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Haloperidol- and Clozapine-Induced Enhancement of Latent Inhibition with Extended Conditioning: Implications for the Mechanism of Action of Neuroleptic Drugs

I. Weiner, Ph.D., E. Shadach, M.A., R. Barkai, M.A., and J. Feldon, D.Phil (Oxon)

Latent inhibition (LI) refers to retarded conditioning to a stimulus as a consequence of its nonreinforced preexposure. LI is impaired in acute schizophrenic patients and in rats treated with amphetamine. Neuroleptic drugs enhance LI, and this effect is selective and specific for this class of drugs. The present experiments tested the proposition that neuroleptic-induced enhancement of LI stems from decreased capacity of stimulus-preexposed animals to switch responding according to the new stimulus-reinforcement contingency in the conditioning stage. LI was assessed using an off-baseline conditioned emotional response (CER) procedure in rats licking for water, consisting of three stages: preexposure to the-to-be conditioned stimulus, tone; conditioning, in which the preexposed stimulus was paired with a foot-shock; and test, in which LI was indexed by animals' degree of suppression of licking during tone presentation. Whereas in previous studies that demonstrated LI enhancement by neuroleptics, preexposure consisted of 10 to 40 tones, and conditioning included two tone-shock pairings, the present experiments used 40 tone preexposures, followed by an extended conditioning stage with five tone-shock pairings. It was expected that under these conditions no LI effect would be evident in untreated animals, but that animals treated with a neuroleptic drug, either during the entire LI procedure or only in conditioning, would show LI. Experiments 1 and 2 showed that LI was obtained in rats treated with haloperidol (0.1 mg/kg in experiment 1, 0.03 and 0.2 mg/kg in experiment 2) but not in the untreated controls. Experiment 3 showed that the same outcome was obtained when haloperidol (0.1 mg/kg) administration was confined to the conditioning stage. Experiment 4 showed that clozapine (5 mg/kg)-treated animals showed LI when the drug was confined to conditioning, but not to the preexposure stage. The implications of these results for the mechanism of action of neuroleptic drugs are discussed. **© 1997 American College of Neuropsychopharmacology [Neuropsychopharmacology 16:42–50, 1997]**

KEY WORDS: *Latent inhibition; Neuroleptics, Switching; Rat*

Latent inhibition (LI) refers to retarded conditioning to a stimulus that has been repeatedly presented without reinforcement (Hall 1991; Lubow 1973, 1989; Lubow and Gewirtz 1995; Lubow et al. 1981; Mackintosh 1975, 1983; Moore and Stickney 1980; Schmajuk and Moore 1985, 1988; Weiner 1990). This retardation is considered to index the capacity of organisms to ignore stimuli that predict no significant consequences and can be demonstrated in a variety of classical and instrumental conditioning procedures and in many mammalian species, including humans. 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 analo-

From the Department of Psychology (IW, ES, RB), Tel-Aviv University, Ramat-Aviv, Tel-Aviv, Israel; and the Laboratory of Behavioral Biology and Functional Toxicology (JF), Swiss Federal Institute of Technology, Institute of Toxicology, Schwerzenbach, Switzerland.

Address correspondence to: Dr. I. Weiner, Department of Psychology, Tel-Aviv University, Ramat-Aviv, Tel-Aviv 69978, Israel.

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gous processes across species (Lubow and Gewirtz 1995). LI is disrupted in amphetamine-treated rats (Killcross and Robbins 1993; Killcross et al. 1994a; Solomon et al. 1981; Warburton et al. 1994; Weiner et al. 1981, 1984, 1988), and this disruption is antagonized by neuroleptics (Warburton et al. 1994). These outcomes had led to the proposition (Feldon and Weiner 1991; Gray et al. 1991; Solomon et al. 1981; Weiner 1990; Weiner et al. 1981, 1984, 1988) that LI disruption can be used to model the widely described failure of schizophrenics to ignore irrelevant stimuli (e.g., Anscombe 1987). The model possesses construct validity in that schizophrenic patients suffering from first psychotic breakdown or being in an acute stage of an otherwise chronic disorder fail to show LI (Baruch et al. 1988; Gray et al. 1992a). LI is also disrupted in human volunteers given amphetamine (Gray et al. 1992b).

