The Latent Inhibition Model of Schizophrenia: Further Validation Using the Atypical Neuroleptic, Clozapine

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Latent inhibition (LI) refers to retarded conditioning to a stimulus that has been repeatedly presented without reinforcement. LI is impaired in schizophrenic patients and in rats treated with amphetamine. Neuroleptic drugs produce two effects in this test paradigm: antagonism of amphetamine-induced disruption of LI, and enhancement of LI when administered on their own. The present experiments tested the effects of the atypical neuroleptic, clozapine, on LI. The experiments used a conditioned emotional response procedure in rats licking for water, consisting of three stages: preexposure, in which the to-be-conditioned stimulus (tone) was repeatedly presented without reinforcement; conditioning, in which the preexposed stimulus was paired with reinforcement (foot shock); and test, in which LI was indexed by animals' degree of suppression of licking during tone presentation. In experiments 1 and 2, the effects of 5.0 and 10.0 mg/kg clozapine on LI were assessed following 20 or 10 tone preexposures, respectively. Experiments 3 and 4 used 40 preexposures and investigated antagonism of amphetamine-induced disruption of LI by 5.0 and 10.0 mg/kg clozapine, respectively. The results demonstrated that clozapine possesses a neuroleptic profile in the LI model, namely, it facilitates the development of LI and antagonizes amphetamine-induced disruption of LI.

Key Words: Latent inhibition, clozapine, schizophrenia, rat

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Introduction

The atypical antipsychotic drug clozapine has been characterized by its low capacity to induce extrapyramidal symptoms in humans and catalepsy in laboratory rodents. In addition, clozapine has been reported to be effective in the treatment of negative symptoms and/or of "treatment-resistant" schizophrenic patients (Gerlach 1991; Jackson et al 1993; Jann 1991; Kane et al 1988; Kane and Marder 1993; Meltzer 1991; Meltzer et al 1989a).

In spite of extensive research, clozapine's neuropharmacologic action has remained an enigma. Suggested mechanisms have included noradrenergic blockade (Chiodo and Bunney 1985), serotonergic blockade (Chen et al 1992; Meltzer et al 1989a), preferential blockade of D1 versus D2 receptors (Coward et al 1989), combined blockade of D1 and D2 receptors (Farde et al 1989), interaction with a new subtype of dopamine receptor...
(Seeman 1992; van Tol et al 1991), and production of specific ratios of blockade between several neurotransmitter systems (Meltzer et al 1989b). Clozapine is also ineffective in traditional animal models of antipsychotic drug action, e.g., it is much weaker in antagonizing amphetamine-induced stereotypies and in blocking avoidance response (Bruhwyl et al 1990).

The present study investigated the behavioral profile of clozapine in the latent inhibition (LI) model. LI refers to retarded conditioning to a stimulus that has been repeatedly presented without reinforcement (Lubow 1973, 1989; Lubow and Gewirtz 1995; Lubow et al 1981; Mackintosh 1975, 1983; Moore and Stickney 1980; Schmajuk and Moore 1985; 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 analogous processes across species (Lubow and Gewirtz 1995). LI is disrupted in amphetamine-treated rats (Killcross and Robbins 1993; Solomon et al 1981; Warburton et al 1994; Weiner et al 1981, 1984, 1988), and this disruption has been proposed as an animal model of the widely described failure of schizophrenia to ignore irrelevant stimuli (Feldon and Weiner 1991; Gray et al 1991; Solomon et al 1981; Weiner 1990; Weiner et al 1981, 1984). The model possesses construct validity in that acute 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).

Typical neuroleptics have been characterized by two effects in the LI model: they restore LI in amphetamine-treated rats, and they enhance LI when administered on their own (Christison et al 1988; Dunn et al 1993; Feldon and Weiner 1988, 1991; Killcross et al 1994; Solomon et al 1981; Warburton et al 1994; Weiner and Feldon 1987; Weiner et al 1987). Dunn et al (1993) have recently shown that LI enhancement is specific and selective for drugs with known antipsychotic efficacy and is not produced by a wide range of nonantipsychotic drugs, and concluded that “there is no animal model that better fulfills the criteria for predictive validity for antipsychotic effects” (p 321).

