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Amphetamine-Induced Disruption of Latent Inhibition Is Not Reinforcer-Mediated

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WEINER, I., R. TARRASCH, E. BERNASCONI, L. M. BROERSEN, T. C. RÜTTIMANN AND J. FELDON. *Amphetamine-induced disruption of latent inhibition is not reinforcer-mediated.* PHARMACOL BIOCHEM BEHAV **56**(4) 817–826, 1997.—Latent inhibition (LI) refers to retarded conditioning to a stimulus that had been repeatedly preexposed without consequences, as compared with a nonpreexposed stimulus. Amphetamine disrupts LI, and this effect was suggested to result from enhanced switching to respond according to the stimulus–reinforcer contingency. Recently, it has been argued that amphetamine disrupts LI by increasing the impact of the reinforcer. This implies that amphetamine should produce stronger conditioning in the nonpreexposed group, and that its influence on LI can be modified only by changing reinforcer parameters. We report two studies, using an off-baseline conditioned emotional response procedure in rats licking for water, that question both predictions. In the first study, a meta-analysis based on 23 replications of the effect of amphetamine on LI, using tone as the preexposed stimulus, showed that LI is significantly attenuated due to drug-induced increased suppression in the preexposed groups only. The second study included two experiments, each using two shock intensities but different preexposed stimuli. Amphetamine disrupted LI at both shock intensities when the stimulus was a steady light, but this effect disappeared when the stimulus was three flashing lights. Thus, the effect of amphetamine could not be modified by manipulating shock intensity, but was modifiable by manipulating the nature of the preexposed stimulus. The results are inconsistent with the hypothesis that amphetamine-induced disruption of LI is solely mediated by drug-induced changes in the effects of reinforcers. © 1997 Elsevier Science Inc.

Latent inhibition Amphetamine Dopamine Switching Schizophrenia Rat

LATENT inhibition (LI) refers to retarded conditioning to a stimulus that has been repeatedly presented without reinforcement (26,27). This retardation is considered to index the capacity of organisms to ignore stimuli that predict no significant consequences, and it can be demonstrated in a variety of classical and instrumental conditioning procedures and in many mammalian species, including humans (21,26–28,30, 32,33,35,40,41). A recent review of human LI data has indicated that LI is similar in humans and animals and can be viewed as reflecting the operation of analogous processes across species (28).

During the last decade, LI disruption has received increasing attention as a viable animal model of the widely described failure of schizophrenics to ignore irrelevant stimuli (6,11,12, 16,17,27,28,38,43,48,50,51). This was first proposed by Solomon et al. (43) and Weiner et al. (50,51), based on their findings that LI is disrupted in rats following systemic administration of the dopamine releasing drug amphetamine, which produces and exacerbates psychotic symptoms in humans. The validity of the LI model has been strengthened by findings that LI is disrupted in acute schizophrenic patients (2,18,20) as well as in normal humans with high scores on questionnaires measuring schizotypy (3,9,25,29) or in those given amphetamine (19).

Although systemic amphetamine-induced disruption of LI is well documented [e.g., (22,23,47,52)], the mechanism of action of this drug on LI remains unclear. One such mechanism can be derived from the switching model of LI (48). In this model, LI is viewed as successively exposing an organism to conflicting environmental contingencies in preexposure (stimulus–no event) and conditioning (stimulus–reinforcement) [for a similar account, see (21)]. The central point in terms of LI development is that although during preexposure the ani-

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mal learns that the conditioned stimulus (CS) signals no event of consequence and is therefore irrelevant, to display LI, the animal must continue to respond to the stimulus as irrelevant during conditioning, in spite of the fact that it comes to signal a significant outcome, reinforcement. Normal animals are under the control of information acquired in preexposure (CS–no event) rather than the new CS–reinforcement contingency, and this constitutes the LI effect.

In regard to neural systems involved in the establishment of LI, the switching model attributes a key role to the hippocampus and the mesolimbic dopamine (DA) system. More specifically, it is proposed that the mesolimbic DA system does not participate in learning to ignore the nonreinforced stimulus in the preexposure stage, but is activated in the conditioning stage when the previously nonreinforced stimulus is followed by reinforcement. Since activation of the mesolimbic DA system leads to rapid behavioral and cognitive switching (7,15,31,36,39,45,46), such activation promotes a rapid switch of responding according to the changed contingency of reinforcement in the conditioning stage. In the intact brain, the predictive relationship acquired by the target CS in preexposure (CS–no event) continues to control behavior in conditioning even though it predicts reinforcement, because the hippocampus inhibits the switching mechanism of the nucleus accumbens [for a detailed exposition of the model, see (48)].

It follows from this account that the disruptive action of amphetamine on LI is exerted at the conditioning stage. Enhancement of dopaminergic transmission after amphetamine administration disrupts the control of the stimulus–no event contingency by promoting rapid switch of responding according to the CS–reinforcement contingency (48). Importantly, the switching model argues that the disruptive influence of amphetamine on LI stems from its action in the preexposed group, in which there is conflicting information between the contingencies of preexposure and conditioning. The model also implies that any parametric manipulation of the LI procedure that changes the relative impact of preexposure versus conditioning, or vice versa, on behavior should modify the effects of amphetamine on LI.

A similar account of the action of amphetamine on LI has been recently advanced by Killcross and colleagues (22,23). However, according to these authors, the rapid control of behavior by the CS–reinforcement contingency is due to amphetamine-induced increase in the impact, or the salience, of the aversive reinforcer. In support of this claim, these authors showed that when the intensity of the foot-shock reinforcer in a within-subjects, on-baseline conditioned emotional response (CER) procedure is manipulated so as to yield an equivalent degree of post-shock suppression in saline- and amphetamine-treated groups (0.28 mA and 0.15 mA, respectively), amphetamine fails to disrupt LI (22). Killcross et al. (22) therefore concluded that a decrease in the nominal magnitude of reinforcer can reverse the attenuation of LI produced by amphetamine.

Two predictions follow from Killcross et al.'s (22) position that amphetamine disrupts LI via increasing the impact of the reinforcer. First, increased impact of the unconditioned stimulus (US) should produce stronger conditioning in the nonpreexposed group, which undergoes regular conditioning. Second, the influence of amphetamine on LI can be modified only by changing US parameters. We report two studies that investigated these predictions. In both, LI was assessed using an off-baseline CER procedure in rats licking for water, consisting of three stages: preexposure, in which the to-be-conditioned stimulus (a tone or a light) was repeatedly presented without being followed by reinforcement; conditioning, in which the preexposed stimulus was paired with reinforcement (a foot-shock); and test, in which LI was indexed by the animals' degree of suppression of licking during stimulus presentation. In the first study, we conducted a meta-analysis based on 23 replications of the effect of amphetamine on LI (extracted from all experiments that tested the effects of various compounds on amphetamine-induced disruption of LI during 3 years in the Tel Aviv laboratory), in order to assess whether LI is significantly attenuated due to drug-induced increased suppression in the nonpreexposed groups. These experiments all used 40 tone preexposures. In the second study, we present two experiments, 2a and 2b, conducted in the Schwerzenbach laboratory, which used two shock levels in conditioning but different preexposure conditions. Experiment 2a used 40 preexposures of a 5-s steady light, whereas Experiment 2b used 10 or 40 preexposures of a more salient stimulus consisting of three 10-s flashing lights. We added the 10 preexposures condition, which conventionally does not yield LI (27), in the expectation that a highly salient stimulus would produce LI under these conditions. The purpose of these experiments was to determine to what extent the effects of amphetamine on LI are modifiable by manipulations of shock intensity and/or the salience of the preexposed stimulus.