Given on their own, neuroleptics enhance LI (Christison et al. 1988; Dunn et al. 1993; Feldon and Weiner 1988, 1991; Killcross et al. 1994b; Peters and Joseph 1993; Weiner and Feldon 1987, 1994; Weiner et al., 1987; Williams, Wellman, Geaney, Rawlins, Feldon, Cowen, personal oral communication). This effect is specific and selective for drugs with known antipsychotic efficacy and is not produced by a wide range of nonantipsychotic drugs (Dunn et al. 1993). In this study, clozapine failed to enhance LI, but we have recently obtained LI potentiation also with clozapine (Weiner et al. in press). Whereas these results lend the LI model predictive validity for antipsychotic effects, the mechanism of action of these drugs in LI is not clear.

One such mechanism can be derived from the switching model of LI (Weiner 1990). In this model, LI is viewed as successively exposing an organism to conflicting environmental contingencies in preexposure (stimulus-no event) and conditioning (stimulus-reinforcement). The central point in terms of LI development is that in conditioning, the animal must remain under the control of information acquired in preexposure (CS-no event), in spite of the fact that the stimulus comes to signal a significant outcome, reinforcement. In terms of neural mechanisms, the switching model attributes a key role to the mesolimbic DA system and the hippocampus. It is proposed that the mesolimbic dopaminergic (DA) system is activated in the conditioning stage when the previously nonreinforced stimulus is followed by reinforcement. Because such activation leads to rapid behavioral and cognitive switching (Cools et al. 1984; Gelissen and Cools 1988; Lyon 1991; Oades 1985; Robbins and Everitt 1982; Swerdlow and Koob 1987; Van den Bos and Cools 1989), it 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 CS in preexposure (CS-no event) continues to control behavior in conditioning, because the hippocampus inhibits the switching mechanism of the nucleus accumbens (Weiner 1990).

It follows from this account that the effects of dopaminergic manipulations on LI are restricted to the conditioning stage. Enhancement of dopaminergic transmission (e.g., after amphetamine administration) should promote rapid switch of responding according to the CS-US contingency and thus disrupt LI. Conversely, blockade of DA transmission by neuroleptic drugs should reduce animals' capacity to switch responding according to the changed contingency of reinforcement in the conditioning stage and thus enhance the LI effect. There is some evidence supporting this position. Thus, animals receiving nonreinforced stimulus preexposure under haloperidol but conditioned without the drug, show a normal, nonfacilitated LI effect (Weiner et al. 1987) and furthermore, haloperidol enhances LI after a low number of preexposures (which does not produce LI in control animals) when administered only in conditioning (Peters and Joseph 1993). The present experiments sought to provide a more explicit test of the switching mechanism and to demonstrate within a single experiment that neuroleptic-induced enhancement of LI indeed occurs at the conditioning stage. Weiner (1990) predicted that if the action of neuroleptics is due to reduced capacity to switch responding according to the changed contingency of reinforcement in the conditioning stage, then neuroleptic-treated animals should show LI when the number of conditioning trials is increased to a level at which normal animals do not display LI. The present experiments tested this prediction. LI was assessed using an off-baseline conditioned emotional response (CER) procedure in rats licking for water, consisting of three stages: preexposure, in which the to-be-conditioned stimulus (a tone) was repeatedly presented without reinforcement; conditioning, in which the preexposed stimulus was paired with reinforcement (a foot-shock); and test, in which LI was indexed by animals' degree of suppression of licking during tone presentation. Whereas in previous studies that demonstrated LI enhancement by neuroleptics, preexposure consisted of 10 to 40 tones and conditioning included two tone-shock pairings, we used 40 nonreinforced tone preexposures, followed by an extended conditioning stage that included five tone-shock pairings. We expected that five CS-US pairings would suffice to overcome the effects of preexposure in untreated animals, but that neuroleptic-treated animals would show LI. Furthermore, we expected that this action of neuroleptics would be evident when the administration of the drug is confined to the conditioning stage. Experiment 1 tested the effects of 0.1 mg/kg haloperidol, and experiment 2 tested the effects of 0.03 and 0.2 mg/kg haloperidol, administered throughout the LI procedure. Experiment 3 tested the effects of 0.1 mg/kg haloperidol administration confined to the conditioning stage.

