2×2 factorial design with main factors of stimulus preexposure-no preexposure, drug-no drug in preexposure, drug-no drug in conditioning, and drug-no drug in test (see Table 1). The data from two animals, one from Placebo-Amphetamine-Amphetamine NPE and one from Amphetamine-Amphetamine-Amphetamine NPE, were lost due to apparatus failure.

RESULTS

A 2×2×2×2 ANOVA with main factors of preexposure, drug-no drug in preexposure, drug-no drug in conditioning and drug-no drug in test was performed on the times to complete licks 80–90 in the absence of the CS (A periods). There were no significant outcomes (F's<1). Since the 2×2×2×2 ANOVA carried out on the suppression ratios of the 16 experimental groups revealed no significant effects of the drug in the test stage (the main effect of Drug in Test and all the interactions with this factor were not significant), a 2×2×2 ANOVA, collapsed over the factor of test, was carried out.

The mean suppression ratios of the eight groups are presented in Fig. 1. As can be seen, the LI effect, i.e., poorer suppression (higher suppression ratios) of the preexposed as compared to the nonpreexposed animals, was evident in three out of four drug conditions. This was supported by the significant main effect of Preexposure, $F(1,54)=41.22$, $p<0.001$. Amphetamine administration in conditioning increased suppression in the preexposed animals, as reflected in the significant Drug in Conditioning × Preexposure interaction, $F(1,54)=17.07$, $p<0.001$. The administration of amphetamine in preexposure also increased suppression (produced lower suppression ratios). However, as can be seen in Fig. 1, this effect was confined to the preexposed group which received amphetamine also in acquisition, i.e., the Amph-Amph condition, whereas no increase in suppression was evident in the PE group which received amphetamine only in preexposure, i.e., the Amph-Placebo condition. Consequently, the LI effect was absent only in the Amph-Amph condition. These outcomes were supported by the significant Drug in Preexposure × Preexposure interaction, $F(1,54)=3.94$, $p<0.05$, and by the Drug in Preexposure × Drug in Conditioning × Preexposure interaction which approached significance, $F(1,54)=3.74$, $p<0.06$. In addition, the absence of LI in the Amph-Amph condition was supported by t-tests based on the error term derived from the ANOVA carried out to compare the amount of suppression between the preexposed and nonpreexposed groups within

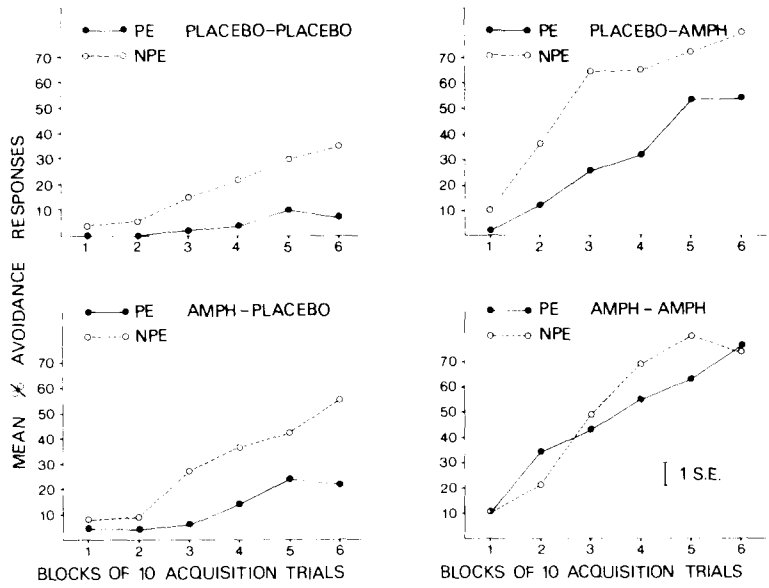

FIG. 2. Mean percent of avoidance responses over 6 blocks of 10 acquisition trials for the preexposed (PE) and nonpreexposed (NPE) groups under four drug conditions in preexposure and conditioning (placebo-placebo, placebo-amphetamine, amphetamine-placebo, and amphetamine-amphetamine). The 1 SE bar on the bottom right hand side of the figure represents one standard error based on the error term derived from the 2×2×2×12 ANOVA.