The LI test yielded one false negative, however, namely clozapine. In contrast, we recently found that clozapine enhances LI (Weiner and Feldon 1994). Dunn et al pointed out that the failure of clozapine to enhance LI is surprising, and demands further study of this drug in the LI model. Indeed, the failure of clozapine to enhance LI has important empirical and theoretical implications. First, it limits considerably the utility of the LI model as a screening tool for detecting antipsychotic potential of drugs. Second, it questions the central postulate on which the LI model is based, namely, that enhancement of organisms’ capacity to ignore irrelevant stimuli is the bona fide antipsychotic action tapped by LI. Third, it raises a question regarding the nature of the antipsychotic action of clozapine. Dunn et al’s results raise the possibility that LI taps an antipsychotic effect that is specific to typical neuroleptics; however, clozapine has also a “typical” action in that it ameliorates positive symptoms; if neuroleptic-induced LI enhancement is a reflection of the latter, then why is it not produced by clozapine? Alternatively, if clozapine indeed fails to enhance LI, then it would suggest that also the “typical” antipsychotic effect of this drug is qualitatively different from that of the typical neuroleptics.

The present study, therefore, examined the ability of clozapine to enhance LI and to antagonize amphetamine-induced disruption of LI. LI was assessed using an off-baseline conditioned emotional response (CER) procedure in rats licking for water, consisting of three stages: pre-exposure, in which the to-be-conditioned stimulus (tone) was repeatedly presented without reinforcement; conditioning, in which the preexposed stimulus was paired with reinforcement (foot shock); and test, in which LI was indexed by animals’ degree of suppression of licking during tone presentation. Experiments 1 and 2 tested the effects of 5 and 10 mg/kg clozapine on LI. Experiments 3 and 4 tested the capacity of 5 and 10 mg/kg clozapine, respectively, to reverse the effects of amphetamine on LI. Experiments 1 and 2 used a low number of preexposures (20 and 10, respectively) that yields a small LI effect in no-drug controls, because this condition is more sensitive in detecting facilitatory drug effects (Dunn et al 1993; Feldon and Weiner 1991; Killcross et al 1994; Morán and Moser 1992; Weiner and Feldon 1987). In experiments 3 and 4, the number of preexposures was increased to 40, to be able to show LI abolition by amphetamine.

**Methods**

**Subjects**

Male Wistar rats (Tel-Aviv University Medical School), approximately 4 months old, were housed 1 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 min each day. During the days on which water was available in the experimental chambers, this was in addition to the daily ration of 1 hour given in the home cages.
Apparatus

The apparatus included 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 drinkometer circuit (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 at 0.75 mA. Equipment programming and data recording were computer controlled.

Procedure

The stages of the CER procedure were as follows.

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

PREEXPOSURE. With the bottle removed, each rat was placed in the experimental chamber. The preexposed (PE) animals received 20 (experiment 1), 10 (experiment 2), or 40 (experiments 3 and 4) 10-sec tones with a variable interstimulus interval (ISI) with a mean of 50 sec. 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 given 5 and 10 min after the start of the session. Tone parameters were identical to those used in preexposure. The 0.75-mA, 1-sec 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.

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, 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 (pretone), and time to complete licks 76–100 (tone-on). 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).

The four stages were given 24 hours apart. Each rat was run throughout the experiment in the same chamber.

Drugs

Clozapine was dissolved in 1 N acetic acid (1.5 mL/10 mg) and diluted with saline to reach the appropriate mg/mL concentration. The appropriate drug dose or an equivalent volume of vehicle was administered ip 30 min prior to the start of preexposure and prior to the start of conditioning. d-Amphetamine sulphate was dissolved in saline. The appropriate drug dose or 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 drugs.