Experiment 4 tested the effects of 5 mg/kg clozapine administered in either the preexposure or the conditioning stage or in both. Clozapine was used for two reasons: first, the effects of haloperidol administration in preexposure persist for more than 24 hours (Weiner et al. 1987), whereas our pilot studies indicated this not to be the case for clozapine, which has a comparatively short half-life (Farde and Nordstrom 1992). Second, it was of interest to test whether an "atypical" neuroleptic would act similarly to a "typical" neuroleptic.

MATERIALS AND METHODS

Subjects

Male Wistar rats (Tel-Aviv University Medical School) approximately 4 months old, were housed one to a cage under reversed cycle lighting. Seven days prior to the beginning of each experiment, they were placed on a 23-hour water restriction schedule and handled for about 2 minutes each day. During the days on which water was available in the experimental chambers, this was in addition to the daily ration of 1h given in the home cages.

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 at 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 (Model 453). The preexposed to-be-conditioned stimulus was a 2.8 kHz tone produced by a Sonalert module (Model SC 628). Shock was supplied by a Campden Instruments shock generator (Model 521/C) and shock scrambler (Model 521/S) set a 0.75 mA. Equipment programming and data recording were controlled by an IBM-compatible personal computer (Amigo-MX).

Procedure

The stages of the CER procedure were as follows:

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

Preexposure (PE). With the bottle removed, each animal was placed in the experimental chamber. The preexposed (PE) animals received 40 5-second tone presentations with an interstimulus interval of 50 seconds. The nonpreexposed (NPE) animals were confined to the chamber for an identical period of time without receiving the tone.

Conditioning. With the bottle removed, each rat received five tone-shock pairings given 5 minutes apart. Tone parameters were identical to those used in preexposure. The 0.75 mA, 1-second shock immediately followed tone termination. The first tone-shock pairing was given 5 minutes after the start of the session. After the fifth pairing, animals were left in the experimental chamber for an additional 5 minutes.

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

Test. Each rat was placed in the chamber and allowed to drink from the bottle. When the rat completed 75 licks, the tone was presented for 5 minutes. The following times were recorded: time to first lick, time to complete licks 1 to 50, time to complete licks 51 to 75 (pretone period), and time to complete licks 76 to 100 (tone-on period). The times to complete licks 76 to 100 were logarithmically transformed. The stages of preexposure, conditioning, rebaseline, and test were given 24 hours apart. Each animal was run throughout the experiment in the same chamber.

Drugs. In experiments 1 to 3, the appropriate drug treatment, 0.1 mg/kg (experiment 1 and 3) or 0.03 and 0.2 mg/kg (experiment 2) of haloperidol in 1 ml saline [prepared from an ampoule containing 5 mg haloperidol in 1 ml of solvent containing 6 mg of lactic acid (Abic Ltd, Israel) diluted in an appropriate volume of saline], or an equivalent volume of saline, was administered IP 45 minutes prior to the start of preexposure and/or 45 minutes prior to conditioning. In experiment 4, clozapine was dissolved in 1N acetic acid (1.5 ml/10 mg) and diluted with saline to reach the appropriate concentration (5 mg/1 ml). Clozapine (5 mg/kg) or an equivalent volume of vehicle was administered IP 30 minutes prior to the start of preexposure and/or 30 minutes prior to conditioning. The rebaseline and test stage were conducted without drugs.

Experiment 1—Effects of 0.1 mg/kg Haloperidol Administered in Preexposure and Conditioning

Eighty animals were randomly assigned to four experimental groups in a 2 × 2 factorial design with main factors of preexposure (0, 40) and drug (0, 0.1 mg/kg haloperidol). The experiment was run in two replications. Data of three subjects were lost due to apparatus failure. Thus, the final analysis included data of 77 subjects.