STUDY 1: META-ANALYSIS OF 23 REPLICATIONS OF THE EFFECTS OF D-AMPHETAMINE ON LATENT INHIBITION

METHOD

Subjects

Male Wistar rats (Tel Aviv University Medical School) approximately 4 months old were housed one to a cage under reversed cycle lighting (lights off 0700–1900 h) for the duration of the experiment. One week prior to the commencement of the behavioral testing, they were weighed and placed on a 23-h water restriction schedule that continued throughout the experiment. During the days of the experimental procedure on which water was available in the test apparatus, this availability was in addition to the daily ration of 1 h given in the home cages. Animals were tested between 0800 and 1700 h.

Apparatus

The apparatus consisted of four Campden Instruments rodent test chambers (model 410), each set in a ventilated sound-attenuating Campden Instruments chest (model 412). A drinking bottle could be inserted into the chamber through a 0.5-cm-diameter hole located in the center of the left wall of the chamber, 2.5 cm above the grid floor. When the bottle was not present, the hole was covered by a metal lid. Licks were detected by a Campden Instruments drinkometer circuit (model 453). The preexposed, to-be-conditioned stimulus was a 2.8-kHz tone produced by a Sonalert module (model SC 628). Shock was delivered through the cage floor. It was supplied by a Campden Instruments shock generator (model 521/C) and shock scrambler (model 521/S) set at 0.75 mA. Equipment programming and data recording were computer-controlled.

Procedure

Pretreatment handling and the stages of the LI procedure are described below. The stages of preexposure, conditioning, rebaseline, and test were given 24 h apart. Each rat was run throughout the experiment in the same chamber.

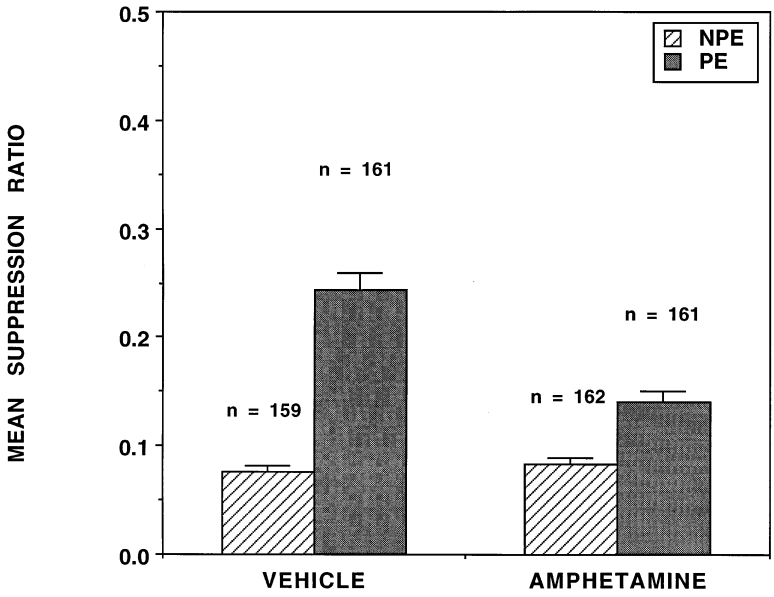

FIG. 1. Means and standard errors of suppression ratios for the preexposed (PE) and nonpreexposed (NPE) groups in two drug conditions: vehicle and 1.0 mg/kg of *d*-amphetamine. The data are derived from 23 replications.

Handling. Prior to the beginning of the experiment, rats were handled for 7 days, for about 2 min each day.

Baseline. On each of 5 days, each rat was placed into the experimental chamber and allowed to drink for 20 min.

Preexposure. With the drinking bottle removed, each rat was placed in the experimental chamber. The preexposed (PE) animals received forty 10-s tones with a variable interstimulus interval (ISI) with a mean of 50 s. The nonpreexposed (NPE) animals were confined to the chamber for an identical period of time but did not receive the tones.

Conditioning. With the bottle removed, each rat received two tone–shock pairings 5 and 10 min after the start of the session. Tone parameters were identical to those used in preexposure. The 0.75-mA, 1-s shock immediately followed tone termination. After the second pairing, rats were left in the experimental chamber for an additional 5 min.

Rebaseline. Each rat was given a drinking session identical to the baseline sessions. Latency to the first lick and the total number of licks were recorded for each rat.

Test. Animals were tested individually. Each rat was placed in the chamber and allowed to drink from the bottle. When the rat completed 75 licks, the tone was presented and lasted 5 min. The following times were recorded: time to first lick, time to complete licks 1–50, time to complete licks 51–75 (pre-tone), latency to first lick after tone presentation, and time to complete licks 76–100 (tone-on). Animals that failed to complete 25 licks within the 5 min during which the stimulus was on were given a score of 300. The amount of suppression of licking was measured using a suppression ratio, A/(A + B), where A is the period prior to the presentation of the stimulus (licks 51–75) and B is the period of the stimulus presentation (licks 76–100). A suppression ratio of 0.01 indicates complete suppression (no LI), and a ratio of 0.50 indicates no change in response rate from the period prior to the presentation of the stimulus to the period of stimulus presentation (LI).

Drugs

The drug [1 mg/kg *d*-amphetamine sulfate (Sigma) dissolved in 1 ml of isotonic saline] or vehicle (an equivalent volume of saline) was administered IP 10 min prior to the start of preexposure and prior to the start of conditioning. The rebaseline and test stages were conducted without the drug or vehicle.

RESULTS

Analysis of variance (ANOVA) carried out on the data from the 23 replications revealed no significant interactions of the replication factor with any of the other factors, and therefore a further ANOVA collapsed over replications was carried out. There were no differences between the groups in time to first lick, time to complete licks 1–50, and time to complete licks 51–75 (pre-tone).

Figure 1 presents the means and standard errors of the suppression ratios of vehicle- or amphetamine-treated PE and NPE groups, collapsed over 23 replications. A 2×2 ANOVA with main factors of preexposure (0, 40) and drug (vehicle, amphetamine) yielded significant main effects of preexposure [$F(1, 693) = 119.2$, $p < 0.001$] and drug [$F(1, 693) = 18.1$, $p < 0.001$], as well as a significant preexposure $\times$ drug interaction [$F(1, 693) = 24.7$, $p < 0.001$]. As can be seen in Fig. 1, LI (i.e., the difference in suppression between the PE and the NPE groups) was largely reduced in amphetamine-treated animals compared with vehicle controls. Moreover, it can be seen that the attenuation of LI by amphetamine was due exclusively to increased suppression in the amphetamine–PE group compared with the vehicle–PE group.