Experiment 1

THE EFFECTS OF 5 AND 10 MG/KG CLOZAPINE ON LI FOLLOWING 20 PREEXPOSURES. One hundred and eight rats were randomly assigned to six experimental groups in a 2 X 3 factorial design with main factors of preexposure (0, 20) and drug (vehicle, 5.0 mg/kg and 10.0 mg/kg clozapine). The experiment was run in three replications. Data from 3 animals were lost due to apparatus failure (1 from the Vehicle-NPE, and 2 from 5.0 mg/kg-NPE group). Thus, the final analysis was performed on the data from 105 animals.

Experiment 2

THE EFFECTS OF 5 AND 10 MG/KG CLOZAPINE ON LI FOLLOWING 10 PREEXPOSURES. Ninety rats were randomly assigned to six experimental groups in a 2 X 3 factorial design with main factors of preexposure (0, 10) and drug (vehicle, 5.0 mg/kg and 10.0 mg/kg clozapine). The experiment was run in two replications. Data from 1 animal (Vehicle-NPE) were lost due to apparatus failure. Thus, the final analysis was performed on the data from 89 animals.

Experiment 3

THE EFFECTS OF 5 MG/KG CLOZAPINE ON AMPHETAMINE-INDUCED DISRUPTION OF LI. Ninety-six rats were randomly assigned to eight experimental groups in a 2 X 2 X 2 factorial design with main factors of preexposure (0, 40), clozapine (0.0, 5.0 mg/kg), and amphetamine (0.0, 1.0
mg/kg). Each rat received two injections prior to preexposure and prior to conditioning. The first injection consisted of either 5.0 mg/kg clozapine or an equivalent volume of vehicle administered ip 30 min prior to the start of preexposure and 30 min prior to conditioning. The second injection consisted of either 1.0 mg/kg d-amphetamine or an equivalent volume of saline administered 10 min prior to the start of preexposure and 10 min prior to conditioning. The experiment was run in two replications. Data from 2 rats were lost due to apparatus failure (1 from the Vehicle–Vehicle–NPE and 1 from the Vehicle–Vehicle–PE group). Thus, the final analysis was performed on the data from 94 animals.

Experiment 4
THE EFFECTS OF 10 MG/KG CLOZAPINE ON AMPHETAMINE-INDUCED DISRUPTION OF LI. Experimental design and drug treatment were identical to experiment 3, except that the dose of clozapine was 10.0 mg/kg. Data from 1 rat were lost due to apparatus failure (from the Vehicle–Vehicle–PE group). Thus, the final analysis was performed on data from 95 animals.

Results
Experiment 1
The six experimental groups did not differ in their times to complete licks 51–75 in the absence of the tone (A period). A 2 × 3 × 3 analysis of variance (ANOVA) with main factors of preexposure (0, 20), drug (0.0, 5.0, and 10.0 mg/kg clozapine), and replication (1, 2, 3), conducted on A periods yielded no significant outcomes (all Fs < 1.0). The overall mean A period was 9.96 sec.

A 2 × 3 × 3 ANOVA with main factors of preexposure (0, 20), drug (0.0, 5.0, 10.0 mg/kg clozapine), and replication (1, 2, 3) carried out on the suppression ratios yielded significant main effects of preexposure \[F(1,87) = 9.46, p < .01\], drug \[F(2,87) = 9.71, p < .001\], and a close to significant effect of replication \[F(2,87) = 2.81, p < .07\]. The latter effect stemmed from the fact that animals in the first replication were generally less suppressed than animals in the other two replications; however, since the general pattern of results was identical in the three replications as reflected in the lack of any significant interactions with the factor of replication, Figure 1 presents the mean suppression ratios of the preexposed and nonpreexposed groups in the three drug conditions combined over the three replications. As can be seen, overall, preexposed groups were less suppressed than the nonpreexposed groups, and clozapine reduced suppression in both the preexposed and the nonpreexposed groups. In addition, it can be seen that, as expected, there is no LI in the vehicle condition, but a clear LI effect in both drug conditions; however, since in the overall analysis the drug × preexposure interaction did not attain the acceptable level of significance, we reanalyzed the data of only the vehicle and the 5 mg/kg clozapine conditions.