Experiment 2—Effects of 0.03 and 0.2 mg/kg Haloperidol Administered in Preexposure and Conditioning

This experiment was identical to experiment 1, but the doses of haloperidol were 0.03 and 0.2 mg/kg. Seventy-two animals were randomly assigned to six groups in a 2 × 3 factorial design with main factors of preexposure (0, 40) and drug (0, 0.03, and 0.2 mg/kg haloperidol). The experiment was run in two replications. Data of three subjects were lost due to apparatus failure. Thus, the final analysis included data of 69 subjects.

Experiment 3—Effects of 0.1 mg/kg Haloperidol Administered in Conditioning

Thirty-six animals were randomly assigned to six experimental groups in a 2 × 3 factorial design with main factors of preexposure (0, 40) and drug in preexposure and conditioning (vehicle-vehicle, vehicle-haloperidol, haloperidol-haloperidol).

Experiment 4—Effects of 5 mg/kg Clozapine Administered in Preexposure or in Conditioning

Ninety-six animals were randomly assigned to eight experimental groups in a 2 × 4 factorial design with main factors of preexposure (0, 40) and drug in preexposure and/or conditioning (vehicle-vehicle, vehicle-clozapine, clozapine-vehicle, clozapine-clozapine). The experiment was run in two replications. Data of four subjects were lost due to apparatus failure. Thus, the final analysis included data of 92 subjects.

RESULTS

Experiment 1

Because none of the analyses yielded an effect of replication or interactions with this factor, the data of the two replications were combined. 2 × 2 ANOVAs with main factors of preexposure (0, 40) and drug (0, 0.1 mg/kg haloperidol) performed on latencies to first lick and total number of licks on rebaseline day and on latencies to first lick, time to complete licks 1 to 50, and time to complete licks 51 to 75 on test day yielded no significant outcomes. A 2 × 2 ANOVA performed on the log times to complete licks 76 to 100 in the presence of the tone yielded significant main effects of preexposure $F(1,73) = 9.77$, $p < .003$ and drug $F(1,73) = 4.48$, $p < .04$, as well as a significant drug × preexposure interaction $F(1,73) = 4.24$, $p < .05$. As can be seen in Figure 1, these outcomes reflect the fact that LI, i.e. faster drinking during tone presentation in the preexposed as compared with nonpreexposed animals, was evident only in the haloperidol-treated animals.

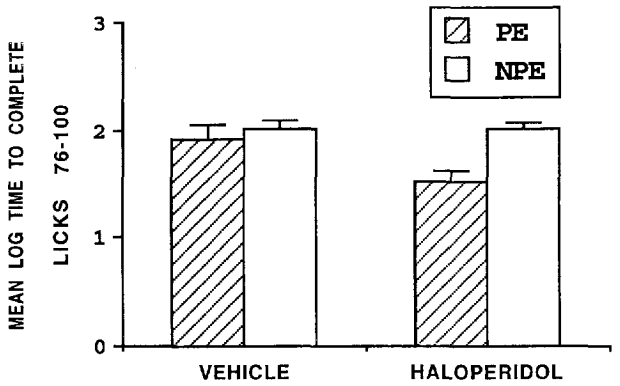

Figure 1. Mean log times and standard errors to complete licks 76 to 100 in the presence of the tone in the preexposed (PE) and the nonpreexposed (NPE) groups in two drug conditions: vehicle, 0.1 mg/kg haloperidol. Forty tone preexposures and five tone-shock pairings were used.

