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Facilitation of latent inhibition by the atypical antipsychotic risperidone

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Abstract

The action of the atypical antipsychotic risperidone on latent inhibition (LI), an animal model of schizophrenia, was investigated. The parameters of the procedure were set at values insufficient to generate LI in control rats. On the first day, rats administered 0.5, 1.0, or 2.0 mg/kg ip risperidone or vehicle were preexposed (PE) to 10 tone presentations. On the second day, they were again injected with drug or vehicle and then submitted to two conditioned stimulus (CS; tone)–unconditioned stimulus (US; shock) pairings. On the third day, suppression of their drinking response under the CS was measured. Nonpreexposed (NPE) animals were submitted to the same procedure except for the tone preexposure. On the suppression test, LI was not observed in control rats as well as in animals given 0.5 mg/kg risperidone. Animals given 1.0 and 2.0 mg risperidone, however, displayed an LI effect. The facilitation of LI by risperidone gives additional support to the LI paradigm as an animal model of schizophrenia.

Keywords: Risperidone; Latent inhibition; LI; Schizophrenia; Animal models; Atypical antipsychotics

1. Introduction

Risperidone is an atypical antipsychotic of high clinical efficacy in treating both positive and negative symptoms of schizophrenia with low incidence of secondary motor effects (Chouinard et al., 1993; Schatzberg and Nemeroff, 1995). Its therapeutic action is considered to be related to its weak D_2 and potent $5HT_2$ receptor blocking action, although it also antagonizes D_1, α_1, and histamine receptors (e.g., Buckley and Meltzer, 1995; Leysen et al., 1994). Research on the mechanism of action of risperidone would be greatly helped if it proved to be effective in an animal model of schizophrenia.

Latent inhibition (LI) is a phenomenon in which an animal exposed to the conditioned stimulus (CS) prior to conditioning subsequently shows difficulty in learning that such stimulus is predictive of an unconditioned stimulus (US) (Lubow, 1973). Because of this feature, LI has been considered to measure the ability to ignore irrelevant simuli (Lubow et al., 1982; Mackintosh, 1975) and has been proposed as a behavioral model of cognitive abnormalities in schizophrenia (Feldon and Weiner, 1991; Gray et al., 1992; Shadach et al., 2000). As a model psychotogenic drug, amphetamine blocks LI in animals (Dunn et al., 1993; Weiner et al., 1988). On the other hand, neuroleptics facilitate LI, under conditions that do not produce the phenomenon in controls, namely, low number of stimulus preexposures or high number of conditioning trials. Robust facilitation has been obtained with both typical and atypical neuroleptics, such as haloperidol (Feldon and Weiner, 1991; Weiner and Feldon, 1987), fluphenazine, chloropromazine, and thioridazine (Dunn et al., 1993), clozapine (Moran et al., 1996), ondansetron (Warburton et al., 1994), alpha-flupenthixol (Killcross et al., 1994), sulpiride (Feldon and Weiner, 1991), and remoxipride (Trimble et al., 1997). The effect is selective and specific to this class of drugs (Dunn et al., 1993). Human experiments give support to the model: the LI effect is disrupted in schizophrenic patients (Baruch et al., 1988b) and in normal subjects given amphetamine (Baruch et al., 1988a), whereas it is facilitated in human beings under haloperidol treatment (Williams et al., 1997).

The purpose of this experiment was to test the responsivity of risperidone on the LI model. Although risperidone was shown to antagonize the disruptive effect of the $5HT_2$

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agonist DOI on LI (Hitchcock et al., 1997), the direct effect of this drug on the model has not been reported. Eventual facilitation of LI by risperidone would add to the generality of the model's sensitivity to antipsychotic drugs. In addition, it would suggest that the improvement in the capacity to ignore irrelevant stimuli is a relevant feature in the therapeutic effectiveness of risperidone.

