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The Latent Inhibition Model Dissociates between Clozapine, Haloperidol, and Ritanserin

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Latent inhibition (LI), i.e., retarded conditioning to a stimulus following its nonreinforced preexposure, is impaired in some subsets of schizophrenia patients and in amphetamine-treated rats. Typical and atypical antipsychotic drugs (APD's) potentiate LI, but to date the model has not dissociated between them. This study demonstrates such a dissociation using haloperidol (0.1 mg/kg), clozapine (5 mg/kg), and ritanserin (0.6 mg/kg) administered in preexposure and/or conditioning. Under conditions which did not yield LI in vehicle controls (40 preexposures and five conditioning trials), both haloperidol and clozapine, but not ritanserin, led to LI when administered in conditioning. Under conditions which led to LI in vehicle controls (40 preexposures and two conditioning trials), clozapine and ritanserin, but not haloperidol, abolished LI when administered in preexposure. It is suggested that LI potentiation via conditioning detects the "typical" action of APD's whereas LI disruption via preexposure detects the "atypical" action of APD's.
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KEY WORDS: *Latent inhibition; Clozapine; Haloperidol; Ritanserin; Rat*

Antipsychotic drugs (APD's) are currently divided into two groups, typical and atypical. There are several criteria for this distinction, extensively reviewed elsewhere (Arnt 1995; Arnt and Skarsfeldt 1998; Brunello et al. 1995; Kinon and Lieberman 1996). The most accepted criteria of atypicality are reduced capacity to cause extrapyramidal side effects, superior therapeutic efficacy for negative symptoms/ treatment-resistant schizophrenia, and reduced capacity to induce catalepsy in rodents.

Animal models are widely used for screening and development of APD's, as well as for elucidating their mechanism of action. In addition to classical models, e.g., inhibition of amphetamine/apomorphine induced hyperactivity and stereotypy and conditioned avoidance, newer models have been developed which are claimed to model processes impaired in schizophrenic patients (for review, see Arnt and Skarsfeldt 1998). One such model that has face, construct, and predictive validity is that of latent inhibition (LI). LI refers to retarded conditioning to a stimulus that had been repeatedly presented without reinforcement, and is considered to index the capacity of organisms to ignore stimuli that predict no significant consequences.

Consistent with the widely documented difficulty to ignore irrelevant stimuli in schizophrenia, LI is disrupted in some subsets of schizophrenic patients (Baruch et al. 1988; Dunn and Scibilia 1996; Gray et al. 1992a, 1995; Vaitl and Lipp 1997; but see Swerdlow et al. 1996b; Williams et al. 1998), and this disruption is modeled by loss of LI in amphetamine-treated rats (Killcross et al. 1994a; Solomon et al. 1981; Weiner et al. 1981, 1984, 1988) and in normal humans (Gray et al.

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1992b; Thornton et al. 1996). The validity of the model is further strengthened by findings that the neural substrates of LI in the rat include the hippocampal formation and the nucleus accumbens, consistent with the temporal lobe and mesolimbic pathology implicated in the pathophysiology of schizophrenia (for review, see Weiner 1990; Weiner and Feldon 1997). These findings have indicated that LI may provide an animal model of a cognitive process which is impaired in schizophrenia and which may be suited for detecting antipsychotic drug action.

Both typical and atypical APD's were shown to produce two effects in the LI model: to block amphetamine-induced disruption of LI, and to potentiate LI under conditions that are insufficient to produce robust LI in control animals, namely, low number of preexposures or high number of conditioning trials (Christison et al. 1988; Dunn et al. 1993; Feldon and Weiner 1991; Gosselin et al. 1996; Killcross et al. 1994b; Moran et al. 1996; Peters and Joseph 1993; Solomon et al. 1981; Trimble et al. 1997, 1998; Warburton et al. 1994; Weiner et al. 1996, 1997). The site at which APD's act to potentiate LI is the conditioning stage, and it has been attributed to DA blockade (Peters and Joseph 1993; Shadach et al. 1999; Weiner 1990; Weiner and Feldon 1997; Weiner et al. 1997).

APD's-induced potentiation of LI is notable in several respects: 1) it predicts antipsychotic activity for both typical and atypical APD's; 2) it is specific and selective for APD's (Dunn et al. 1993); 3) it is obtained also in normal humans (Williams et al. 1996, 1997); and 4) most importantly, it does not require previous administration of DA agonists or other drugs so that the model does not rely on pharmacological means to elicit the behavioral index of antipsychotic activity. While these features lend the LI model important advantages as a tool for screening both typical and atypical APD's, to date the model has not been able to dissociate between these two classes of drugs. The present experiments were designed to demonstrate such a dissociation.