Experiment 2

Because none of the analyses yielded an effect of replication or interactions with this factor, the data of the two replications were combined. 2 × 3 ANOVAs with main factors of preexposure (0, 40) and drug (0, 0.03, and 0.2 mg/kg haloperidol) performed on latencies to first lick and total number of licks on rebaseline day and on latencies to first lick, time to complete licks 1 to 50, and time to complete licks 51 to 75 on test day, yielded no significant outcomes. A 2 × 3 ANOVA performed on the log times to complete licks 76 to 100 in the presence of the tone, yielded a significant main effect of preexposure $F(1,63) = 6.64$, $p < .02$ and an almost significant effect of drug $F(2,63) = 2.97$, $p < .06$, as well as a significant drug × preexposure interaction $F(2,63) = 3.09$, $p < .05$. As can be seen in Figure 2, these outcomes reflect the fact that LI, i.e., shorter times to complete licks 76 to 100 in the preexposed as compared with nonpreexposed animals, was evident in haloperidol-treated but not in saline-injected animals. Post hoc two-tailed t tests based on the error term derived from the ANOVA revealed a significant difference between the preexposed and nonpreexposed animals (i.e., LI) in the 0.03 and 0.2 mg/kg haloperidol conditions $t(63) = 2.40$, $p < .01$, and $t(63) = 2.45$, $p < .01$, respectively, but not in the vehicle condition.

Experiment 3

2 × 3 ANOVAs with main factors of preexposure (0, 40) and drug in preexposure and conditioning (vehicle-vehicle, vehicle-haloperidol, haloperidol-haloperidol) performed on latencies to first lick and total number of licks on rebaseline day and on latencies to first lick, time to complete licks 1 to 50, and time to complete licks 51 to 75 on test day, yielded no significant outcomes. A 2 × 3

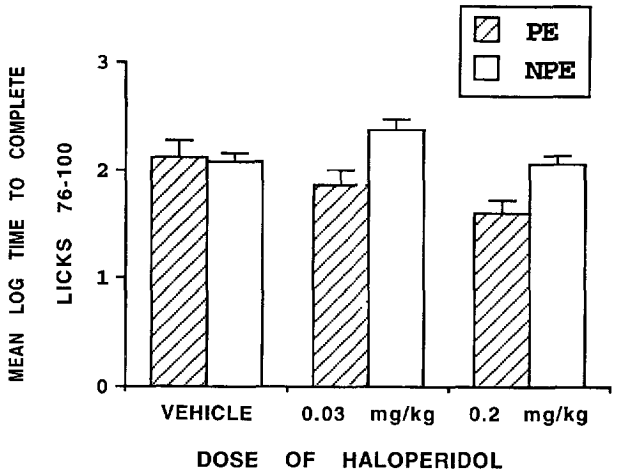

Figure 2. Mean log times and standard errors to complete licks 76 to 100 in the presence of the tone in the preexposed (PE) and the nonpreexposed (NPE) groups in three drug conditions: vehicle, 0.03 mg/kg haloperidol and 0.2 mg/kg haloperidol. Forty tone preexposures and five tone-shock pairings were used.

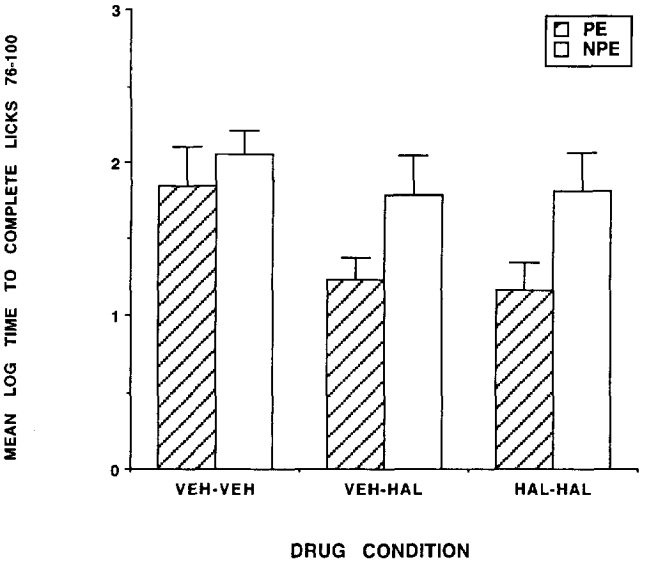

Figure 3. Mean log times and standard errors to complete licks 76 to 100 in the presence of the tone in the preexposed (PE) and the nonpreexposed (NPE) groups in three drug conditions: vehicle in preexposure and conditioning, vehicle in preexposure and 0.1 mg/kg haloperidol in conditioning, 0.1 mg/kg haloperidol in preexposure and conditioning. Forty tone preexposures and five tone-shock pairings were used.