each of the four drug conditions. Significant differences in the suppression ratios between the preexposed and the nonpreexposed groups were found in the Placebo-Placebo condition, $t(54)=5.61$, $p<0.01$, the Placebo-Amphetamine condition, $t(54)=3.92$, $p<0.01$, and in the Amphetamine-Placebo condition, $t(54)=5.50$, $p<0.01$. No difference was found in the Amphetamine-Amphetamine condition, $t(54)=0.82$.

EXPERIMENT 2

METHOD

Subjects

Seventy-two male Wistar rats (Tel-Aviv University Medical School, Israel), approximately 3 months old, served as subjects. They were housed one to a cage under reversed cycle lighting.

Apparatus

The conditioned avoidance response (CAR) apparatus consisted of three identical Campden Instruments shuttle boxes, measuring 48.5×23×20 cm. The barrier between the two compartments of the box consisted of an aluminum wall with a central inverted U-shaped gate (10×7 cm). Each box was set in a ventilated, sound-insulated chest. The preexposed to-be-conditioned stimulus was a 5-sec, 2.8 kHz tone produced by a Sonalert module (Model SC 628). Shock was supplied to the grid floor by a Campden Instruments scrambled shock generator (Model 521C) set a 1 mA. A Rockwell AIM 65 microprocessor was used for equipment programming and data recording.

Procedure

Apparatus familiarization. On each of 5 days, animals were individually placed in the shuttle box for 30 minutes. This stage was given in order to match the conditions of Experiment 1 (5 days of baseline).

Preexposure. On the sixth day each animal was placed in the shuttle box with the house lights on and received 50, 5-sec tone presentations on a variable interval (VI) 60-sec schedule, ranging from 20 to 100 sec. The nonpreexposed (NPE) animals were confined to the shuttle box for an identical period of time, but did not receive the tones. At the end of the preexposure session, animals were returned to their home cages.

Conditioning. Twenty-four hr after preexposure, each animal was placed in the shuttle box with the house lights on and received 60 avoidance trials, presented on a VI 60-sec schedule ranging from 30 to 90 sec. Each avoidance trial started with a 5-sec tone followed by a 30-sec shock, the tone remaining on with the shock. If the animals crossed the barrier to the opposite compartment during the 5-sec tone, the tone was terminated and no shock was delivered. A crossing response during shock terminated the tone and the shock. If the animal failed to cross within 35 sec from the onset of the tone the shock was terminated automatically.

Two measurements were recorded during conditioning: total number of shuttle crossings and the latencies of the avoidance/escape responses. The 60 trials were divided into 12 blocks of 5 trials, and all analyses of conditioning were carried out on the percentage of avoidance responses in each of the twelve 5-trial blocks, with blocks as a repeated measurement factor. For graphical presentation, the data were collapsed into six blocks of 10 acquisition trials.

Drug Injections

The appropriate drug, either 1.5 mg/kg dl-amphetamine sulphate dissolved in 1 ml of isotonic saline or an equivalent