While atypical APDs are characterized by a broad receptor profile, their mixed DA2-5HT2 receptor antagonism has been the feature most often suggested to account for their greater antipsychotic efficacy in general, and their efficacy in improving negative symptoms in particular (Arnt and Skarsfeldt 1998; Blin et al. 1996; Fiorella et al. 1995; Leysen et al. 1993; Meltzer 1989; Meltzer and Nash 1991; Nordstrom et al. 1993; Schotte et al. 1996; Seeger et al. 1995). The serotonergic component of atypicality is particularly relevant to LI, because LI is disrupted by brain serotonin depletion (Asin et al. 1980; Cassaday et al. 1993b; Lorden et al. 1983; Solomon et al. 1978, 1980), as well as by systemic administration of the 5-HT2 antagonist ritanserin (Cassaday et al. 1993a). In spite of this, there is no evidence that atypical APD's disrupt LI, although it has been suggested that a competition between a 5HT2-mediated disruptive effect and a DA2-mediated potentiating effect may explain why clozapine fails to potentiate LI or does so within a certain dose range only (Dunn et al. 1993; Moran et al. 1996; Trimble et al. 1998).

Since serotonergic antagonists disrupt LI when given in both the preexposure and conditioning stages (Cassaday et al. 1993a), and atypical APD's potentiate LI when given in conditioning but not when given in preexposure (Weiner et al. 1997; Shadach et al. 1999), it follows that if atypical APD's disrupt LI via serotonergic antagonism, the site of such an effect must be the preexposure stage. The reason that such an effect has gone undetected may stem from the fact that most experiments testing the effects of atypical APD's on LI used parameters of preexposure and conditioning which did not yield LI in controls, thus not allowing the demonstration of LI disruption. Clearly, the latter requires conditions which yield LI in controls; however, experiments which tested clozapine under conditions which led to LI in controls (Dunn et al. 1993; Trimble et al. 1998; Weiner et al. 1996), found neither potentiation nor disruption of LI. Since in these experiments clozapine was administered in both the preexposure and conditioning stages, it is possible that its administration in conditioning masked the expression of its LI disruptive effect in preexposure.

The present study tested the effects of the prototype typical and atypical APD's, haloperidol (0.1 mg/kg) and clozapine (5 mg/kg), as well as of the selective 5HT2 antagonist ritanserin (0.6 mg/kg) on LI, using two sets of conditions. Experiments 1–3 used 40 preexposures and five conditioning trials, which do not lead to LI in control rats (e.g., Weiner et al. 1997), and Experiments 4–6 used 40 preexposures and two conditioning trials, which produce LI in normal rats (e.g., Weiner et al. 1996). The doses of haloperidol and clozapine were chosen because they had previously been shown by us to potentiate LI when administered in conditioning or in both preexposure and conditioning (Feldon and Weiner 1991; Shadach et al. 1999; Weiner and Feldon 1987; Weiner et al. 1996, 1997); the 50:1 ratio between these two drugs was based on data from ex vivo and in vivo studies of D2 receptor occupancy in the rat brain (Baldessarini and Frankenburg 1991; Schotte et al. 1996). The dose of ritanserin was shown by Cassaday et al. (1993a) to disrupt LI when given in both stages. In all of the present experiments, the drugs were administered in either the preexposure stage, the conditioning stage, or in both.

We expected that: 1) with parameters which do not lead to LI in controls, both haloperidol and clozapine will be without an effect when administered in preexposure and will potentiate LI when administered in conditioning and in both stages, whereas ritanserin will be without an effect in all three administration condi-

tions; and 2) with parameters which lead to LI in controls, haloperidol will be without an effect in all three administration conditions; clozapine will have no effect when administered in conditioning and in both stages but will disrupt LI when administered in preexposure; ritanserin will have no effect when administered in conditioning but will disrupt LI when administered in preexposure and in both stages.

MATERIALS AND METHODS

Subjects

Male Wistar rats (Harlan Laboratories, Jerusalem) approximately 4 months old and weighing 250–580 g, were housed four to a cage under reversed cycle lighting (lights on: 19:00–07:00) with ad lib food and water except for the duration of the LI experiment (see below).

Apparatus and Procedure

LI was tested in Campden Instruments rodent test chambers (Model 410) with a retractable bottle. 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 10 sec, 80 dB, 2.8 kHz tone produced by a Sonalert module (Model SC 628). Shock was supplied through the floor by a Campden Instruments shock generator (Model 521/C) and shock scrambler (Model 521/S) set at 0.4 mA and 1 sec duration. Equipment programming and data recording were computer controlled.

Prior to the beginning of each LI experiment, rats were handled for about 2 min daily for five days. A 23 h water restriction schedule was initiated simultaneously with handling and continued throughout the experiment. On the next five days, rats were trained to drink in the experimental chamber for 20 min/day. Water in the test apparatus was given in addition to the daily ration of 1h given in the home cages. The LI procedure was conducted on days 11-14 and consisted of the following stages. *Preexposure:* with the bottle removed, the preexposed (PE) rats received 40 tone presentations with an inter-stimulus interval of 50 sec. The nonpreexposed (NPE) rats were confined to the chamber for an identical period of time without receiving the tone. *Conditioning:* with the bottle removed, each rat received five (Experiments 1–3) or two (Experiments 4–6) tone-shock pairings given 5 min apart. Shock immediately followed tone termination. The first tone-shock pairing was given 5 min after the start of the session. After the last pairing, rats were left in the experimental chamber for an additional 5 min. *Retraining:* rats were given a 15-min drinking session as in initial training. Data of rats that failed to complete 600 licks were dropped from the analysis. *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 min. The following times were recorded: time to first lick, time to complete licks 1–50, time to complete licks 51–75 (before tone onset), and time to complete licks 76–100 (after tone onset). Times to complete licks 76–100 were logarithmically transformed to allow parametric analysis of variance. Longer log times indicate stronger suppression of drinking. LI is defined as significantly shorter log times to complete licks 76–100 of the preexposed as compared to nonpreexposed rats.

