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RAPID COMMUNICATION

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Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic olanzapine

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Abstract Prepulse inhibition (PPI) of the startle reflex provides an operational measure of sensorimotor gating. Deficits in PPI are observed in schizophrenia patients and can be modelled in animals by administration of noncompetitive NMDA antagonists such as phencyclidine (PCP) or dizocilpine (MK-801). Previous studies indicate that the atypical antipsychotic clozapine restores PPI in PCP-treated animals while the typical antipsychotic haloperidol does not. Olanzapine (LY170053) is a novel putative atypical antipsychotic that shares many pharmacological and behavioral properties with clozapine. The present study assessed the ability of olanzapine (0, 1.25, 2.5, 5.0 or 10.0 mg/kg) to antagonize deficits in PPI produced by PCP (1.5 mg/kg) and dizocilpine (0.1 mg/kg). At the two highest doses, olanzapine significantly increased PPI in PCP- and dizocilpine-treated animals without affecting PPI or baseline startle reactivity by itself. These results support the notion that olanzapine is functionally similar to clozapine and may have utility as an atypical antipsychotic agent.

Key words Schizophrenia · Clozapine · Startle · Sensorimotor gating · NMDA · Dizocilpine

Introduction

The atypical antipsychotic clozapine possesses many characteristics that distinguish it from the traditional or "typical" neuroleptics such as haloperidol. Clozapine reduces positive as well as negative symptoms of schizophrenia, is effective in the treatment of neuroleptic-resistant schizophrenia patients and is associated with a very low incidence of extrapyramidal side effects (Kane et al. 1988). Much attention has been focussed in recent years on the development of new compounds that possess the unique beneficial effects of clozapine but that do not lead to agranulocytosis, the major side effect of clozapine that limits its clinical use. Olanzapine (LY170053, 2-methyl-4-(4-methyl-1-piperazinyl)-1OH-thieno[2, 3-b][1, 5]benzodiazepine) is a novel thienobenzodiazepine that closely resembles clozapine in terms of its pharmacological and behavioral profiles but to date has not been reported to produce agranulocytosis. Like clozapine, olanzapine has been found to antagonize dopamine (D_1, D_2, D_4), serotonin ($5\text{-}HT_2$) and cholinergic receptors (Moore et al. 1993) and has been shown to be functionally similar to clozapine in several preclinical behavioral tests. For example, olanzapine increases punished responding in an operant conflict procedure, substitutes for clozapine in a drug discrimination paradigm, and is devoid of cataleptic effects at behaviorally active doses (Moore et al. 1992).

Because these earlier studies suggest that olanzapine and clozapine are similar, it has been suggested that olanzapine may be a novel atypical antipsychotic that could succeed clozapine in the treatment of schizophrenia (Moore et al. 1992). The effects of olanzapine in preclinical tests that more directly model certain deficits observed in schizophrenia, however, remain to be determined. One paradigm that has face, construct, and predictive validity for the information processing deficits seen in schizophrenia patients is prepulse inhibition (PPI) of the startle reflex (Geyer et al. 1990; Swerdlow et al. 1994). In PPI, presentation of a weak stimulus (the prepulse) immediately prior to an intense startling stimulus (the pulse) results in a diminution in the magnitude of the startle response to the pulse. PPI is reduced in schizophrenia patients and can be disrupted in animals by a variety of pharmacological agents including the noncompetitive NMDA antagonists phencyclidine (PCP) and dizocilpine (MK-801) (Geyer et al 1990). Interestingly, disruptions in PPI produced by noncompetitive NMDA antagonists are reversed by clozapine but not traditional antipsychotics such as haloperidol (Geyer et al. 1990; Bakshi et al. 1994; Schwarzkopf et al. 1994). It has been suggested that the unusual multifaceted pharmacological profile of clozapine may underlie its unique ability to antagonize PCP- and dizocilpine-induced defi-

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cits in PPI (Bakshi et al. 1994). It is thus of importance and interest to determine if olanzapine might also antagonize deficits in PPI produced by the noncompetitive NMDA antagonists PCP and dizocilpine.

Materials and methods

A total of 148 male Sprague-Dawley rats weighing 300–350 g (Harlan Laboratories, San Diego, Calif.) were housed in groups of two or three in clear plastic cages in a climate-controlled animal colony and were maintained on a reversed day/night cycle with lights off at 7:00 a.m. Food (Harlan Teklad, Madison, Wisc.) and water were freely available throughout the experiments except during behavioral testing. Animals were handled gently by the experimenter 1 week before testing to minimize stress during the experiment. Each animal was tested only once. Phencyclidine hydrochloride and dizocilpine maleate ({(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine}; MK-801) were purchased from Research Biochemicals Incorporated (Natick, Mass.) and were dissolved in 0.9% saline. Olanzapine (Eli Lilly, Indianapolis, Ind.) was initially dissolved in 0.1 N HCl and saline and then titrated with 0.1 N NaOH to a final pH of 6.0. All doses are expressed as the salt.