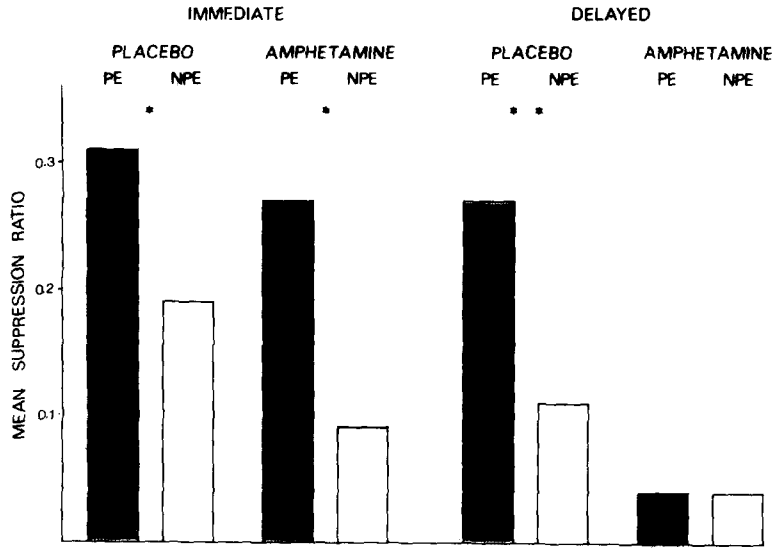

FIG. 3. Mean suppression ratios of preexposed (PE) and nonpreexposed (NPE) groups as a function of two delays between preexposure and conditioning (0 and 24 hr) and two drug conditions (placebo and amphetamine). All groups were under drug treatment in both the preexposure and conditioning stages. The test was conducted without the drug. The ** and * signs represent a significant difference ($p<0.01$ and $p<0.05$, respectively) between the PE and NPE groups.

volume of saline, was administered IP 15 min prior to the start of each stage (preexposure and conditioning).

Experimental Design

The 72 animals were randomly assigned to one of the eight experimental conditions in a 2×2×2 design, consisting of stimulus preexposure-no preexposure, drug-no drug in preexposure, and drug-no drug in conditioning (see Table 1). An additional 8 naive animals were given only avoidance conditioning in order to test whether apparatus familiarization affected avoidance performance. The data of two animals, one from Placebo-Amphetamine NPE group and one from Amphetamine-Placebo PE group, were lost due to microprocessor failure.

RESULTS

The mean total number of avoidances in the group given no apparatus familiarization was 10.12, as compared to 11.33 in the comparable group that received apparatus familiarization. Thus, apparatus familiarization in the present experiment did not affect avoidance conditioning.

Amphetamine Effects on Activity

Amphetamine administration resulted in increased activity, i.e., higher number of crossings, in both the preexposure and conditioning stages. This was supported by a 2×2 ANOVA performed on the mean total number of crossings in preexposure with main factors of PE-NPE and drug-no drug in PE, which yielded a main effect of Drug, $F(1,62)=36.41$, $p<0.001$, and a 2×2×2 ANOVA with main factors of PE-NPE, drug-no drug in PE and drug-no drug in conditioning, performed on the mean total numbers of crossings, which yielded a main effect of Drug in Conditioning, $F(1,62)=30.15$, $p<0.001$.

Amphetamine Effects on Avoidance and Latent Inhibition

Figure 2 presents the mean percent of avoidance responses over six blocks of 10 trials for the preexposed and nonpreexposed animals in the four drug conditions. The data were analyzed by a 2×2×2×12 ANOVA with main factors of PE-NPE, drug-no drug in PE, drug-no drug in conditioning, and a repeated measurement factor of blocks. The presence of LI, i.e., poorer avoidance performance of the preexposed as compared to nonpreexposed groups, was supported by the significant main effect of Preexposure, $F(1,62)=12.70$, $p<0.001$, and by the significant Preexposure × Blocks interaction, $F(11,682)=3.33$, $p<0.001$. In addition, the administration of amphetamine in conditioning facilitated avoidance, as reflected in the main effect of Drug in Conditioning, $F(1,62)=44.19$, $p<0.001$, as well as in a significant Drug in Conditioning × Blocks interaction, $F(11,682)=8.66$, $p<0.001$. No other outcomes were significant. However, inspection of Fig. 2 suggests that the LI effect was present in the Placebo-Placebo, Placebo-Amph and Amph-Placebo conditions, but was absent in the Amph-Amph condition. This pattern of results was identical to that obtained in Experiment 1. These data together with our original intention to examine the presence of LI in each of the four drug conditions prompted us to compare the total number of avoidances in the PE and NPE groups in each drug condition using one-tail t-tests based on the error term of the ANOVA, although the Drug in Preexposure × Drug in Conditioning × Preexposure interaction was not significant, $F(1,62)=1.98$,