2. Method

2.1. Subjects

Naïve male Wistar rats weighing approximately 300 g at the beginning of the experiment were used. They were housed singly under a 12–12-h light/dark cycle (lights off at 20:00 h) under controlled temperature (21 ± 10°C). Animals were kept on a 23-h water restriction schedule throughout the experiment. Food was freely available in the home cage.

2.2. Apparatus

Experiments were run in four operant conditioning chambers (32 × 25 × 21 cm), encased in sound-attenuating isolation boxes (all equipment from Med Associates). A ventilation fan (ENV-025F28) provided background noise. A removable drinking bottle was located on one wall of the box. Licks were detected by a lickometer circuit (ENV-25A). Tone stimuli (5 s, 70 dB, 2.8 kHz) were generated by a Sonalert module (SC 628). Shock stimuli (1.0 mA, 1 s) were supplied by a shock generator (ENV 410A) and scrambler (ENV-412) and applied via stainless steel bars 0.25 cm in diameter spaced 1.5 cm apart. A 486 IBM personal computer was programmed to control stimulus presentation and data recording.

2.3. Procedure

The experimental procedure employed, based on that by Weiner and Feldon (1987), consisted of four phases, conducted at the same time of the day during the morning period.

2.3.1. Baseline training (Days 1–5)

Animals were individually placed in the experimental chamber and remained there until they had completed 600 licks. The subject was then returned to its home cage and allowed to drink for 30 min.

2.3.2. Preexposure (Day 6)

The bottle was removed and each subject was placed in the experimental chamber. The preexposed (PE) animals received 10 presentations of a 5-s tone, with an intertrial interval of 30 s. The nonpreexposed (NPE) animals were confined to the chamber for an identical length of time, but they did not receive the tone.

2.3.3. Conditioning (Day 7)

Each animal was again placed in the experimental chamber with the water bottle removed. Five minutes later, the subject was given two tone–shock pairings, 5 min apart. The tone was identical to that used in the preexposure. Each tone presentation was immediately followed by a scrambled foot-shock (1 s, 1.0 mA). Animals were removed from the box 5 min after the second shock.

2.3.4. Testing (Day 8)

The water bottle was replaced and each animal was allowed to drink freely. When the rat had completed 90 licks, the tone was presented. The tone continued until additional 10 licks had been made. If the subject failed to complete these 10 licks within 300 s, the session was terminated. A suppression ratio (SR) was calculated as the time between licks 80 and 90 (pre-CS period) divided by the time between licks 80 and 100 (pre-CS period + CS period).

2.4. Drug administration

Risperidone (Research Biochemicals International) was dissolved in a small amount of acetic acid and diluted in a 5.5% glucose solution. Animals in the drug groups were administered risperidone (0.5, 1.0, and 2.0 mg/kg ip) 60 min prior to the preexposure (Day 6) and conditioning (Day 7) phases. An equivalent volume of vehicle (1.0 ml/kg) was administered to animals in the corresponding control groups.

2.5. Statistics

SRs were analyzed by a 2 × 2 ANOVA with main factors of preexposure and drug.

3. Results

Fig. 1 presents the mean SR of drug and vehicle groups, in each of the three dose conditions. The top panel A shows the results of the 0.5 mg/kg risperidone group, whereas panels B and C present the SRs of groups receiving 1.0 and 2.0 mg/kg of the drug, respectively. As expected, when a low level of stimulus preexposure is employed, no LI effect was observed in all of the vehicle groups. At the lower dose of risperidone (0.5 mg/kg), the LI effect is also absent. However, at the higher doses of 1.0 and 2.0 mg/kg, there is increasing difference between PE and NPE groups.