Drugs

All drugs were administered IP in a volume of 1 ml/kg prior to the preexposure and/or conditioning stages. Haloperidol, prepared from an ampoule containing 5 mg haloperidol in 1 ml solvent containing 6 mg lactic acid (Abic Ltd, Israel) and diluted with saline, was administered 60 min prior to the behavioral sessions at a dose of 0.1 mg/kg. Clozapine (Novartis, Switzerland), dissolved in 1N acetic acid (1.5ml/10mg) and diluted with saline, was administered 30 min prior to the behavioral sessions at a dose of 5 mg/kg. Ritanserin (Janssen, Belgium), sonicated in 2% Tween 80 and diluted with saline, was administered 30 min prior to the behavioral sessions at a dose of 0.6 mg/kg. No-drug controls received an equivalent volume of the corresponding vehicle.

Experimental Design

All the experiments included eight experimental groups in a 2 x 2 x 2 design with main factors of preexposure (NPE, PE), drug in preexposure (vehicle, drug [haloperidol, clozapine, or ritanserin]), and drug in conditioning (vehicle, drug [haloperidol, clozapine, or ritanserin]). Experiments 2, 3, 4, and 5 tested 44–48 rats. Since some statistical results in Experiments 1 and 6 came close to the acceptable level of significance, an additional replication was conducted for each experiment.

Statistical Analysis

Times to complete licks 50–75 and mean log times to complete licks 76–100 were analyzed by 2 x 2 x 2 ANOVA with main factors of preexposure (0, 40), drug in preexposure (vehicle, drug), and drug in conditioning (vehicle, drug). In all cases of significant interactions, post-hoc two-tailed t-tests based on the error term derived from the ANOVA were used to assess the difference between the PE and NPE groups within the relevant drug conditions.

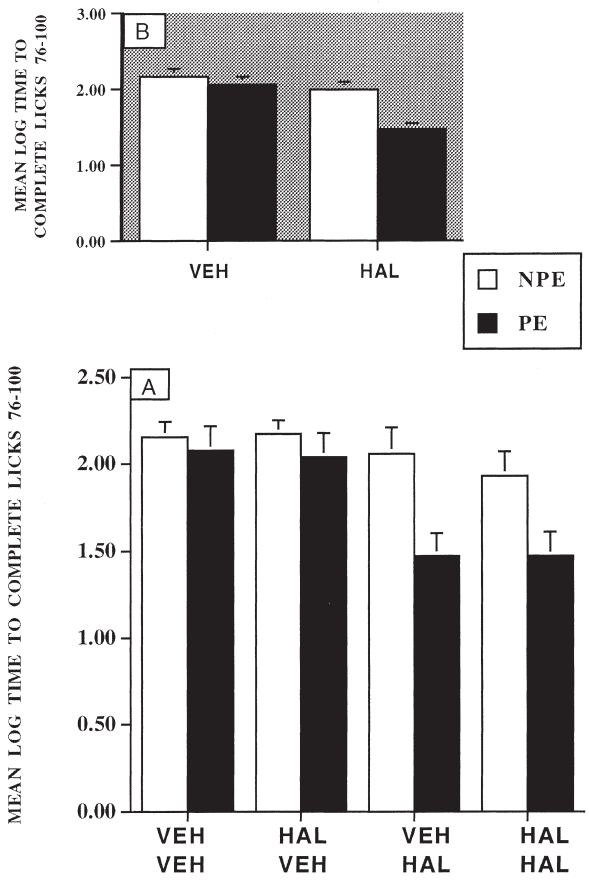

Figure 1. **A**. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions in preexposure and conditioning: vehicle-vehicle, haloperidol-vehicle, vehicle-haloperidol, and haloperidol-haloperidol. **B**. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (PE) and nonpreexposed (NPE) groups in two drug conditions in conditioning: vehicle or haloperidol. Forty tone preexposures and five tone-shock pairings were used.