The four experimental groups did not differ in their times to complete licks 51–75 in the absence of the tone (A period). A 2 × 2 × 3 ANOVA with main factors of preexposure (0, 20), drug (0.0, 5.0 mg/kg clozapine), and replication (1, 2, 3) conducted on A periods yielded no significant outcomes (all Fs < 1.0). The overall mean A period was 9.81 sec. The analysis of the suppression ratios yielded significant main effects of preexposure \[F(1,57) = 7.72, p < .01\], drug \[F(1,57) = 21.66, p < .001\], and replication \[F(1,57) = 4.67, p < .02\], as well as a significant preexposure × drug interaction \[F(1,57) = 4.02, p < .05\]. Post hoc two-tailed \(t\) tests based on the error term derived from the ANOVA, comparing the preexposed and nonpreexposed groups within each drug condition, revealed a significant LI effect in the clozapine condition \([t(57) = 3.32, p < .001]\), but not in the vehicle condition \([t(57) < 1]\). In addition, \(t\) tests comparing the preexposed and the nonpreexposed groups in the two conditions revealed that the preexposed clozapine group was significantly less suppressed than the preexposed vehicle group \([t(57) = 4.8, p < 0.001]\), whereas the difference between the nonpreexposed clozapine and vehicle groups was not significant \([t(57) = 1.9, p > .05]\). Thus, the comparison of only the 5 mg/kg dose of
clozapine with vehicle yielded a statistically significant enhancement of LI, which was attributable entirely to the action of the drug in the preexposed group.

**Experiment 2**

A 2 × 3 × 2 ANOVA with main factors of preexposure (0, 10), drug (0.0, 5.0, and 10 mg/kg clozapine), and replication (1, 2), conducted on A periods and suppression ratios yielded no significant main effect of replication or interactions with this factor (all Fs < 1.0). Consequently, the data of the two replications were combined for the purposes of statistical analysis.

The six experimental groups did not differ in their times to complete licks 51–75 in the absence of the tone (A period). A 2 × 3 ANOVA with main factors of preexposure (0, 10) and drug (0.0, 5.0, and 10.0 mg/kg clozapine) conducted on A periods yielded no significant outcomes (all Fs < 1.0). The overall mean A period was 8.79 sec.

Figure 2 presents the mean suppression ratios of the preexposed and nonpreexposed groups in the three drug conditions. As can be seen, LI is absent in the vehicle condition, but present in both clozapine conditions. In addition, clozapine produced a dose-dependent decrease in suppression of licking in both the preexposed and the nonpreexposed groups. These outcomes were supported by a 2 × 3 ANOVA with main factors of preexposure (0, 10) and drug (0.0, 5.0, 10.0 mg/kg clozapine) carried out on the suppression ratios, which yielded significant main effects of preexposure [F(1,83) = 8.81, p < .004] and drug [F(2,83) = 20.02, p < .001], as well as a significant preexposure × drug interaction [F(2,83) = 4.00, p < .03]. Post hoc two-tailed t tests based on the error term derived from the ANOVA, comparing the preexposed and nonpreexposed groups within each drug condition, revealed a significant LI effect in the 5 mg/kg and 10 mg/kg clozapine conditions [t(83) = 3.16, p < .01, and t(83) = 2.21, p < .05, respectively], but not in the vehicle condition [t(83) < 1].

**Experiment 3**

A 2 × 2 × 2 × 2 ANOVA with main factors of preexposure (0, 40), clozapine (0.0, 5.0 mg/kg), amphetamine (0.0, 1.0 mg/kg), and replication (1, 2), conducted on A periods and suppression ratios, yielded no significant main effect of replication or interactions with this factor (all Fs < 1.0). Consequently, the data of the two replications were combined for the purposes of statistical analysis.

A 2 × 2 × 2 ANOVA with main factors of preexposure (0, 40), clozapine (0.0, 5.0 mg/kg), and amphetamine (0.0, 1.0 mg/kg) conducted on A periods yielded no significant outcomes (all Fs < 1). The overall mean A period was 9.41 sec.