Statistical analysis supports this description. At the lower dose of 0.5 mg/kg risperidone, the 2 × 2 ANOVA revealed no significant main effect of preexposure [$F(1,35) = 0.038$, NS] or drug condition [$F(1,35) = 0.018$, NS], as well as no significant interaction between the preexposure and drug conditions [$F(1,35) = 0.445$, NS], confirming the absence of LI. At the dose of 1.0 mg/kg, statistical analysis showed a significant drug effect

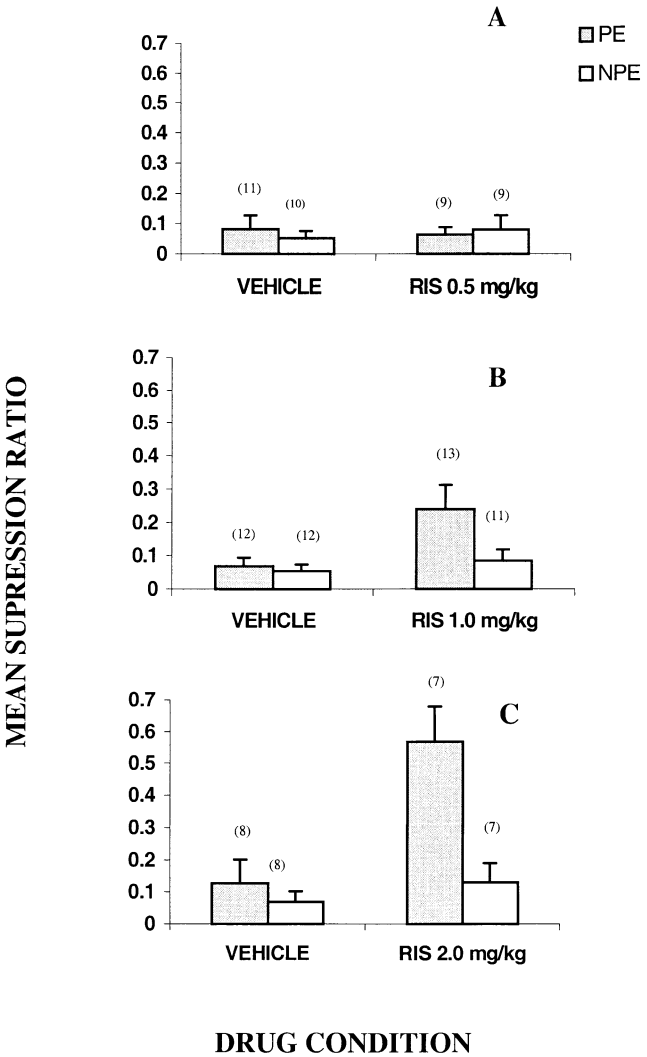

Fig. 1. Mean and standard errors of SRs for groups of rats given risperidone (RIS) or vehicle (VEHICLE). (A) Top panel: RIS 0.5 mg/kg; (B) middle panel: RIS 1.0 mg/kg; (C) bottom panel: RIS 2.0 mg/kg. The *n* for each group is shown inside the corresponding bar.

[$F(1,44)=4.922$, $P<.05$] and a tendency towards a significant preexposure effect [$F(1,44)=3.441$, $P<.10$]. Yet, no significant Preexposure × Drug interaction was obtained [$F(1,44)=2.400$, NS], although the probability level associated to this interaction ($P=.128$) was close to the criterion for a significant tendency ($.05<P<.10$). At 2.0 mg/kg, there was a significant effect of the preexposure [$F(1,26)=11.977$, $P<.01$] and drug [$F(1,26)=12.120$, $P<.01$] conditions, as well as a significant Preexposure × Drug interaction [$F(1,26)=6.979$, $P<.05$].

4. Discussion

Risperidone at 2.0 mg/kg facilitated LI in rats preexposed to the stimulus to be conditioned. When suppression of a drinking response associated with an aversive CS was measured, control animals did not show LI, that is, there was no difference between the PE and NPE vehicle groups, whereas rats treated with 2.0 mg/kg of risperidone presented a clear LI effect, that is, PE subjects exhibited lower suppression of drinking than NPE. The difference is due to the effect of the neuroleptic on the PE groups, since no decrease in suppression was observed in the NPE drug groups. A tendency towards LI facilitation was also observed in subjects receiving 1.0 mg/kg of the drug, but not in the 0.5 mg/kg treatment condition.