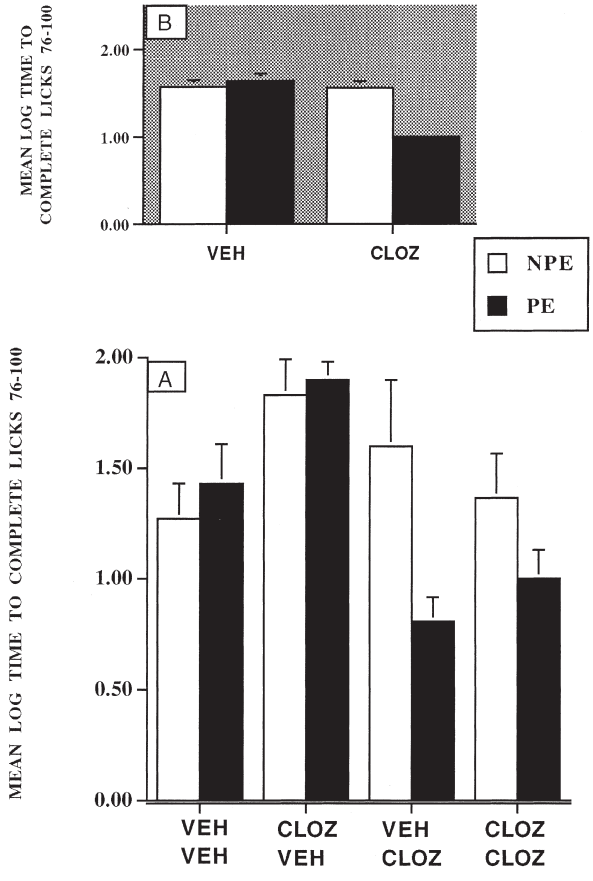

Figure 2. **A**. Means and standard errors of the log times to complete licks 76–100 (after tone onset) in the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions in preexposure and conditioning: vehicle-vehicle, clozapine-vehicle, vehicle-clozapine, clozapine-clozapine. **B**. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (PE) and nonpreexposed (NPE) groups in two drug conditions in conditioning: vehicle or clozapine. Forty tone preexposures and five tone-shock pairings were used.

RESULTS

Experiment 1: The Effects of 0.1 mg/kg Haloperidol on LI with 40 Preexposures and 5 Conditioning Trials

The experiment included 88 rats, run in two replications. The eight experimental groups did not differ in their times to complete licks 51–75 before tone onset (all p's $> .5$; overall mean A period = 5.28 sec). Figure 1A presents the mean log times to complete licks 76–100 (after tone onset) of the preexposed and nonpreexposed groups in the four drug conditions in preexposure and conditioning: vehicle-vehicle, haloperidol-vehicle, vehicle-haloperidol, and haloperidol-haloperidol. ANOVA yielded significant main effects of preexposure [$F(1,80) = 9.35$, $p < .005$], and drug in conditioning [$F(1,80) = 13.43$, $p < .001$], as well as a significant preexposure $\times$ drug in conditioning interaction [$F(1,80) = 4.14$, $p < .05$].

The mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the two drug conditions constituting the preexposure $\times$ drug in conditioning interaction, i.e., vehicle in conditioning or haloperidol in conditioning, are depicted in Figure 1B. As can be seen, there was no difference in suppression between the preexposed and nonpreexposed groups, i.e., no LI, in rats which received vehicle in conditioning. In contrast, rats which received haloperidol in conditioning exhibited LI, i.e., lower suppression of the preexposed as compared to the nonpreexposed group. Post-hoc t-tests confirmed the existence of LI in the haloperidol condition [$t(44) = 3.72$, $p < .01$] but not in the vehicle condition [$t(40) = 0.68$, NS].

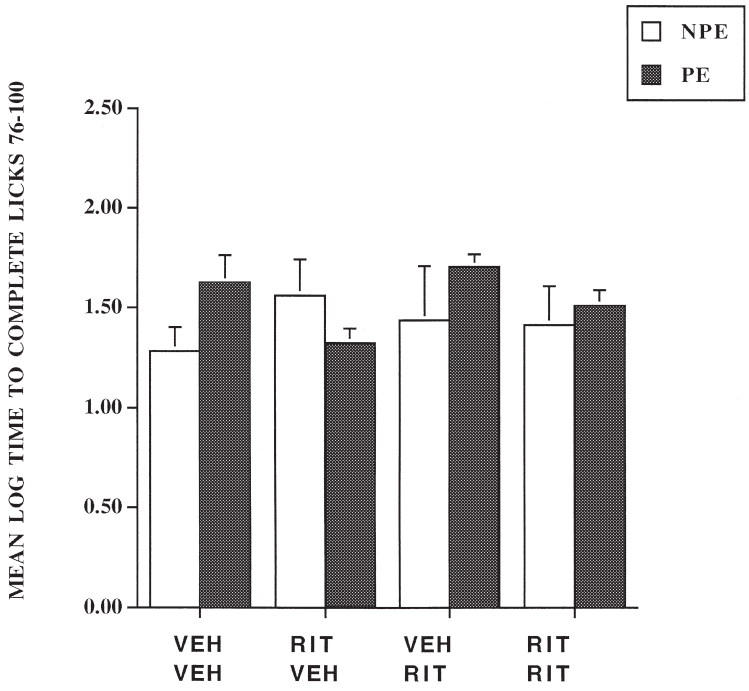

Figure 3. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions in preexposure and conditioning: vehicle-vehicle, ritanserin-vehicle, vehicle-ritanserin, and ritanserin-ritanserin. Forty tone preexposures and five tone-shock pairings were used.