To further examine whether the attenuating effect of amphetamine on LI is a function of the impact of shock, we divided the 23 replications into three categories according to the degree of suppression exhibited by the vehicle–NPE group within each replication, as reflected in the mean times to com-

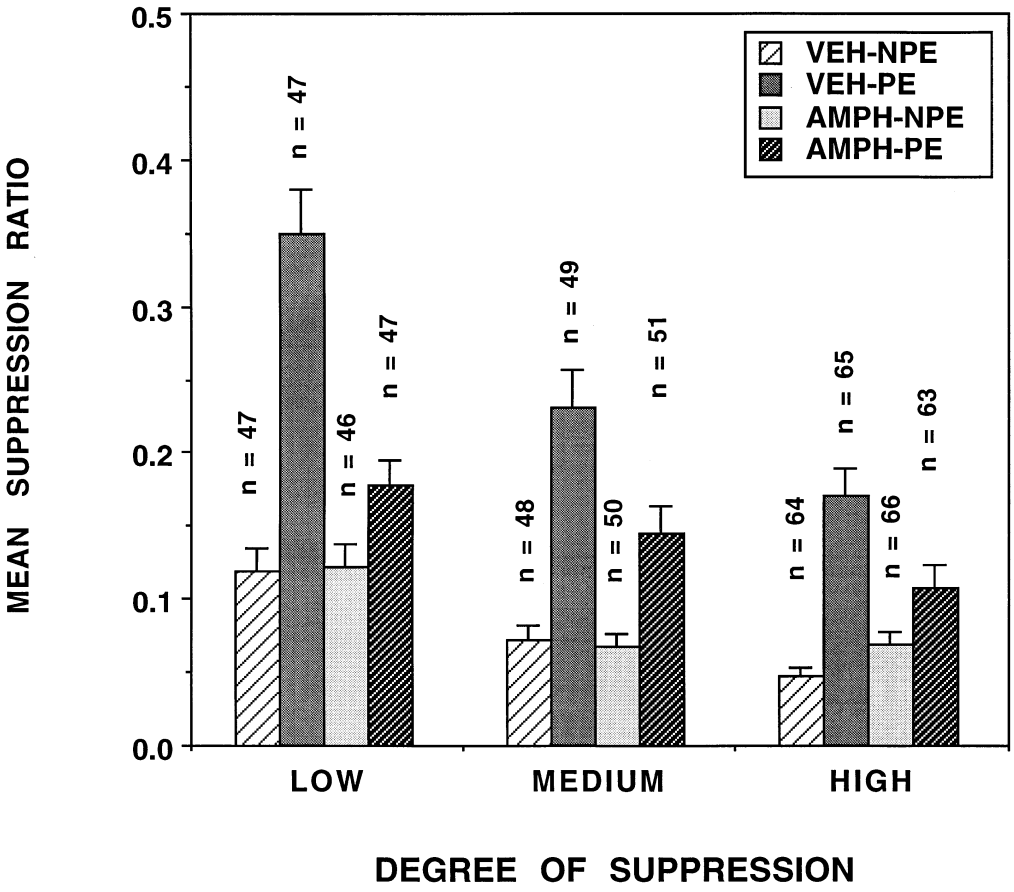

FIG. 2. Means and standard errors of suppression ratios for vehicle-treated or amphetamine-treated preexposed (PE) and nonpreexposed (NPE) groups following the division of the 23 replications into three categories according to the degree of suppression exhibited by the vehicle–NPE group within each replication.

plete licks 76–100 in the presence of the tone: low, mean time < 75 s; medium, mean time 75–150 s; high, mean time > 150 s. Figure 2 presents the means and standard errors of the suppression ratios of vehicle-treated or amphetamine-treated PE and NPE groups in the three categories of degree of suppression. A $3 \times 2 \times 2$ ANOVA with main factors of degree of suppression (low, medium, high), preexposure (0, 40), and drug (vehicle, amphetamine) yielded significant main effects of degree of suppression [$F(2, 631) = 31.9$, $p < 0.001$], preexposure [$F(1, 631) = 138.0$, $p < 0.001$], and drug [$F(1, 631) = 27.4$, $p < 0.001$], as well as a significant preexposure $\times$ drug interaction [$F(1, 631) = 35.1$, $p < 0.001$]. There were no significant interactions between the factor of degree of suppression and any of the other factors. While the three categories differed in the overall level of suppression, at all three degrees of suppression the amphetamine–PE groups were more suppressed than the vehicle–PE groups, and in no case were the amphetamine–NPE groups more suppressed than the vehicle–NPE groups. Thus, the attenuation of LI by amphetamine is clearly due to better learning in only the PE groups, and is independent of the overall level of conditioned suppression.

Finally, we counted the number of replications in which the amphetamine-treated group exhibited more suppression than the vehicle group, and the number of replications in which the amphetamine group exhibited less suppression than the vehicle group, separately for the PE and NPE condition, and computed the χ^2 test for goodness of fit for each condition. In the PE condition, there were five replications in which the vehicle group was more suppressed than the amphetamine group, as compared with 18 replications in which the amphetamine group was more suppressed than the vehicle group ($\chi^2 = 7.35$, $p < 0.01$). In the NPE condition, there were 12 replications in which the vehicle group was more suppressed than the amphetamine group, as compared with 11 replications in which the amphetamine group was more suppressed than the vehicle group (NS).

An identical pattern of results was obtained with two additional measures of conditioned suppression: latency to emit the first lick following tone presentation and a logarithmic transformation of the time to complete 25 licks in the presence of the tone. The results obtained with the former measure were presented, in abbreviated form, by Gray et al. (17).

STUDY 2: EFFECTS OF AMPHETAMINE ON LATENT INHIBITION—VARIATIONS IN SHOCK INTENSITY AND STIMULUS SALIENCE

This study included two experiments: Experiment 2a and Experiment 2b. Both experiments used two shock levels in conditioning (0.5 and 1.0 mA) but different to-be-conditioned stimuli—one 5-s steady light in Experiment 2a and three 10-s flashing lights in Experiment 2b. In addition, Experiment 2a

used two levels of preexposure (0 and 40 presentations of stimuli), whereas Experiment 2b used three levels (0, 10, and 40 presentations).

METHOD

Subjects

Experimental subjects were male Wistar rats (Institute of Toxicology, Schwerzenbach, Switzerland) approximately 10 weeks old, as in Study 1.