ANOVA performed on the log times to complete licks 76 to 100 in the presence of the tone yielded significant main effects of preexposure $F(1,30) = 8.37$, $p < .01$ and drug $F(2,30) = 3.65$, $p < .04$. As can be seen in Figure 3, these outcomes reflect the fact that overall, preexposed animals exhibited shorter times to complete licks 76 to 100 than nonpreexposed animals, and haloperidol treated animals exhibited shorter times to complete licks 76 to 100 than vehicle controls. However, it can be seen in Figure 3 that the effect of preexposure is evident almost exclusively in the haloperidol-treated conditions, and that the decreased suppression after haloperidol administration is much more pronounced in the preexposed groups. Consequently, although the drug × preexposure interaction was not significant $F(2,30) < 1$, post hoc two-tailed t-tests based on the error term derived from the ANOVA were carried out to compare the times to complete licks 76 to 100 of the preexposed and the nonpreexposed groups within each drug condition. These tests revealed that as expected, there was a significant difference between the preexposed and nonpreexposed animals (i.e., LI) in the vehicle-haloperidol and haloperidol-haloperidol conditions $t(30) = 2.05$, $p < .05$ and $t(30) = 2.40$, $p < .05$, respectively, but not in the vehicle condition $t(30) = 0.70$, NS.

Experiment 4

Because none of the analyses yielded an effect of replication or interactions with this factor, the data of the two replications were combined. 2 × 2 × 2 ANOVAs with main factors of preexposure (0, 40), drug in preexposure (vehicle, clozapine), and drug in conditioning (vehicle, clozapine) performed on latencies to first lick and total number of licks on rebaseline day and on latencies to first lick, time to complete licks 1 to 50, and time to complete licks 51 to 75 on test day, yielded no significant outcomes.

Figure 4 presents the mean log times to complete licks 76 to 100 in the presence of the tone in the preexposed and nonpreexposed groups in the four drug conditions: vehicle-vehicle, vehicle-clozapine, clozapine-vehicle, and clozapine-clozapine. As can be seen, LI is absent in the vehicle-vehicle and clozapine-vehicle condition, but present in the vehicle-clozapine and clozapine-clozapine conditions. In addition, clozapine in conditioning produced a decrease in the overall suppression of licking. These outcomes were supported by a 2 × 2 × 2 ANOVA with main factors of preexposure (0, 40), drug in preexposure (vehicle, clozapine) and drug in conditioning (vehicle, clozapine), which yielded a significant main effect of drug in conditioning $F(1,84) = 21.72$, $p < .0001$, and a significant preexposure × drug in conditioning interaction $F(1,84) = 5.02$, $p < .05$. Figure 5 depicts this interaction. As can be seen, there is LI in animals treated with clozapine during conditioning and no LI in animals treated with vehicle during conditioning.

DISCUSSION

Neuroleptics have been shown to enhance LI in off-baseline CER procedures using parameters that do not