Two days before testing, all animals underwent a brief startle session consisting of 17 PULSE ALONE trials of 120 dB and three PREPULSE+PULSE trials in which the prepulse intensity was 12 dB above the background noise (presented in pseudo-random order) in order to establish equally matched treatment groups. Startle boxes and the baseline startle session have been detailed previously (Bakshi et al. 1994). The following test session, consisting of two components separated by 1 min of background noise (65 dB, on throughout the session), was utilized for all experiments. The first component was designed to match the test session employed previously to detect successfully a reversal of PCP-induced deficits in PPI by clozapine (Bakshi et al. 1994). The second component was designed to test for possible olanzapine-induced increases in PPI, since it has previously been shown that low intensity prepulses elicit a level of PPI that can be augmented by clozapine (Swerdlow and Geyer 1993). Because the main purpose of the present investigation was to assess the ability of olanzapine to antagonize PCP-induced deficits in PPI, the component based on the Bakshi study was presented first. In the first component, a 40-ms, 120-dB burst was presented either alone (PULSE ALONE trial) or was preceded 100 ms by 20-ms bursts that were 68, 71, or 77 dB (3, 6, or 12 dB above the background noise) (PREPULSE+PULSE trials). In addition, several NO STIMULUS trials were presented. The second component of the test session also consisted of five distinct trial types: a 120-dB PULSE ALONE trial; three PREPULSE+PULSE trials (prepulses were 1, 2 or 4 dB above background noise); and a NO STIMULUS trial. In each component, all trials were presented several times (for a total of 48 trials in each component) in a pseudo-random order and an average of 15 s separated consecutive trials.

Two experiments were conducted using separate groups of animals. In the first, animals were pretreated with either saline or 1.25, 2.5, 5.0, or 10 mg/kg olanzapine (IP) and 20 min later with either saline or PCP (1.5 mg/kg, SC) and 10 min later, placed in startle chambers for behavioral testing. In the second experiment, either saline or olanzapine (10 mg/kg, IP) was administered 15 min prior to injection of either saline or dizocilpine (0.1 mg/kg, SC). Fifteen minutes after the final injection, animals were placed into startle chambers. Doses of PCP and dizocilpine were selected on the basis of their ability to robustly disrupt PPI in previous studies (Geyer et al. 1990; Bakshi et al. 1994).

Data from components 1 and 2 were analyzed initially using separate four-factor analyses of variance (ANOVA) with pretreatment and treatment as between-subjects factors and block (first and second halves of each component) and trial type as repeated measures. When the block factor did not significantly interact with any other factor, the results of three-factor ANOVA are reported (pretreatment, treatment, and trial types). All post-hoc comparisons of means were conducted using Tukey's test. Alpha was set at 0.05. Although PPI was disrupted by the NMDA antagonists for PREPULSE+PULSE trials in which the prepulse intensity was 2 or 3 dB above the background noise (no PPI was observed for any treatment group at the 1-dB prepulse intensity), olanzapine did not produce any statistically reliable effects on PULSE ALONE, NOSTIM or PREPULSE+PULSE trials in which the prepulse intensity was 1, 2, or 3 dB above the background noise. For the sake of brevity, these data are not presented.

Results

Figure 1 illustrates the effects of several doses of olanzapine on deficits in PPI produced by 1.5 mg/kg PCP. Analyses of variance for the first [$F(1, 102)=270.73$, $P<0.001$] and second [$F(1, 102)=64.54$, $P<0.001$] components of the test session revealed main effects of PCP treatment. Further analyses showed that PCP significantly reduced PPI for all PREPULSE+PULSE trial types depicted in Fig. 1 ($P<0.01$). In contrast to PCP, olanzapine by itself did not have any statistically significant effects on PPI in either the first [$F(1, 102)=0.71$, NS] or second [$F(1, 102)=1.11$, NS] component of the startle session (data not shown). A significant pretreatment ×treatment interaction, however, was observed for the first component of the test session [$F(4, 102)=4.04$, $P<0.005$], and a significant trial type×pretreatment ×treatment interaction [$F(8, 204)=4.49$, $P<0.001$] was

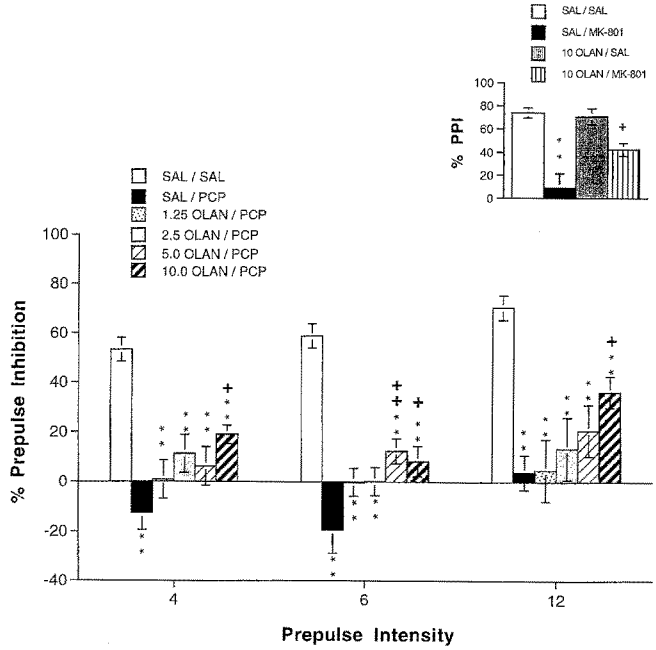

Fig. 1 Effects of olanzapine on PCP- or MK-801-induced deficits in PPI. Values represent mean±SEM for each treatment. Doses in mg/kg. *SAL* saline, *OLAN* olanzapine, *PCP* 1.5 mg/kg phencyclidine, *MK-801* 0.1 mg/kg dizocilpine. $+P<0.05$, $^{++}P<0.01$, compared to SAL/PCP group; $^{**}P<0.01$ compared to SAL/SAL group. *Inset*, data from 12-dB PREPULSE+PULSE trials in second half of component 1. $^{**}P<0.01$ compared to SAL/SAL group,$+P<0.05$, compared to SAL/MK-801 group