Apparatus

The apparatus consisted of four Coulbourn Instruments test cages (model E10-10), each set in a ventilated sound-attenuating Coulbourn Instruments isolation cubicle (model E10-20). A drinking bottle with a tube opening of 3 mm diameter could be inserted into the chamber through a 3 × 4-cm hole located in the center of the right wall of the chamber, 1.5 cm above the grid floor. When the bottle was not present, the hole was covered by a metal lid. Licks were detected by a Coulbourn Instruments infrared optical lickometer (model E24-01). In Experiment 2a, preexposure and conditioning sessions were conducted in darkness, and the preexposed, to-be-conditioned stimulus was a 5-s, 28-V, 40-mA light located on the right wall of the chamber 26 cm above the grid floor. In Experiment 2b, the chambers were illuminated during the sessions by the light that served as the stimulus in Experiment 2a, and the preexposed, to-be-conditioned stimulus consisted of three lights flashing at a rate of 2 Hz for 10 s, mounted in a horizontal row 8 cm apart from each other on the right wall of the chamber, 17.5 cm above the grid floor. Shock was delivered through the cage floor. It was supplied by a Coulbourn Instruments shocker (model E13-12) and scanner (model E13-13) set at either 0.5 or 1.0 mA.

A Coulbourn Instruments infrared activity monitor (model E24-61) was mounted on the ceiling. It was operated in the "movement unit" mode, in which a 10-ms pulse is produced each time the monitor detects a change in the animal's infrared heat pattern. This results in a series of pulses ("activity counts") at a frequency proportional to the amount of movement made by the animal.

Equipment programming and data recording were controlled by a Compaq IBM-compatible personal computer (486/DX2/66).

Procedure

Pretreatment handling and the baseline and rebaseline stages of the LI procedure were performed as in Study 1. Other LI stages are described below. Preexposure, conditioning, rebaseline, and the two test sessions were given 24 h apart. Each rat was run throughout the experiment in the same chamber.

Preexposure. With the bottle removed, each rat was placed in the experimental chamber. In Experiment 2a, PE animals received forty 5-s steady light presentations, and the NPE animals were confined to the chamber for an identical period of time but did not receive the lights. In Experiment 2b, the PE animals received 10 or 40 presentations of three 10-s flashing lights. Half of the NPE animals were confined to the chamber for a duration equivalent to the 10-presentation PE condition, and half for a duration equivalent to the 40-presentation PE condition. A variable ISI with a mean of 20 s was used in both experiments.

Conditioning. With the bottle removed, each rat received two light–shock pairings 5 and 10 min after the start of the session. Light parameters were identical to those used in preexposure. The 1-s shock (0.5 or 1.0 mA) immediately followed light termination. After the second pairing, rats were left in the experimental chamber for an additional 5 min.

Test. Animals were tested on two consecutive days in squads of four. Each of the four animals was placed in the chamber and allowed to drink from the bottle. After each animal had completed 275 licks, the light was presented and kept on for 15 min. The following times were recorded: time to first lick, time to complete licks 1–250, time to complete licks 251–275 (pre-light), and time to complete licks 276–300 (light on). All animals completed the last 25 licks during the stimulus-on time. The amount of suppression of licking was measured with a suppression ratio, A/(A + B), where A is the period prior to the presentation of the stimulus (licks 251–275) and B is the period of the stimulus presentation (licks 276–300).

Drugs

Administration of the drug or vehicle was performed as in Study 1.

Experimental Design

In Experiment 2a, 75 rats were randomly assigned to eight experimental groups in a 2 × 2 × 2 factorial design with main factors of preexposure [NPE (0), PE (40)], shock level [low (0.5 mA), high (1.0 mA)], and drug (vehicle, amphetamine). The number of animals in each group was as follows: PE–low–amphetamine, 10; PE–low–vehicle, 11; PE–high–amphetamine, 11; PE–high–vehicle, 10; NPE–low–amphetamine, 8; NPE–low–vehicle, 8; NPE–high–amphetamine, 9; NPE–high–vehicle, 8.

In Experiment 2b, 72 rats were randomly assigned to 12 experimental groups ($n = 6$ in each group) in a 3 × 2 × 2 factorial design with main factors of preexposure (0, 10, 40), shock level [low (0.5 mA), high (1.0 mA)], and drug (vehicle, amphetamine).

RESULTS

Experiment 2a: Effects of Amphetamine on LI at Low and High Shock Intensity Using Steady Light Stimulus

Activity. A 2 × 2 ANOVA with main factors of preexposure (0, 40) and drug (vehicle, amphetamine) carried out on the total number of activity counts during preexposure, and a 2 × 2 × 2 ANOVA with main factors of preexposure (0, 40), shock (low, high), and drug (vehicle, amphetamine) carried out on the total number of activity counts during conditioning, showed that amphetamine-treated animals were more active than vehicle controls throughout the preexposure and conditioning sessions [$F(1, 71) = 23.79$, $p < 0.001$ and $F(1, 67) = 9.29$, $p < 0.005$, respectively]. No other main effects or interactions were significant.

Conditioned suppression. The eight experimental groups did not differ in their times to complete licks 251–275 in the absence of the light (*A* period). A 2 × 2 × 2 ANOVA with main factors of preexposure (0, 40), shock level (low, high), and drug (vehicle, amphetamine), and a repeated measurement factor of 2 days, conducted on *A* periods yielded no significant outcomes. The overall mean *A* period was 5.60 s.