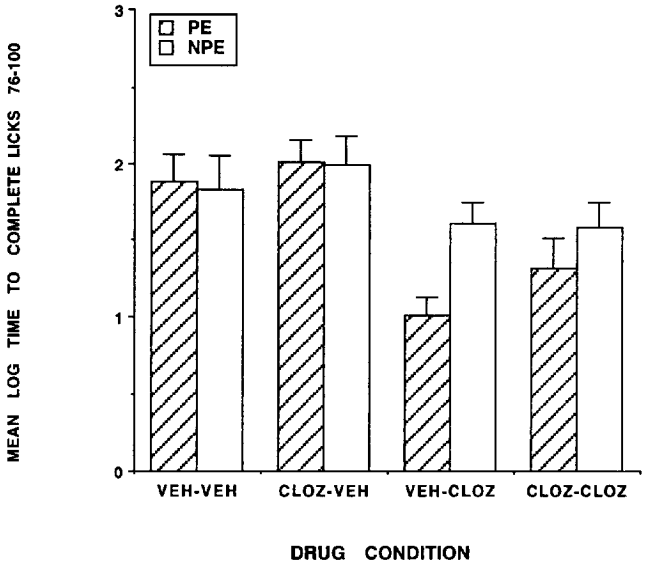

Figure 4. Mean log times and standard errors to complete licks 76 to 100 in the presence of the tone in the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions: vehicle in preexposure and conditioning, 5 mg/kg clozapine in preexposure and vehicle in conditioning, vehicle in preexposure and 5 mg/kg clozapine in conditioning, and 5 mg/kg clozapine in preexposure and conditioning. Forty tone preexposures and five tone-shock pairings were used.

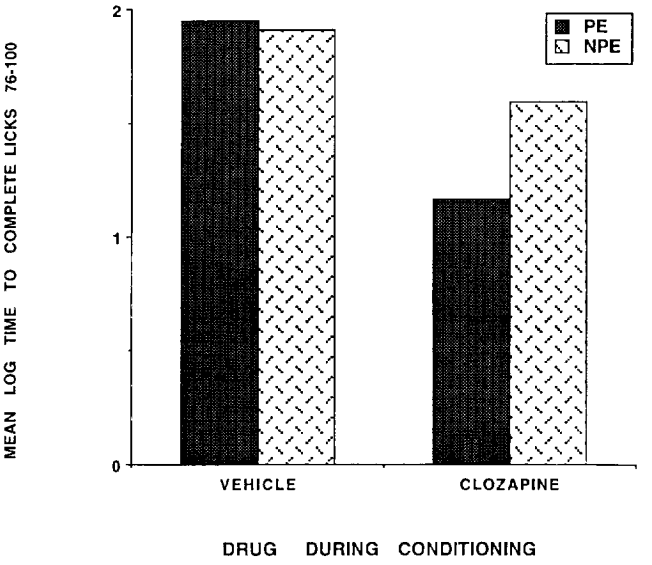

Figure 5. Mean log times and standard errors to complete licks 76 to 100 in the presence of the tone in the preexposed (PE) and the nonpreexposed (NPE) groups in two drug conditions in conditioning: vehicle or 5 mg/kg clozapine. Forty tone preexposures and five tone-shock pairings were used.

suffice to produce a robust LI effect in no-drug animals, namely, a low number of stimulus preexposures (10 or 20) and two conditioning trials (Christison et al. 1988; Dunn et al. 1993; Feldon and Weiner 1988, 1991; Peters and Joseph 1993; Weiner and Feldon 1987; Weiner et al. 1987, in press). The present experiments define an additional set of parameters under which neuroleptic-treated animals show LI whereas no-drug animals do not show the effect—namely, conventional number of preexposures (40) followed by an extensive conditioning session involving a relatively large number of conditioning trials. Furthermore, they show that also under these conditions, neuroleptics exert their effect on LI in the conditioning stage, as is the case when a low number of preexposures is used (Peters and Joseph 1993). These results have several implications.

First, they provide an additional LI procedure that can be used for tapping the facilitatory effects of neuroleptics on LI.

Second, they demonstrate again the ubiquity of the LI-enhancing effect of neuroleptics and thus provide further support for the predictive validity of the LI model of antipsychotic drug action.

Third, they provide additional evidence that the "atypical" neuroleptic clozapine acts in the LI model like typical neuroleptics. We have recently shown that two other characteristic effects of neuroleptics on LI—facilitation of LI after a relatively low number of preexposures and attenuation of amphetamine-induced disruption of LI—are produced also by clozapine (Weiner et al. in press). These findings are of importance in view of the ongoing debate regarding the "atypicality" of clozapine and its mode of action (Brier et al. 1994; Carpenter et al. 1985, 1988; Gerlach and Casey 1994; Kane and Freeman 1994; Kane and Marder 1993; Meltzer 1989, 1991; Meltzer et al. 1989a,b; Mortimer 1994; Nutt 1990; Tandon et al. 1993; Tandon and Kane 1993).