Figure 3 presents the mean suppression ratios of the preexposed and nonpreexposed groups in the four drug conditions: vehicle–vehicle (VEH–VEH), vehicle–amphetamine (1 mg/kg) (VEH–AMPH), clozapine (5.0 mg/kg)–vehicle (CLOZ–VEH), and clozapine (5.0 mg/kg)–amphetamine (1.0 mg/kg) (CLOZ–AMPH). Forty preexposures were used.
seen, LI, i.e., lower suppression in the preexposed as compared to the nonpreexposed groups, was present in the vehicle–vehicle and clozapine–vehicle conditions, whereas amphetamine-treated animals failed to demonstrate LI, irrespective of the administration of clozapine. This was supported by a $2 \times 2 \times 2$ ANOVA with main factors of preexposure (0, 40), clozapine (0.0, 5.0 mg/kg), and amphetamine (0.0, 1.0 mg/kg), which revealed significant main effects of preexposure [$F(1,86) = 17.20, p < .001$] and amphetamine [$F(1,86) = 5.63, p < .02$], as well as a significant interaction of preexposure × amphetamine [$F(1,86) = 5.45, p < .03$]. Post hoc two-tailed $t$ tests based on the error term derived from the ANOVA, comparing the preexposed and nonpreexposed groups within each drug condition, revealed a significant LI effect in the vehicle–vehicle condition [$t(86) = 3.06, p < .001$] and in the clozapine–vehicle condition [$t(86) = 3.55, p < .001$], but not in the vehicle–amphetamine and the clozapine–amphetamine conditions [$t(86) < 1$ for both]. Thus, clozapine at the dose of 5 mg/kg failed to antagonize amphetamine-induced disruption of LI. In addition, the ANOVA yielded a significant interaction of clozapine × amphetamine [$F(1,86) = 4.15, p < .05$]. Inspection of Figure 3 suggests that this outcome reflects the fact that clozapine on its own reduced suppression of drinking in both the preexposed and nonpreexposed animals compared with the other treatment conditions. This was supported by the results of post hoc two-tailed $t$ tests based on the error term derived from the ANOVA, comparing between the four drug conditions collapsed over the factor of preexposure, which showed that animals in the clozapine–vehicle condition were less suppressed than in the other three conditions: vehicle–vehicle [$t(86) = 2.66, p < .01$], vehicle–amphetamine [$t(86) = 2.76, p < .01$], and clozapine–amphetamine [$t(86) = 3.34, p < .01$]. The latter three conditions did not differ significantly from each other (all $t$s < 1).

**Experiment 4**

A $2 \times 2 \times 2 \times 2$ ANOVA with main factors of preexposure (0, 40), clozapine (0.0, 10.0 mg/kg), amphetamine (0.0, 1.0 mg/kg), and replication (1, 2), conducted on A periods and suppression ratios, yielded no significant main effect of replication or interactions with this factor (all $F$s < 1.0). Consequently, the data of the two replications were combined for the purposes of statistical analysis.

The times (in seconds) to complete licks 51–76 (A period) in the eight experimental groups were: Vehicle–Vehicle–NPE 5.03; Vehicle–Vehicle–PE 6.30; Vehicle–Amphetamine (AMPH)–NPE 6.45; Vehicle–AMPH–PE 5.50; Clozapine (CLOZ)–Vehicle–NPE 7.05; CLOZ–Vehicle–PE 5.54; CLOZ–AMPH–NPE 6.20; CLOZ–AMPH–PE 12.98. The longer A period exhibited by the CLOZ–AMPH–PE group was reflected in the results of a $2 \times 2 \times 2$ ANOVA with main factors of preexposure (0, 40), clozapine (0.0, 10.0), and amphetamine (0.0, 1.0), which yielded a significant interaction of preexposure × amphetamine × clozapine [$F(1,87) = 4.87, p < .03$].

Figure 4 presents the mean suppression ratios of the preexposed and the nonpreexposed groups in the four drug conditions: vehicle–vehicle (VEH–VEH), vehicle–amphetamine (1 mg/kg) (VEH–AMPH), clozapine (10.0 mg/kg)-vehicle (CLOZ–VEH), and clozapine (10.0 mg/kg)-amphetamine (1.0 mg/kg) (CLOZ–AMPH). Forty preexposures were used.