The procedure used to detect neuroleptic facilitatory effects employed a very low level of CS preexposure. The small number of unreinforced stimulus presentations did not allow the emergence of LI in vehicle-treated animals. However, they were sufficient to generate LI in risperidone-treated animals, since the CS–US association was disrupted when the stimulus was presented in the conditioning trials. This disruption was evident in the test phase by the low suppression of licking in PE animals when the CS was on, whereas no reduction of suppression in the NPE drug-treated groups was observed. There is evidence that the facilitatory effect of neuroleptics takes place in the conditioning phase (Shadach et al., 1999, 2000). Thus, it is possible that the facilitation observed in the present experiment was due to the action of risperidone on the conditioning stage. If so, this result could be interpreted as a risperidone-induced decrease in the salience of the reinforcer (Killcross et al., 1994), although the fact that the neuroleptic did not affect suppression in the NPE groups would not support this view. An alternative explanation would be that risperidone-treated animals did not switch responding according to the changed contingency presented in the conditioning phase, persisting on responding to the stimulus according to its function in preexposure (Shadach et al., 1999; Weiner, 1990). However, since the drug was not tested separately in the preexposure and conditioning phases, it is not possible at the moment to assert conclusively in which of these phases the observed facilitation took place.

Most neuroleptics enhance LI at doses that correlate well with their clinical potency (Dunn et al., 1993). Risperidone, however, was most effective in the present experiment at a dose well above its therapeutic effective range (Baldessarini, 1996). A possible explanation for the lack of effect at lower doses could be the competition between the facilitatory effect of D_2 antagonism and the disruptive effect of $5HT_2$ antagonism on LI. As noted above, the facilitatory effect of neuroleptics has been shown to occur in the conditioning phase, and it has been attributed to DA blockade (Peters and Joseph, 1993; Weiner, 1990; Weiner and Feldon, 1997; Weiner et al., 1997). On the other hand, a disruptive effect on LI takes place in the preexposure stage and is probably mediated by $5HT_2$ antagonism (Shadach et al., 2000). Since risperidone is a mixed $D_2/5HT_2$ receptor antagonist, and since the neuroleptic was administered both in the preexposure and conditioning stages, it is possible that risperidone

was restricted in its ability to enhance LI because of a competition between its inhibitory effects on preexposure and its potentiating effects on conditioning. Such a competition has been suggested as an explanation for clozapine effects on LI (Dunn et al., 1993; Shadach et al., 2000). The relative potency of serotonergic and dopaminergic actions of risperidone is dose-dependent, and the $5HT_2/D_2$ receptor occupancy ratio becomes progressively smaller as the dose increases (Schotte et al., 1996). Thus, at the higher doses used in the present experiment, the drug effect on the dopaminergic system may have prevailed over its serotonergic action, unmasking the facilitatory effect of risperidone on LI.

LI has been proposed as both an animal and a human model of schizophrenia. As such, it has proved to be sensitive to the antipsychotic properties of drugs such as haloperidol, clozapine, remoxipride, olanzapine, sulpiride, and ondansetron (Dunn et al., 1993; Feldon and Weiner, 1991; Gosselin et al., 1996; Moran et al., 1996; Moser et al., 1996; Trimble et al., 1997; Warburton et al., 1994; Weiner and Feldon, 1987). As an atypical antipsychotic, risperidone is now added to this list. Since the LI paradigm is presumed to measure the capacity of organisms to ignore irrelevant stimuli, it is reasonable to assume that the facilitation of LI induced by these drugs is related to a change in stimulus control mediated by the central effects of these drugs. Risperidone is both a $5HT_2$ and a D_2 antagonist. Studies using specific blockers and manipulating the stage at which drug administration occurs could help in determining which transmission systems are most relevant in relieving the attention impairment exhibited by psychotic patients.

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