A 2 × 2 × 2 × 2 ANOVA with main factors of preexposure

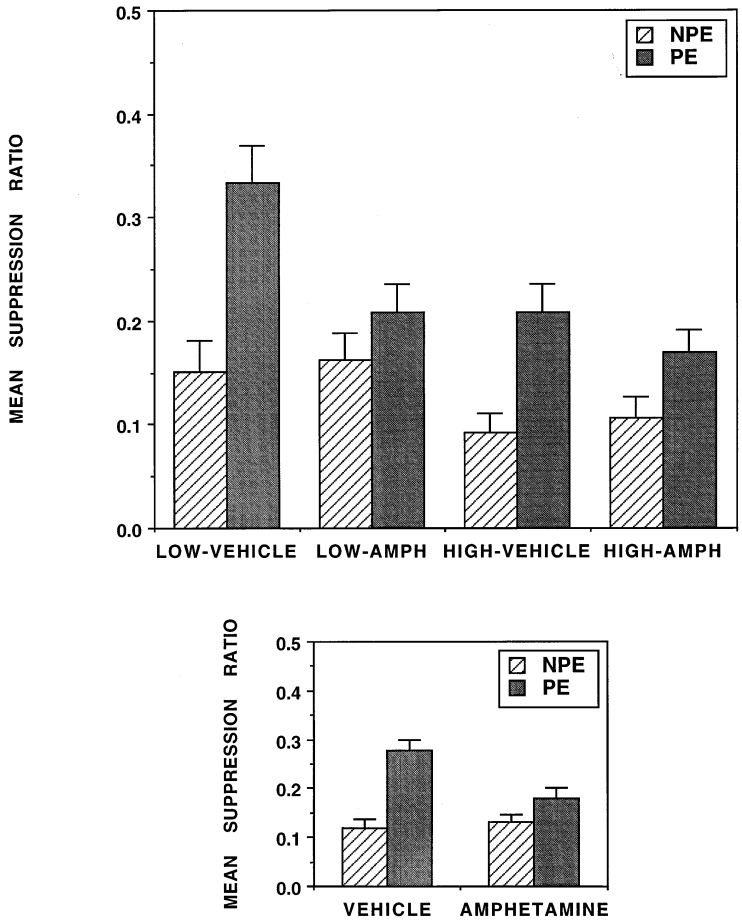

FIG. 3. Upper panel: Means and standard errors of suppression ratios for the preexposed (PE) and nonpreexposed (NPE) groups, collapsed over two daily sessions, in four conditions: low shock–vehicle, low shock–amphetamine, high shock–vehicle, high shock–amphetamine. Lower panel: Means and standard errors of suppression ratios for vehicle-treated or amphetamine-treated PE and NPE groups, representing the drug × preexposure interaction.

(0, 40), shock level (low, high), and drug (vehicle, amphetamine), and a repeated measurement factor of 2 days, carried out on the suppression ratios yielded a significant main effect of days [$F(1, 67) = 23.54$, $p < 0.001$], but no interaction of days with any of the other factors. Figure 3, upper panel, presents the mean suppression ratios of the PE and NPE groups, collapsed over two daily sessions, in the four conditions: low shock–vehicle, low shock–amphetamine, high shock–vehicle, high shock–amphetamine. As can be seen in the figure, higher shock intensity produced stronger lick suppression (i.e., lower ratio) compared with lower intensity. This was supported by a significant main effect of shock [$F(1, 67) = 13.34$, $p < 0.001$]. In addition, the figure shows that at both shock levels, LI (i.e., lower suppression of the PE as compared with the NPE group) is present in vehicle-treated animals but absent in the amphetamine-treated animals. This was supported by a significant main effect of preexposure [$F(1, 67) = 29.47$] and a significant preexposure × drug interaction [$F(1, 67) = 5.45$, $p < 0.03$]. Fig. 3, lower panel, depicts this interaction: amphetamine attenuated LI exclusively via its action in the PE groups.

RESULTS

Experiment 2b: Effects of Amphetamine on LI at Low and High Shock Intensity Using Flashing Light Stimulus

Activity. Data for 12 animals from preexposure were lost due to programming error. A 2 × 2 ANOVA with main factors of preexposure [NPE, PE (10 and 40 presentations collapsed)] and drug (vehicle, amphetamine) carried out on the total number of activity counts of the remaining 60 animals during preexposure, and a 3 × 2 × 2 ANOVA with main factors of preexposure (0, 10, 40), shock (low, high), and drug (vehicle, amphetamine) carried out on the total number of activity counts during conditioning, showed that amphetamine-treated animals were more active than vehicle controls throughout the preexposure and conditioning sessions [$F(1, 56) = 29.59$, $p < 0.001$ and $F(1, 60) = 14.81$, $p < 0.001$, respectively]. No other main effects or interactions were significant.

Conditioned suppression. The 12 experimental groups did not differ in their times to complete licks 251–275 in the absence of the lights (*A* period). A 3 × 2 × 2 ANOVA with main factors of preexposure (0, 10, 40), shock level (low, high),

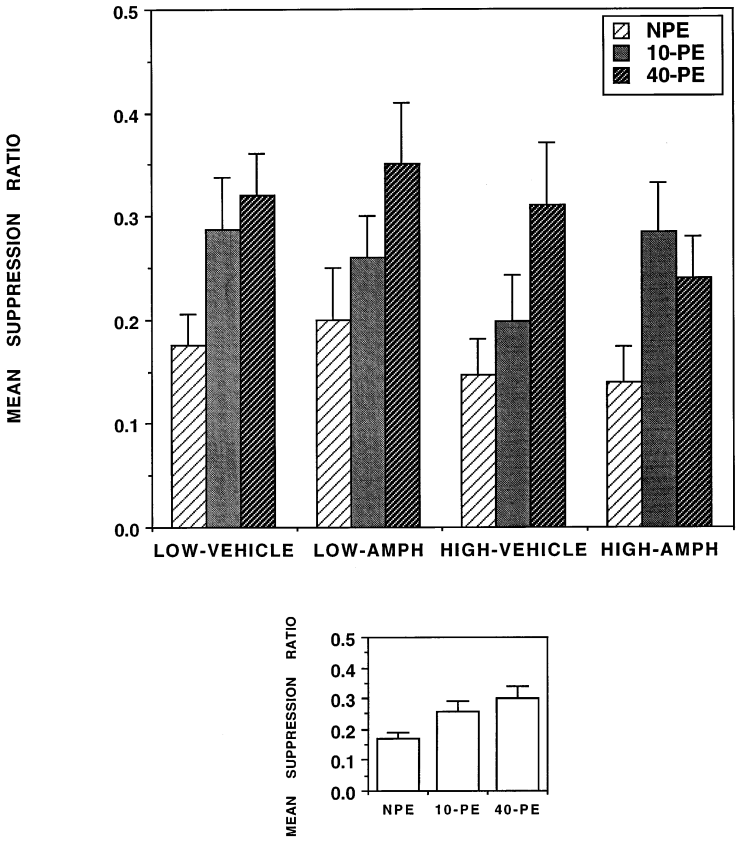

FIG. 4. Upper panel: Means and standard errors of suppression ratios for the preexposed (10-PE or 40-PE) and nonpreexposed (NPE) groups, collapsed over two daily sessions, in four conditions: low shock–vehicle, low shock–amphetamine, high shock–vehicle, high shock–amphetamine. Lower panel: Means and standard errors of suppression ratios for the three preexposure levels, representing the main effect of preexposure.

and drug (vehicle, amphetamine), and a repeated measurement factor of 2 days, conducted on *A* periods yielded no significant outcomes. The overall mean *A* period was 8.20 s.

A $3 \times 2 \times 2 \times 2$ ANOVA with main factors of preexposure (0, 10, 40), shock level (low, high), and drug (vehicle, amphetamine), and a repeated measurement factor of 2 days, carried out on the suppression ratios yielded a significant main effect of days [$F(1, 60) = 35.09$, $p < 0.001$], but no interaction of days with any of the other factors. Figure 4, upper panel, presents the mean suppression ratios of the PE (10 or 40) and NPE groups, collapsed over two daily sessions, in the four conditions: low shock–vehicle, low shock–amphetamine, high shock–vehicle, high shock–amphetamine. As can be seen in the figure, higher shock intensity produced stronger lick suppression (i.e., lower ratio) compared with lower intensity. This was supported by a significant main effect of shock [$F(1, 60) = 4.43$, $p < 0.04$]. In addition, the figure shows that at both shock levels, LI (i.e., lower suppression of the two PE groups as compared with the NPE group) is present in vehicle-treated as well as in amphetamine-treated animals. This was supported by a significant main effect of preexposure [$F(2, 60) = 4.36$, $p < 0.02$]. Fig. 4, lower panel, depicts this main effect: the degree of conditioned suppression is a direct function of number of preexposures, with both 10 and 40 preexposures yielding LI.