Experiment 2: The Effects of 5 mg/kg Clozapine on LI with 40 Preexposures and 5 Conditioning Trials

The experiment included 48 rats; the data of three rats were dropped from the analysis. The eight experimental groups did not differ in their times to complete licks 51–75 (all p's $> .5$; overall mean A period = 4.98 sec). Figure 2A presents the mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the four drug conditions in preexposure and conditioning: vehicle-vehicle, clozapine-vehicle, vehicle-clozapine, and clozapine-clozapine.

ANOVA yielded significant main effects of drug in preexposure [$F(1,37) = 4.27$, $p < .05$], drug in conditioning [$F(1,37) = 6.36$, $p < .05$], and a significant preexposure × drug in conditioning interaction [$F(1,37) = 4.22$, $p < .05$]. Figure 2B depicts this interaction. As can be seen, there was no LI in rats which received vehicle in conditioning, whereas rats which received clozapine in conditioning exhibited LI. Post-hoc t-tests confirmed the existence of LI in the clozapine condition [$t(21) = 2.29$, $p < .05$] but not in the vehicle condition [$t(20) = 0.33$, NS].

Experiment 3: The Effects of 0.6 mg/kg Ritanserin on LI with 40 Preexposures and 5 Conditioning Trials

The experiment included 48 rats. The eight experimental groups did not differ in their time to complete licks 51–75 (all p's $> .05$; overall mean A period = 9.61 sec). Figure 3 presents the mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the four drug conditions in preexposure and conditioning: vehicle-vehicle, ritanserin-vehicle, vehicle-ritanserin, and ritanserin-ritanserin. As can be seen, there was no LI in any of the conditions.

ANOVA yielded no significant outcomes: preexposure [$F(1,40) = 1.13$, $p = .29$], drug in preexposure [$F(1,40) = 0.31$, $p = .58$], drug in conditioning [$F(1,40) = 0.38$, $p = .54$], preexposure × drug in conditioning interaction [$F(1,40) = 0.34$, $p = .56$], preexposure × drug in preexposure interaction [$F(1,40) = 2.92$, $p = .09$], drug in preexposure × drug in conditioning interaction [$F(1,40) = 0.19$, $p = .66$], and preexposure × drug in preexposure × drug in conditioning interaction [$F(1,40) = 0.87$, $p = .36$].

Experiment 4: The Effects of 0.1 mg/kg Haloperidol on LI with 40 Preexposures and 2 Conditioning Trials

The experiment included 48 rats; the data of four rats were dropped from the analysis. The eight experimental groups did not differ in their times to complete licks 51–75 (all p's $> .05$; overall mean A period = 7.98 sec).

Figure 4 presents the mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the four drug conditions in preexposure and conditioning: vehicle-vehicle, haloperidol-vehicle, vehicle-haloperidol, and haloperidol-haloperidol. As can be seen, LI was present in all four drug conditions. In addition, haloperidol in conditioning led to overall lower suppression. These outcomes were supported by signif-

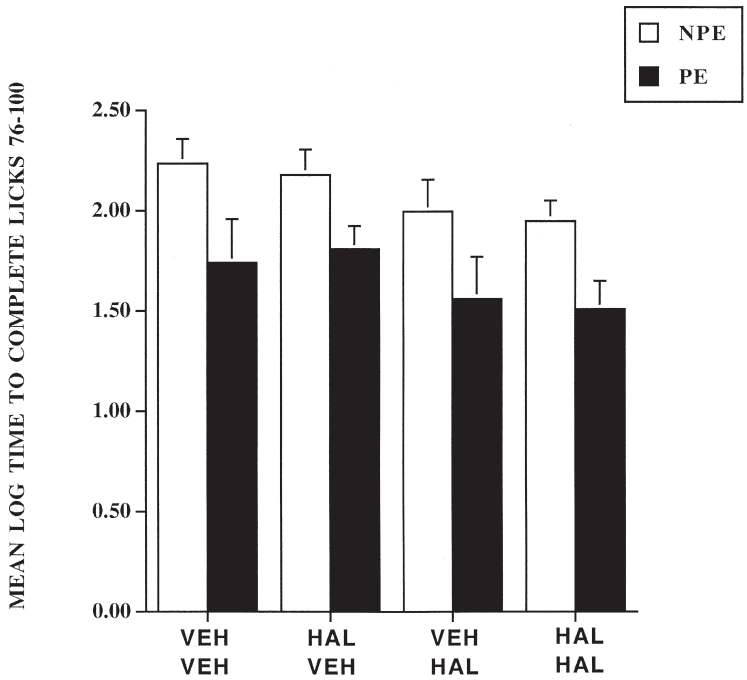

Figure 4. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions in preexposure and conditioning: vehicle-vehicle, haloperidol-vehicle, vehicle-haloperidol, and haloperidol-haloperidol. Forty tone preexposures and two tone-shock pairings were used.

icant main effects of preexposure [$F(1,36) = 16.90$, $p < .001$], and drug in conditioning [$F(1,36) = 5.05$, $p < .05$].