Fourth, they shed light on the mechanism underlying the LI-enhancing action of neuroleptics. Thus, when the parameters of the LI procedure are manipulated so as to increase the impact of the CS-US contingency on behavior, normal animals switch to respond according to the changed contingency of reinforcement in the conditioning stage. In contrast, neuroleptic-treated animals continue to respond to the stimulus according to the information acquired in preexposure. Neuroleptics, as well as other means of DA blockade, are known to reduce animals' capacity to switch ongoing behavior in response to changed environmental contingencies (Cools et al. 1984; Gelissen and Cools 1988; Oades 1985; Van den Bos and Cools 1989). The present results support the notion that such reduced switching capacity underlies also the LI-potentiating effect of these drugs (Weiner 1990).

Contrary to the present results, Killcross et al. (1994b) have recently reported that the neuroleptic alpha-flupenthixol loses its capacity to enhance LI when the impact of conditioning is increased by increasing the intensity of reinforcement (footshock). Using 12 or

36 preexposures, these authors showed that no-drug animals developed LI after 36 but not 12 preexposures, and that alpha-flupenthixol enhanced LI in the latter but not in the former condition, consistent with previous demonstrations that neuroleptics produce LI after fewer preexposures than are required in nontreated animals. The major message of this study was, however, that the enhancing effect of the drug seen after 12 preexposures disappeared when shock intensity was increased. Although this outcome appears inconsistent with the present results, it should be realized that the parameters used by Killcross et al. (1994b) not only increased the impact of conditioning but also decreased the impact of preexposure (low number of preexposures that by themselves sufficed not to yield LI in normal animals). We would predict that the enhancing effect of alpha-flupenthixol would be evident with increased shock level if animals were given 36 nonreinforced preexposures. Under these conditions (conventional number of preexposures and increased shock level), no LI would be evident in control animals but would be seen under the neuroleptic, much like the result obtained here with increased number of conditioning trials. Thus, although Killcross et al. (1994b) stated that their result is not explicable in terms of the switching model, it is entirely consistent with this model both in emphasizing the role of DA manipulations in the conditioning stage and in showing that the effects of these manipulations are modifiable by altering the parameters of conditioning.

Fifth, the present results are consistent with the proposal (Weiner 1990) that dopaminergic mechanisms are not involved in the acquisition of stimulus irrelevance (learning to ignore the nonreinforced stimulus in the preexposure stage), but rather determine the subsequent expression of this learning in conditioning (continuing to ignore the preexposed stimulus when it is followed by reinforcement). This in turn implies that the effects of dopaminergic agents on LI should be in general highly sensitive to alterations in the parameters of preexposure and conditioning that determine the relative impact of preexposure versus conditioning on behavior, as shown here and by Killcross et al. (1994a,b) with increasing the relative impact of conditioning, and by De la Casa et al. (1993) with increasing the relative impact of preexposure.

Finally, the present results may have implications for the therapeutic action of neuroleptics. It has been suggested that many schizophrenic symptoms can be roughly subsumed under the categories of increased and decreased switching capacity (see Lyon 1991; Frith 1992). Thus, on the one hand, the schizophrenic deficit has been described as an inability to maintain a major response set or a dominant interpretation of a given situation, excessive yielding to the immediate situational content to another (Anscombe 1987; Bleuler 1911; Broen 1968; Frith 1979; Magaro 1980; Payne 1966; Shakow 1962). On the other hand, schizophrenics are known to exhibit behavioral inflexibility and to show impairments on frontal lobe tests that consist of perseveration (Karnath and Wallesch 1992; Mortimer et al. 1989; Robbins 1991; Spitzer et al. 1993; Wolkin et al. 1992). Thus, it is possible that neuroleptics alleviate some of the schizophrenic symptoms by modulating switching capacity.

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