DISCUSSION

A meta-analysis conducted on the results of 23 replications of the effect of amphetamine on LI showed that LI was significantly attenuated due to drug-induced increased suppression in the PE groups only. There was no indication that amphetamine increased suppression in the NPE groups. Furthermore, when we divided the 23 replications into three categories according to the degree of suppression exhibited by the NPE–vehicle groups, this variable did not interact with amphetamine administration, as should have been the case if the effect of amphetamine on LI were due to a drug-induced increase in general learning capacity and/or in the functional impact of the US, or if floor or ceiling effects were involved.

It could be argued that floor effects prevented the detection of enhanced conditioning in the amphetamine-treated NPE groups, or that such enhancement is not fully apparent in these animals because suppression in the placebo control condition is already maximal. However, examination of the times taken by the amphetamine–NPE and the vehicle–NPE groups to complete the 25 licks in the presence of the tone indicates that: a) these times were remarkably similar (mean time to complete licks 76–100 in the presence of the tone for vehicle groups was 130 ± 9.3 s, and for amphetamine groups was 127 ± 7.1 s), and b) both groups had plenty of room to reach full

suppression, which would be indicated by mean times approaching 300 s.

The results of the meta-analysis show that the attenuation of LI by amphetamine is clearly due to better learning in only the PE groups. This is inconsistent with the claim that amphetamine disrupts LI by increasing the functional impact, or the salience, of the shock US, because this implies that the drug increases conditioned suppression nondifferentially in the PE and NPE groups. The results of Experiments 2a and 2b question this claim even further. In Experiment 2a, which used a 5-s steady light as the preexposed and conditioned stimulus, amphetamine disrupted LI at both high and low shock intensities. Thus, we did not find evidence that the disruptive influence of amphetamine can be counteracted by decreasing the intensity of the foot shock (22). There is a possibility, of course, that we did not reduce the shock level sufficiently to obtain the desired effect. It will be recalled that in Killcross et al.'s (22) study, amphetamine failed to disrupt LI only when the degree of post-shock suppression [or overall rates of conditioning (this is not clear from their paper: see p. 189 vs. p. 191)] was equated in the amphetamine-treated and saline-treated groups, so that the two groups were conditioned with different shock intensities. While it is possible that the effect reported by Killcross et al. can be obtained only under such conditions, it should be noted that in Experiment 2a (as in those included in the meta-analysis), the degree of conditioned suppression in the amphetamine-treated and vehicle-treated NPE groups was almost identical (see Fig. 3). Likewise, examination of the times taken by these groups to complete the 25 licks in the presence of the light indicates that they were highly similar, and if anything, there was lower suppression in the amphetamine group conditioned with high shock (mean time to complete licks 276–300 for the groups conditioned with low shock was 51 $\pm$ 14 s for the vehicle group and 57 $\pm$ 20 s for the amphetamine group; with high shock, the time was 110 $\pm$ 33 s for the vehicle group and 84 $\pm$ 22 s for the amphetamine group).

A mirror analysis can be applied to the results of Experiment 2b. In this experiment, which used three flashing lights as the preexposed and conditioned stimulus, amphetamine failed to disrupt LI at both shock intensities and at both preexposure levels (10 and 40). Thus, in this experiment, increasing shock intensity did not reinstate the capacity of amphetamine to disrupt LI, as would be expected according to Killcross et al.'s (22) hypothesis. However, as in the case of Experiment 2a, it is possible to claim that we did not increase the shock level sufficiently to reinstate the efficacy of the drug.

Another reason for the discrepancy between our and Killcross et al.'s (22) results could stem from differences in the CER procedures used, namely, a between-subjects off-baseline procedure using licking as compared with a within-subjects on-baseline CER procedure using lever-press. In this context, it should be noted that we obtained the same results as those of our present Experiments 2a and 2b using identical parameters and an on-baseline procedure, i.e., animals were allowed to drink during both the preexposure and conditioning sessions (unpublished observations). Thus, the off/on-baseline distinction does not seem to account for the difference in our results, but other procedural differences might.

Although the results of Experiments 2a and 2b cannot, therefore, be taken as conclusive evidence that the effect of amphetamine cannot be modified by manipulating shock intensity, they do show conclusively that this effect is modifiable by manipulating the nature of the preexposed stimulus, irrespective of shock intensity. More specifically, it appears that increasing stimulus salience counteracts the disruptive effect of amphetamine on LI. That stimulus salience may be the critical factor operating in Experiment 2b is supported by the finding that in this experiment, 10 preexposures sufficed to produce LI, whereas typically a higher number of preexposures is necessary (27,30). Alternatively, it is possible that during flashing light presentation, each flash is perceived as a discrete stimulus, and that therefore, this preexposure condition is functionally equivalent to a very high number of preexposures (i.e., 10 flashing light presentations = 100 discrete stimuli). De la Casa et al. (8) showed that increasing the duration of the preexposed stimulus counteracted the disruptive effects of amphetamine on LI. Because number of preexposures and total duration of preexposure are interchangeable in their effect on LI magnitude (27), it is possible that the same mechanism operated in our and De la Casa et al.'s experiments. Another factor that could underlie the different effects of amphetamine in Experiments 2a and 2b is the different overall illumination environments within the test chambers. LI is highly context specific, and it was proposed that amphetamine acts on LI by disrupting contextual control (27,28). It is possible that a certain level of illumination or some interaction between the level of illumination and the nature of the stimulus, which would also determine the relative salience of the stimulus, modulated the contextual control of LI and subsequently the effects of amphetamine. Whatever the critical parameter that determined the effect of the stimuli we used, the fact that changing stimulus variables modulates the effect of amphetamine on LI cannot be accommodated by Killcross et al.'s (22) explanation of the effects of this drug on LI.