Experiment 5: The Effects of 5 mg/kg Clozapine on LI with 40 Preexposures and 2 Conditioning Trials

The experiment included 44 rats; the data of three rats were dropped from the analysis. The eight experimental groups did not differ in their times to complete licks 51–75 (all p's $> .5$; overall mean A period = 8.85 sec). Figure 5 presents the mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the four drug conditions in preexposure and conditioning: vehicle-vehicle, clozapine-vehicle, vehicle-clozapine, and clozapine-clozapine. As can be seen, LI was present in rats which received vehicle in both the preexposure and the conditioning stages, as well as in rats

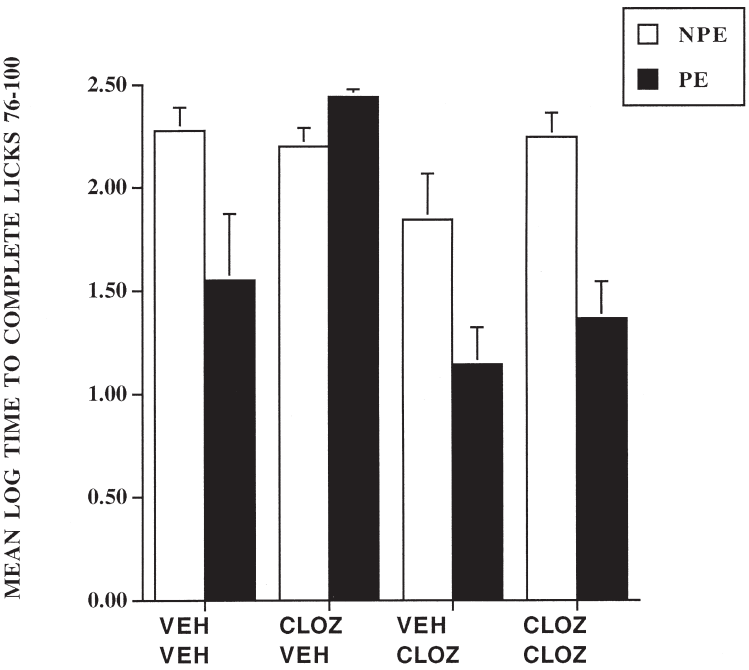

Figure 5. Means and standard errors of the log times to complete licks 76–100 (after tone onset) in the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions in preexposure and conditioning: vehicle-vehicle, clozapine-vehicle, vehicle-clozapine, and clozapine-clozapine. Forty tone preexposures and two tone-shock pairings were used.

which received clozapine in conditioning, irrespective of the drug received in preexposure (vehicle-clozapine and clozapine-clozapine conditions).

In contrast, there was no LI in rats which received clozapine in preexposure and vehicle in conditioning. These outcomes were supported by significant main effects of preexposure [$F(1,33) = 14.74$ $p < .001$], drug in conditioning [$F(1,33) = 12.08$, $p < .005$], and a significant preexposure × drug in preexposure × drug in conditioning interaction [$F(1,33) = 4.56$, $p < .05$]. Post-hoc t-tests revealed a significant LI effect in the vehicle-vehicle [$t(9) = 2.83$, $p < .025$], vehicle-clozapine [$t(8) = 2.60$, $p < .05$], and clozapine-clozapine [$t(7) = 3.10$, $p < .025$] conditions, but not in the clozapine-vehicle condition [$t(9) = 0.90$, NS].

Experiment 6: The Effects of 0.6 mg/kg Ritanserin on LI with 40 Preexposures and 2 Conditioning Trials

The experiment included 88 rats, run in two replications; the data of four rats were dropped from the analysis. The eight experimental groups did not differ in their times to complete licks 51–75 (all p's $> .05$; overall mean A period = 9.17 sec). Figure 6A presents the mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the four drug conditions in preexposure and conditioning: vehicle-vehicle, ritanserin-vehicle, vehicle-ritanserin, and ritanserin-ritanserin. As can be seen, LI was present in rats which received vehicle in both the preexposure and conditioning stages as well as in rats which received vehicle in preexposure and ritanserin in conditioning.

No LI was found in rats which received ritanserin in preexposure, irrespective of drug received in conditioning. ANOVA yielded a significant main effect of preexposure [$F(1,76) = 4.40$, $p < .05$] and a significant preexposure × drug in preexposure interaction [$F(1,76) = 4.39$, $p < .05$]. The mean log times to complete licks 76–100 of the preexposed and nonpreexposed groups in the two drug conditions constituting the preexposure × drug in preexposure interaction, i.e., vehicle in preexposure or ritanserin in preexposure, are depicted in Figure 6B. As can be seen, there was LI in rats which received vehicle in preexposure. In contrast, rats which received ritanserin in preexposure did not exhibit LI. Post-hoc t-tests confirmed the existence of LI in the vehicle condition [$t(38) = 2.91$, $p < .01$], but not in the ritanserin condition [$t(42) = 0.01$, NS].