$p<0.17$. Significant differences between the PE and NPE groups were obtained in the Placebo-Placebo condition, $t(62)=1.68$, $p<0.05$, the Placebo-Amphetamine condition, $t(62)=3.00$, $p<0.005$, and Amphetamine-Placebo condition, $t(62)=2.01$, $p<0.025$. No significant difference between the PE and NPE groups was obtained in the Amphetamine-Amphetamine condition, $t(62)=0.62$.

EXPERIMENT 3

In a previous study [30] we found that acute 1.5 mg/kg dl-amphetamine administration did not disrupt LI in a CER procedure. The procedure used in that study differed from that used in Experiment 1 of the present report in four respects: previously, 30 tone preexposures were used; preexposure and conditioning were given in a single session; test was given 2 hr later; one drug injection was given prior to the preexposure-conditioning session. Experiment 3 sought to determine the effects of these procedural differences. For this purpose, two conditions of preexposure-conditioning interval were used: Immediate (PE and conditioning given in one session) and Delayed (PE and conditioning given 24 hr apart). In both conditions 30 tone preexposures were used. Two drug injections, one preceding PE and one preceding conditioning, were given; in the 24 hr delay condition the drug was administered 15 min before preexposure and 15 min before conditioning, while in the 0-delay condition, one injection was given 15 min prior to the start of the preexposure-conditioning session and the second 5 min before the start of conditioning; test was carried out 24 hr later without the drug. Fifty-six male Wistar rats were randomly assigned to eight groups in a $2\times2\times2$ design, consisting of two levels of stimulus preexposure (0, 30), drug-no drug in preexposure and conditioning, and two time delays between preexposure and conditioning (immediate and 24 hr) (see Table 1). The general CER procedure was indentical to that of Experiment 1.

RESULTS

Figure 3 presents the mean suppression ratios of the four groups in the Immediate and the Delayed conditions. The data from each delay condition were analyzed using a 2×2 ANOVA with main factors of preexposure and drug. In the Immediate condition, the 2×2 ANOVA performed on the times to complete licks 80–90 in the absence of CS (A periods) revealed no significant outcomes ($F's<1$). The analysis on the suppression ratios in this condition revealed only a significant main effect of Preexposure, $F(1,24)=4.91$, $p<0.04$, reflecting the presence of LI, i.e., poorer suppression of the PE as compared to the NPE groups. Both the main effect of Drug and the interaction of this factor with Preexposure were not significant ($F's<1$). Thus, in the Immediate condition, LI was present in both the Placebo and Amphetamine animals. In the Delayed condition, the 2×2 ANOVA performed on the times to complete licks 80–90 in the absence of CS revealed no significant differences ($F's<1$). The analysis on the suppression ratios revealed a significant main effect of Preexposure, $F(1,24)=4.38$, $p<0.05$, a significant main effect of Drug, $F(1,24)=13.80$, $p<0.01$, and a significant Preexposure $\times$ Drug interaction, $F(1,24)=4.60$, $p<0.05$. As can be seen in Fig. 3, these results reflect the presence of LI in the Placebo groups as opposed to the absence of the LI effect in the Amphetamine groups. The latter outcome was due primarily to greater suppression in the Amphetamine PE condition.