![Figure 4](image_url)

**Figure 4.** Means and standard errors of suppression ratios for the preexposed (PE) and nonpreexposed (NPE) groups in four drug conditions: vehicle–vehicle (VEH–VEH), vehicle–amphetamine (1 mg/kg) (VEH–AMPH), clozapine (10.0 mg/kg)-vehicle (CLOZ–VEH), and clozapine (10.0 mg/kg)-amphetamine (1.0 mg/kg) (CLOZ–AMPH). Forty preexposures were used.
Discussion

In experiments 1 and 2, which used 20 and 10 tone preexposures, respectively, no LI was evident in the vehicle condition; preexposed and nonpreexposed animals did not differ in their suppression of drinking during tone presentation. In both experiments, clozapine at the doses of 5 and 10 mg/kg led to the emergence of LI, i.e., lower suppression in the PE as compared to the NPE group, although a significant drug × preexposure interaction was obtained only in experiment 2. Our results indicate that with low number of preexposures, 5 mg/kg dose is more efficacious than 10 mg/kg dose in potentiating LI.

These results differ from those of Dunn et al (1993), who reported on the absence of clozapine-induced potentiation of LI. Although the precise reason for this discrepancy is unclear, it may stem from procedural differences between the two studies. In Dunn et al’s experiments, preexposure and conditioning were given in one session, whereas in our experiments, the two stages were given 24 hours apart. In addition, Dunn et al used repeated drug administration (7 days, including 6 days prior to the LI procedure). The importance of these procedural differences is attested to by the fact that in Dunn et al’s experiments, acute haloperidol treatment did not enhance LI, whereas in a two-stage LI procedure it does, whether given in both preexposure and conditioning, or in conditioning alone (Peters and Joseph 1993; manuscript in preparation). Moreover, we obtained an identical pattern of results with amphetamine (Weiner et al. 1984, 1988). Thus, when preexposure and conditioning are conducted in one session, acute amphetamine treatment does not disrupt LI, unless preceded by repeated administration, as is the case with haloperidol-induced enhancement of LI in Dunn et al’s study. In contrast, when preexposure and conditioning are given 24 hours apart, then acute amphetamine treatment disrupts LI, just as haloperidol treatment enhances LI under the same conditions. These results indicate that the one-session and two-session LI procedures have different sensitivity to drug action, which may account for the different results with clozapine obtained here and by Dunn et al (1993).

Clozapine did not produce LI enhancement when 40 nonreinforced preexposures were used (experiments 3 and 4). This loss of facilitatory effect is consistent with other reports that enhancement of LI is more readily detectable when the preexposure parameters used are insufficient to produce robust LI in control animals (Dunn et al 1993; Feldon and Weiner 1991; Moran and Moser 1992; Weiner and Feldon 1987), and could reflect a true limit of the LI procedure. Dunn et al (1993) suggested that with high number of preexposures a ceiling of inattention to the preexposed stimulus is attained that cannot be further increased by neuroleptics.

Consistent with previous findings (Killcross and Robbins 1993; Solomon et al 1981; Warburton et al 1994; Weiner et al 1981, 1984, 1988), LI was abolished by 1 mg/kg amphetamine. Amphetamine-induced disruption was antagonized by 10 (experiment 4) but not by 5 (experiment 3) mg/kg of clozapine, indicating that a higher dose of clozapine is needed for restoring LI in amphetamine-treated animals than for potentiating LI in normal animals. This dose-related difference in the efficacy of clozapine to potentiate LI under the two conditions may be related to the degree of dopamine blockade needed for the two effects, with a stronger blockade needed for LI restoration in amphetamine-treated animals.