DISCUSSION

Experiments 1–3 employed parameters of preexposure and conditioning (40 preexposures and five conditioning trials) which did not produce LI in the vehicle condition: preexposed and nonpreexposed vehicle-treated animals did not differ in their suppression of drinking during tone presentation. Likewise, no LI was evident in rats which received haloperidol or clozapine only in the preexposure stage. In contrast, haloperidol or clozapine administered in the conditioning stage, irrespective of drug condition in preexposure, led to the emergence of LI, i.e., lower suppression in the preexposed as compared to the nonpreexposed group. Ritanserin administration was without an effect. These results show within one experimental design that APD-induced potentiation of LI is due exclusively to the action of these drugs in the conditioning stage, supporting previous findings obtained in separate experiments (Peters and Joseph 1993; Weiner et al. 1987, 1997).

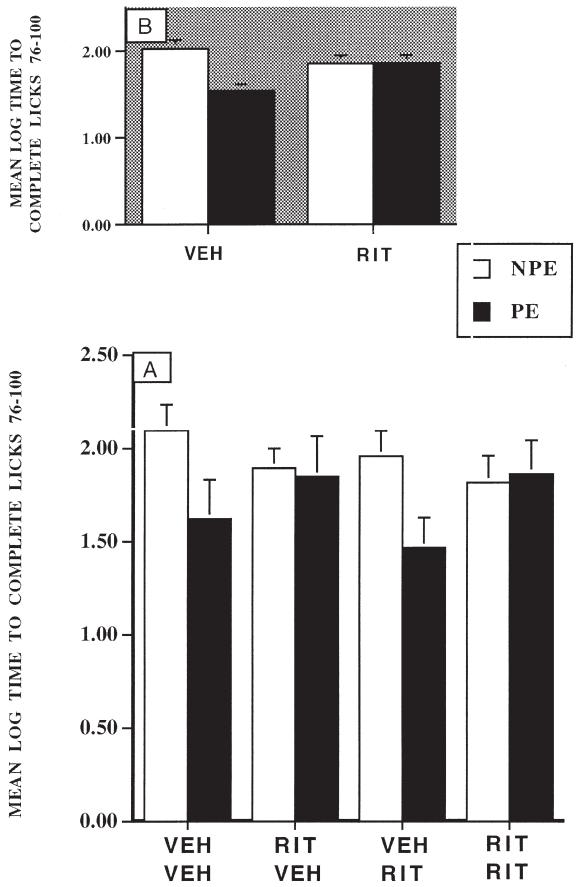

Figure 6. **A**. Means and standard errors of the log times to complete licks 76–100 (after tone onset) in the preexposed (PE) and the nonpreexposed (NPE) groups in four drug conditions in preexposure and conditioning: vehicle-vehicle, ritanserin-vehicle, vehicle-ritanserin, and ritanserin-ritanserin. **B**. Means and standard errors of the log times to complete licks 76–100 (after tone onset) of the preexposed (PE) and nonpreexposed (NPE) groups in two drug conditions in preexposure: vehicle or ritanserin. Forty tone preexposures and two tone-shock pairings were used.

Furthermore, since the potentiating effect was obtained with haloperidol, which is a DA2 blocker and not with the 5HT2 antagonist ritanserin, these results indicate that the potentiating effect is DA-mediated and that 5HT antagonism plays no role in such potentiation. By extension, it suggests that the 5 HT2 component of clozapine is not involved in LI potentiation.

Experiments 4–6 employed parameters of preexposure and conditioning (40 preexposures and two conditioning trials) that produced LI in the vehicle condition: preexposed vehicle-treated animals had lower suppression of drinking during tone presentation than nonpreexposed. Under these conditions, the three drugs produced three different patterns of results. Haloperidol left LI intact in all administration conditions, clozapine disrupted LI when administered in preexposure, and ritanserin disrupted LI when administered in preexposure and in both stages. The latter result replicates that of Cassaday et al. (1993a) but we now show that ritanserin-induced LI disruption at this dose is due to its action in the preexposure stage.

Lack of LI potentiation with clozapine and haloperidol administered in both stages is consistent with previous results showing that APD's do not facilitate LI under conditions which lead to LI in control rats (Dunn et al. 1993; Killcross et al. 1994b; Ruob et al. 1998; Weiner et al. 1996). The results with clozapine provide a first demonstration that under such conditions, this drug can disrupt LI when given in preexposure, although clearly, this is limited to the dose tested here. As for the mechanism of this disruptive action, it is unlikely to stem from DA blockade, since DA mechanisms are not involved in preexposure: both amphetamine (Weiner et al. 1984, 1988) and APD's (haloperidol and clozapine) (Shadach et al. 1999; Weiner et al. 1987, 1997; in this report) do not affect LI when administered in preexposure only. Since the preexposure-based disruptive effect was also exerted by the selective 5HT2 antagonist ritanserin, it is likely that clozapine-induced disruption was 5HT2-mediated.