Taken together, the present results are inconsistent with the hypothesis that the amphetamine-induced disruption of LI is solely mediated by drug-induced changes in the effects of reinforcers nondifferentially in the PE and NPE groups. Rather, they are consistent with the more general position taken by the switching model, that amphetamine shifts the relative balance between the behavioral impact of preexposure and conditioning, and that this effect is restricted to the PE group (48,53). This in turn implies that the effects of amphetamine on LI should be highly sensitive to alterations in the parameters of both preexposure and conditioning that determine their relative impact on behavior [for a parallel analysis of the effects of dopaminergic blockers on LI, see (48,53)]. Within this framework, the use of a highly salient stimulus as in Experiment 2b, or of long stimulus duration, as in De la Casa et al.'s (8) experiment, increases the relative impact of preexposure and thus weakens the capacity of amphetamine to enhance responding according to the CS–US contingency. Importantly, within this framework, changes in US intensity are also expected, under certain conditions, to modify the effects of amphetamine, because such changes shift the balance between the impact of preexposure and conditioning, i.e., decreasing shock intensity decreases the impact of conditioning, and vice versa for increasing shock intensity. The major point made by the switching model is that the effect of amphetamine on LI is modifiable by stimulus as well as by reinforcer variables. The only way to assess the contribution of these variables is to conduct thorough parametric studies in which the parameters of both preexposure and conditioning are systematically manipulated. What we showed here is that, under some conditions, changes in stimulus parameters are more effective in modifying the effect of amphetamine than changes in reinforcer parameters (shock intensity). There are likely to be other conditions in which the opposite would hold

true. Finally, it should be noted that the above arguments apply to CER procedures using aversive reinforcers. Killcross et al. (22) showed that amphetamine was ineffective in disrupting LI in a parallel appetitive paradigm. In view of the accumulating evidence that the effects of amphetamine on LI are highly sensitive to procedural parameters, this finding most likely represents yet another instance of such sensitivity, namely, that the efficacy of amphetamine in disrupting LI is also a function of the nature of the reinforcer. Presumably, there is a set of preexposure and conditioning parameters under which amphetamine would disrupt LI also with appetitive reinforcers.

The present results may have implications for the LI model and the reported impairment of LI in schizophrenics. As was pointed out by Weiner (48), amphetamine-induced enhanced switching may provide an animal analogue of the inability to maintain a major response set or a dominant interpretation of a given situation, excessive yielding to immediate situational demands, and enhanced behavioral and cognitive switching, which characterize the schizophrenic syndrome (1,4,5,13,14,31, 34,37,42,45). The finding that amphetamine fails to disrupt LI under certain conditions brings into question the generality and suitability of amphetamine-induced disruption of LI for providing such an analogue. However, the relationship between LI disruption and schizophrenia is complex. Thus, although acute schizophrenic patients, suffering from first psychotic breakdown or being in an acute stage of an otherwise chronic disorder, do not show LI (2,18,20), LI is reinstated in chronic schizophrenics, irrespective of neuroleptic treatment (20). Interestingly, a similar inverse relationship exists between LI disruption and the dose of amphetamine. Thus, in both rats and humans, LI is disrupted by low doses of amphetamine but is left intact by high doses of the drug (19,49). Therefore, it is possible that spared LI following amphetamine administration may provide an animal analogue to the reinstated LI in the chronic state of this disorder. If this is the case, then elucidation of the behavioral, pharmacological, and neural mechanisms that underlie such spared LI may provide important insights into the mechanisms underlying spared or reinstated LI in schizophrenia.

Finally, previous findings that LI is disrupted by low doses of amphetamine that produce hyperactivity and enhance DA release in the nucleus accumbens [e.g., (10,24,44)] had led to the hypothesis that both LI disruption and locomotor activation are subserved by a common mechanism, namely, enhanced DA release in the nucleus accumbens (16,48). This common account leads to the inference that amphetamine-induced activity and reduction of LI should be related. The present finding that amphetamine increased activity in preexposure and conditioning in both experiments, whereas it abolished LI only in one of them, does not support this inference. Alternatively, the dissociation between the effects of amphetamine on activity and LI may indicate that different neural mechanisms operate under conditions leading to LI disruption and those that do not.

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REFERENCES

1. Anscombe, F.: The disorder of consciousness in schizophrenia. Schiz. Bull. 13:241–260; 1987.
2. Baruch, I.; Hemsley, D.; Gray, J. A.: Differential performance of acute and chronic schizophrenics in a latent inhibition task. J. Nerv. Ment. Dis. 176:598–606; 1988.
3. Baruch, I.; Hemsley, D. R.; Gray, J. A.: Latent inhibition and "psychotic proneness" in normal subjects. Pers. Indiv. Differ. 9: 777–783; 1988.
4. Bleuler, E.: Dementia praecox or the group of schizophrenias. New York: International Universities Press; 1911.
5. Broen, W. E.: Schizophrenia: Research and theory. New York: Academic Press; 1968.
6. Christison, G. W.; Atwater, G. E.; Dunn, L. A.; Kilts, C. D.: Haloperidol enhancement of latent inhibition: Relation to therapeutic action? Biol. Psychiatry 23:746–749; 1988.
7. Cools, A.; Jaspers, R.; Schwartz, M.; Sontag, K. H.; Vrijmoed de Vries, M.; Van den Bereken, J.: Basal ganglia and switching motor programs. In: McKenzie, J. S.; Kemm, R. E.; Wilcock, N., eds. The basal ganglia. New York: Plenum Press; 1984:513–544.
8. De la Casa, L. G.; Ruiz, G.; Lubow, R. E.: Amphetamine-produced attenuation of latent inhibition is modulated by stimulus preexposure duration: Implications for schizophrenia. Biol. Psychiatry 33:707–711; 1993.
9. De la Casa, L. G.; Ruiz, G.; Lubow, R. E.: Latent inhibition and recall/recognition of irrelevant stimuli as a function of preexposure duration in high and low psychotic-prone normals. Br. J. Psychol. 84:119–132; 1993.
10. Di Chiara, G.: On the preferential release of mesolimbic dopamine by amphetamine. Neuropsychopharmacology 5:243–244; 1991.
11. Dunn, L. A.; Atwater, G. E.; Kilts, C. D.: Effects of antipsychotic drugs on latent inhibition—Sensitivity and specificity of an animal behavioral model of clinical drug action. Psychopharmacology 112:315–323; 1993.
12. Feldon, J.; Weiner, I.: The latent inhibition model of schizophrenic attention disorder: Haloperidol and sulpiride enhance rats' ability to ignore irrelevant stimuli. Biol. Psychiatry 29:635–646; 1991.
13. Frith, C. D.: Consciousness, information processing and schizophrenia. Br. J. Psychiatry 134:225–235; 1979.
14. Frith, C. D.: The cognitive neuropsychology of schizophrenia. Essays in cognitive psychology. Hillsdale, NJ: Lawrence Erlbaum Associates Ltd.; 1992.
15. Gelissen, M.; Cools, A.: Effect of intracaudate haloperidol and apomorphine on switching motor patterns upon current behavior of cats. Behav. Brain Res. 29:17–26; 1988.
16. Gray, J. A.; Feldon, J.; Rawlins, J. N. P.; Hemsley, D. R.; Smith, A. D.: The neuropsychology of schizophrenia. Behav. Brain Sci. 14:1–84; 1991.
17. Gray, J. A.; Joseph, M. H.; Hemsley, D. R.; Young, A. M. J.; Warburton, E. C.; Boulenguez, P.; et al.: The role of mesolimbic dopaminergic and retrohippocampal afferents to the nucleus accumbens in latent inhibition: Implications for schizophrenia. Behav. Brain Res. 71:19–31; 1995.
18. Gray, N. S.; Hemsley, D. R.; Gray, J. A.: Abolition of latent inhibition in acute, but not chronic, schizophrenics. Neurol. Psychiatry Brain Res. 1:83–89; 1992.
19. Gray, N. S.; Pickering, A. D.; Hemsley, D. R.; Dawling, S.; Gray, J. A.: Abolition of latent inhibition by a single 5 mg dose of *d*-amphetamine in man. Psychopharmacology 107:425–430; 1992.
20. Gray, N. S.; Pilowsky, L. S.; Gray, J. A.; Kerwin, R. W.: Latent inhibition in drug naive schizophrenics: Relationship to duration of illness and dopamine D2 binding using SPET. Schizophr. Res. 17:95–107; 1995.