In addition to LI potentiation, clozapine produced an overall decrease in suppression. Clozapine has been shown to exert anxiolytic effects in both animal models of anxiety (e.g., Wiley et al 1993) and in clinical practice (Gerlach 1991). The disinhibitory effect of the drug on conditioned suppression most probably reflects such an anxiolytic effect, as is found with anxiolytic drugs (Dunn et al 1993; Feldon and Weiner 1989); however, antianxiety drugs, while reducing conditioned suppression, do not produce LI enhancement, or disrupt LI (Dunn et al 1993; Feldon and Weiner 1989), supporting the specificity and selectivity of the LI-enhancement effect for modeling antipsychotic action (Dunn et al 1993).

The present study confirms that two characteristic effects of neuroleptics on LI—facilitation of LI following a relatively low number of preexposures and attenuation of amphetamine-induced disruption of LI—are produced also by clozapine. This finding is 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; Kerwin 1994; Meltzer 1991; Meltzer et al. 1989a, 1989b; Mortimer 1994; Nutt 1990; Tandon et al. 1993; Tandon and Kane 1993). In this context, the present results indicate that in the LI model, clozapine possesses a “typical” profile. The most likely neural substrate for these effects of clozapine is blockade of D2 receptors, presumably in the mesolimbic dopamine system, since the development of LI is apparently subserved by mesolimbic mechanisms (Gray et al 1991, 1995; Weiner 1990). Clozapine does seem to differ from the typical neuroleptic, haloperidol, in two respects. First, unlike haloperidol, which enhances LI and antagonizes amphetamine-induced disruption at the same doses (manuscript in preparation), a higher dose of clozapine appears to be needed for the latter than for the former effect. This
difference most probably reflects the weaker dopamine blockade produced by clozapine in comparison to typical neuroleptics (Farde et al. 1989; Farde and Nordström 1992; Louwerens et al 1993; Meltzer 1989, 1991; Mortimer 1994). Interestingly, this suggests that low dopamine-2 receptor occupancy suffices for LI enhancement, as it suffices for an antipsychotic action (Mortimer 1994). Second, clozapine produces a stronger reduction in fear conditioning than haloperidol at comparable doses (Feldon and Weiner 1988, 1991; Weiner and Feldon 1987; Weiner et al 1987; manuscript in preparation). This may be related to its serotonergic action, because serotonin-2 (5-HT2) antagonists appear to exhibit anxiolytic activity in some animal models as well as in humans (Leonard 1994). It is of interest to speculate that the anxiety-reducing effect of clozapine may contribute to its clinical efficacy in treating acute symptoms of psychosis, because the addition of antianxiety drugs to the antipsychotic regimen is reported to result in more effective relief of symptoms (Barbee et al. 1992; Mortimer 1994); however, it must be noted that although clozapine is a potent 5-HT2 antagonist, it did not act as such in the LI model, since selective 5-HT2 antagonists (e.g., ritanserin) disrupt LI (Cassaday et al 1993). This lack of serotonergic effect is consistent with the claim that serotonergic blockade is not an essential component of antipsychotic drug action (Gerlach 1991; Seeman 1992), although it may be restricted to positive symptoms of schizophrenia, since the selective 5-HT2 antagonist ritanserin has been reported to reduce negative symptoms (Duinkerke et al 1993; Reymtjen et al 1986).

The present results provide further support for the predictive validity of the LI model as a screening test for compounds with antipsychotic potential. A major problem in the search for antipsychotic drugs is the lack of adequate animal models, and this problem is particularly salient in the case of atypical neuroleptics, which are inactive in most classical models (Gerlach 1991). The LI model appears to be equally sensitive to typical and atypical neuroleptics differing in their in vitro and in vivo pharmacology (Weiner et al 1994), and it taps antipsychotic potential with both acute (Feldon and Weiner 1988, 1991; Warburton et al 1994; Weiner and Feldon 1987; Weiner et al 1987, 1994) and repeated drug administration (Christison et al 1988; Dunn et al 1993). Moreover, whereas antagonism of amphetamine-induced disruption of LI is a drug–drug model, the facilitation of LI does not require the administration of a dopamine agonist, so the model does not rely on pharmacologic means to elicit the behavior of interest. Finally, the LI model has a direct relevance to the clinic because it models a cognitive process that is disrupted in acute schizophrenia.

References


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