Two points should be noted with regard to LI disruption obtained here. First, Hitchcock et al. (1997) reported that LI was disrupted by the 5HT2 agonist DOI confined to the preexposure stage. We have no ready explanation for this inconsistency but we believe that the bulk of extant data on the effects of serotonergic manipulations on LI indicates that LI is disrupted by reductions in serotonin (Asin et al. 1980; Cassaday et al. 1993a,b; Lorden et al. 1983; Solomon et al. 1978, 1980). Second, the fact that clozapine disrupted LI via preexposure but spared LI when administered in both stages indicates that clozapine's action in conditioning overrode its disruptive effect in preexposure. Assuming that the effects of clozapine in preexposure are 5HT-mediated, this implies that 5HT2 and DA2 antagonistic actions of clozapine compete in LI. As noted in the Introduction, the possibility of such a competition has been raised previously by Dunn et al. (1993) and Trimble et al. (1998).

Our results support this suggestion, and further indicate that: 1) the competing actions of clozapine are exerted at different stages of the LI procedure and can therefore take place only if the drug is administered in both stages; and 2) the manifestation of such a competition will be dependent on the parameters of the LI procedure. In addition, since the relative potency of the two actions are dose-dependent, with 5HT2 receptor occupancy predominating at lower doses and DA2 receptor occupancy occurring at higher doses (Schotte et al. 1996), the effects of clozapine on LI should be dose-dependent (Trimble et al. 1998). Given the above, depending on the parametric conditions and doses of clozapine, the serotonergic component should be able to override the dopaminergic component, or vice versa, leading to either potentiated LI, intact LI, or disrupted LI. This may explain why clozapine-induced potentiation of LI is obtained within a relatively narrow dose range (Moran et al. 1996; Trimble et al. 1998).

Taken together, the present results show that the LI model can dissociate between haloperidol and clozapine, so that: 1) both drugs potentiate LI via their action at the conditioning stage under conditions which do not lead to LI in controls; and 2) clozapine but not haloperidol disrupts LI via action at the preexposure stage under conditions which lead to LI in controls. In addition, the results suggest that the LI potentiating and disrupting effect of clozapine may be due to its DA2 and 5HT2 antagonism, respectively.

Clearly, these conclusions are restricted to the specific doses used here. Thorough dose-response studies are needed in order to establish whether such a dissociation is reliable, and to ascertain that the disruptive effect is 5HT mediated. Likewise, further studies are needed to test additional atypical compounds in the LI model in order to validate its capacity to differentiate between typical and atypical APD's, and to determine how the effects of different atypical APD's are influenced by the balance between their DA2 and 5HT2 antagonistic actions. However, the present results provide preliminary evidence that the LI model may have the capacity to dissociate between typical and atypical APD's.

Several behavioral models claimed to model processes impaired in schizophrenia have been shown to discriminate between typical and atypical APD's, e.g., PCP-induced disruption of prepulse inhibition (Bakshi and Geyer 1995; Swerdlow et al. 1996a), PCP-induced disruption of social interaction (Sams-Dodd 1996, 1997) and PCP-induced enhancement of immobility in the forced swim test (Noda et al. 1995). If shown effective in further studies, the LI model would differ from these models in two important respects. First, the dissociation between typical and atypical APD's in the above mod-

els consists of ineffectiveness of typical versus effectiveness of atypical APD's, whereas in the LI model, both classes of APD's should be effective but in a differential manner. Second, the LI model would not require previous drug administration for the manifestation of both actions of APD's, but would detect both of them with parametric manipulations of the LI procedure.

It is commonly asserted that both typical and atypical APD's are effective against positive symptoms whereas atypical APD's have higher efficacy for negative symptoms/ treatment-resistant schizophrenia, and that therefore, an animal model which is sensitive to both classes of APD's, may have predictive validity for the former condition whereas a model which is sensitive to atypical but not typical APD's may have predictive validity for the latter condition/s (Arnt and Skarsfeldt 1998; Brunello et al. 1995; Kinon and Lieberman 1996). Viewed in this light, LI potentiation may have predictive validity for the treatment of positive symptoms and LI disruption may have predictive validity for the treatment of negative symptoms/treatment resistant schizophrenia. The latter is also congruent with the claim that D2 antagonism is effective for treating positive symptoms and 5HT2 antagonism plays a role in the alleviation of negative symptoms (Leysen et al. 1993; Meltzer 1989; Meltzer and Nash 1991; Schotte et al. 1996).

In this context, our finding that ritanserin also disrupts LI via preexposure, is consistent with reported efficacy of this compound against negative symptoms (Weisel et al. 1994), although this drug is more effective when used in combination with typical APD's and may have limited antipsychotic efficacy when given alone (Awouters et al. 1988; Duinkerke et al. 1993; Gelders et al. 1986; Reyntjens et al. 1986). However, it should be noted that our results do not qualify ritanserin as an APD, because its effects on LI mimicked neither those of haloperidol nor those of clozapine; rather, it produced a third pattern of effects in the two LI procedures.

In sum, if confirmed in dose-response studies and tests with additional APD's, the present findings could provide a basis for an animal model that would differentiate between typical and atypical APD's without the use of pro-psychotic drugs, and thus provide a useful tool for screening novel agents with atypical antipsychotic profile with potential relevance to the treatment of negative symptoms/ treatment-resistant schizophrenia.

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