GENERAL DISCUSSION

Experiments 1 and 2 showed that LI was disrupted following 2 injections of 1.5 mg/kg dl-amphetamine. This provides additional confirmation that neither prolonged administration nor high doses of amphetamine are needed in order to abolish LI. It should be noted that the abolition of LI was reflected in opposite behavioral effects in the CER and the CAR procedures, in the former, suppression of behavior (enhanced suppression of licking), and in the latter, enhancement of behavior (facilitated avoidance). This suggests that the abolition of LI by amphetamine was not due to some nonspecific neurochemical or behavioral effect of the drug but rather to a specific action on the learning process underlying the development of LI. Experiment 3 demonstrated that the critical variable for obtaining LI disruption with two amphetamine injections is the time interval between the two injections.

The present results are in line with Robinson and Becker's [21] conclusions regarding the most suitable injection paradigm for producing the phenomenon of behavioral sensitization which, according to these authors, provides a suitable animal analogue of psychosis. Robinson and Becker [21] maintained that the dose of amphetamine is not a crucial variable and that relatively low doses are more appropriate since high doses of the drug increase the risk of producing neurotoxic effects. Moreover, long-term treatment is not necessary to produce behavioral sensitization and, in fact, a single injection is sufficient. Most importantly for the present results, Robinson and Becker [21] emphasized that a critical variable for obtaining behavioral sensitization is the interval between drug treatments. To produce robust behavioral sensitization, amphetamine must be given intermittently, with injections given relatively far apart being more efficacious than those given at short intervals. The present finding that two amphetamine injections, one given prior to preexposure and one prior to conditioning with an interval of 30 min did not disrupt LI, whereas the same two injections given 24 hr apart did disrupt LI, provides strong support for their claim.

Robinson and Becker's [21] model of behavioral sensitization has focused on amphetamine-induced motor effects, i.e., sensitization of locomotion and stereotypy. The present results extend the model to attentional processes, demonstrating that the behavioral sensitization paradigm produces, in addition to motor effects, a cognitive analogue of the schizophrenic syndrome, namely, an inability to ignore irrelevant stimuli.

As for the brain mechanisms underlying LI disruption by low amphetamine doses, the most convincing clue has been provided by Solomon and Staton [26] who demonstrated a dissociation between the mesolimbic and the striatal dopamine systems in the mediation of LI: microinjections of d-amphetamine into the nucleus accumbens but *not* the caudate putamen abolished LI. Indeed, there is abundant evidence that the mesolimbic DA system mediates the locomotor effects produced by low doses of amphetamine whereas striatal DA mechanisms mediate stereotyped behaviors produced by high doses of the drug (e.g., [2, 8, 9, 18, 19, 27]). These results suggest that both the locomotor enhancement and the abolition of LI produced by low doses of amphetamine may be mediated by the mesolimbic dopamine system. In contrast, high doses of the drug which produce stereotypy via the striatal system do not affect LI. There is evidence that the two DA systems are activated

differentially by low and high doses of amphetamine. Porrino *et al.* [20] demonstrated that 1 mg/kg of d-amphetamine maximized metabolic activation (as measured by radiolabelled 2-deoxyglucose utilization) in the nucleus accumbens. In contrast, the administration of 5 mg/kg of the drug had no effect on the metabolic activity of the nucleus accumbens but increased glucose utilization in the nigrostriatal system. Hitzemann *et al.* [6] reported that the administration of high doses (6 mg/kg) of amphetamine increased the sensitivity of the nigrostriatal system but decreased the sensitivity of the mesolimbic system to amphetamine: microinjections of the drug into the caudate produced enhanced stereotypy whereas microinjections into the nucleus accumbens induced an attenuated motor response as compared to controls. The differential activation of the two systems by low and high doses of amphetamine may underlie LI disruption with low doses and the disappearance of LI disruption following high doses. The involvement of the mesolimbic system in the disruption of LI is supported by the findings that hippocampal [1,25] and septal ([31]: Feldon *et al.*, in preparation) lesions abolish LI. It is of interest to note that recent findings suggest a role of hippocampal dopamine in the hyperactivity induced by low doses of amphetamine [7].

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