21. Hall, G.: Perceptual and associative learning. New York: Oxford University Press; 1991.
22. Killcross, A. S.; Dickinson, A.; Robbins, T. W.: Amphetamine-induced disruptions of latent inhibition are reinforcer-mediated: Implications for animal models of schizophrenic attentional dysfunction. Psychopharmacology 115:185–195; 1994.
23. Killcross, A. S.; Robbins, T. W.: Differential effects of intra-accumbens and systemic amphetamine on latent inhibition using an on-baseline, within-subject conditioned suppression paradigm. Psychopharmacology 110:479–489; 1993.
24. Kuczenski, R.; Segal, D.: Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. J. Neurosci. 9:2051–2065; 1989.
25. Lipp, O. V.; Vaitl, D.: Latent inhibition in human Pavlovian differential conditioning: Effect of additional stimulation after preexposure and relation to schizotypal traits. Pers. Indiv. Differ. 13:1003–1012; 1992.
26. Lubow, R. E.: Latent inhibition. Psychol. Bull. 79:398–407; 1973.
27. Lubow, R. E.: Latent inhibition and conditioned attention theory. Cambridge, UK: Cambridge University Press; 1989.
28. Lubow, R. E.; Gewirtz, J. C.: Latent inhibition in humans: Data, theory, and implications for schizophrenia. Psychol. Bull. 117:87–103; 1995.
29. Lubow, R. E.; Ingberg-Sachs, Y.; Zalstein-Orda, N.; Gewirtz, J. C.: Latent inhibition in low and high "psychotic-prone" subjects. Pers. Indiv. Differ. 13:563–572; 1992.
30. Lubow, R. E.; Weiner, I.; Schnur, P.: Conditioned attention theory. In: Bower, G. H., ed. The psychology of learning and motivation. New York: Academic Press; 1981:1–49.
31. Lyon, M.: Animal models of mania and schizophrenia. In: Willner, P., ed. Behavioral models in psychopharmacology: Theoretical, industrial and clinical perspectives. Cambridge, UK: Cambridge University Press; 1991:253–310.
32. Mackintosh, N. J.: A theory of attention: Variations in the associability of stimuli with reinforcement. Psychol. Rev. 82:276–298; 1975.
33. Mackintosh, N. J.: Conditioning and associative learning. New York: Oxford University Press; 1983.
34. Magaro, P. A.: Cognition in schizophrenia and paranoia: The integration of cognitive processes. Hillsdale, NJ: Lawrence Erlbaum; 1980.
35. Moore, J. W.; Stickney, K. J.: Formation of attentional-associative networks in real time: Role of the hippocampus and implications for conditioning. Physiol. Psychol. 8:207–217; 1980.
36. Oades, R. D.: The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Neurosci. Biobehav. Rev. 9:261–282; 1985.
37. Payne, R. W.: The measurement and significance of overinclusive thinking and retardation in schizophrenic patients. In: Hoch, P.; Zubin, J., eds. Psychopathology of schizophrenia. New York: Grune and Stratton; 1966.
38. Robbins, T. W.: The case for frontostriatal dysfunction in schizophrenia. Schiz. Bull. 16:391–402; 1990.
39. Robbins, T. W.; Everitt, B. J.: Functional studies of the central catecholamines. Int. Rev. Neurobiol. 23:303–365; 1982.
40. Schmajuk, N. A.; Moore, J. W.: Real-time attentional models for classical conditioning and the hippocampus. Physiol. Psychol. 13:278–290; 1985.
41. Schmajuk, N. A.; Moore, J. W.: The hippocampus and the classically conditioned nictitating membrane response: A real-time attentional-associative model. Psychobiology 16:20–35; 1988.
42. Shakow, D.: Segmental set: A theory of the formal psychological deficit in schizophrenia. Arch. Gen. Psychiatry 6:17–33; 1962.
43. Solomon, P. R.; Crider, A.; Winkelman, J. W.; Turi, A.; Kamer, R. M.; Kaplan, L. J.: Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: Relationship to schizophrenic attention disorder. Biol. Psychiatry 16:519–537; 1981.
44. Staton, D. M.; Solomon, P.: Microinjections of *d*-amphetamine into the nucleus accumbens and caudate-putamen differentially affect stereotypy and locomotion in the rat. Physiol. Psychol. 12:159–162; 1984.
45. Swerdlow, N. R.; Koob, G. F.: Dopamine, schizophrenia, mania and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. Behav. Brain Res. 10:197–245; 1987.
46. Van den Bos, R.; Cools, A. R.: The involvement of the nucleus accumbens in the ability of rats to switch to cue-directed behaviors. Life Sci. 44:1697–1704; 1989.
47. Warburton, E. C.; Joseph, M. H.; Feldon, J.; Weiner, I.; Gray, J. A.: Antagonism of amphetamine-induced disruption of LI in rats by haloperidol and ondansetron: Implications for a possible antipsychotic action of ondansetron. Psychopharmacology 114: 657–664; 1994.
48. Weiner, I.: Neural substrates of latent inhibition: The switching model. Psychol. Bull. 108:442–461; 1990.
49. Weiner, I.; Izraeli-Telerant, A.; Feldon, J.: Latent inhibition is not affected by acute or chronic administration of 6 mg/kg *dl*-amphetamine. Psychopharmacology 91:345–351; 1987.
50. Weiner, I.; Lubow, R. E.; Feldon, J.: Chronic amphetamine and latent inhibition. Behav. Brain Res. 2:285–286; 1981.
51. Weiner, I.; Lubow, R. E.; Feldon, J.: Abolition of the expression but not the acquisition of latent inhibition by chronic amphetamine in rats. Psychopharmacology 83:194–199; 1984.
52. Weiner, I.; Lubow, R. E.; Feldon, J.: Disruption of latent inhibition by acute administration of low doses of amphetamine. Pharmacol. Biochem. Behav. 30:871–878; 1988.
53. Weiner, I.; Shadach, E.; Barkai, R.; Feldon, J.: Haloperidol and clozapine-induced enhancement of latent inhibition with extended conditioning: Implications for the mechanism of action of neuroleptic drugs. Neuropsychopharmacology; in press.