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ORIGINAL INVESTIGATION

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Combined α_2-adrenergic/D_2 dopamine receptor blockade fails to reproduce the ability of clozapine to reverse phencyclidine-induced deficits in prepulse inhibition of startle

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Abstract *Rationale:* The combination of idazoxan, a specific α_2-adrenoceptor antagonist with raclopride, a selective D_2/D_3 receptor antagonist, has been recently proposed to produce an "atypical" antipsychotic profile comparable to that of clozapine, based on an animal study which analysed dopamine efflux in the medial prefrontal cortex and the preclinical test of conditioned avoidance response (CAR) for evaluation of antipsychotic potential. Accordingly, the combination of a "typical" antipsychotic with idazoxan has been proposed as an augmentation strategy in treatment-resistant schizophrenia, although its therapeutic potential remains difficult to predict. *Objectives:* Given the momentum stimulated by these reports, the present study investigated whether the combination of idazoxan with raclopride is indeed sufficient to mimic the ability of clozapine to reverse prepulse inhibition (PPI) deficits in rats, a behavioral paradigm that models PPI deficits observed in the schizophrenia spectrum, and currently the only test which reliably appears to distinguish between "typical" antipsychotics and compounds with "atypical" antipsychotic potential. *Methods:* The effects of the combination idazoxan/raclopride were examined in two PPI paradigms: 1) phencyclidine (PCP)-induced disruption of PPI, which has been shown to be preferentially reversed by "atypical" antipsychotics; 2) apomorphine-induced disruption of PPI which can be reversed by either "typical" high-potency D_2 dopamine antagonists or "atypical" antipsychotics. *Results:* In contrast to clozapine, combining idazoxan with raclopride failed to reverse PCP-induced deficits in PPI. In addition, there was no evidence of an enhancing effect of idazoxan on the blockade of apomorphine-induced disruption of PPI by raclopride. *Conclusion:* The present results challenge the hypothesis that simple α_2/D_2 blockade is sufficient to produce clozapine-like "atypical" antipsychotic activities, and support the consensus that the PPI paradigm represents the most sophisticated behavioral preclinical test for detecting selective "atypical" profile of antipsychotics.

Keywords Idazoxan · Raclopride · Sensorimotor gating · Treatment-resistant schizophrenia · Noradrenaline · Augmentation strategy

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Introduction

Clozapine is considered the prototype of the so called "atypical" antipsychotics because of its unique clinical profile showing significantly better efficacy than classical antipsychotics on negative and cognitive symptoms without any extrapyramidal side effects and superior response in treatment-resistant schizophrenia (Kinon and Lieberman 1996; Chakos et al. 2001). Increasing attention has been paid to the relative importance of the affinity of clozapine for a variety of brain neurotransmitter non-dopaminergic receptors and the peculiar interaction of this drug with dopamine (DA) receptors (Coward 1992; Reynolds 1997; Kapur and Remington 2001). Based on a previous clinical report that showed augmentation of "typical" antipsychotic drug treatment by the specific α_2-adrenoceptor antagonist idazoxan, particularly in patients with high levels of baseline negative symptoms (Litman et al. 1996), Hertel et al. recently performed an experimental study (Hertel et al. 1999) leading to a highly challenging conclusion. These authors investigated in rats the combination of idazoxan with ra-

clopride, a selective dopamine $D_{2/3}$ antagonist, showing that the addition of idazoxan significantly increased dopamine output selectively in the medial prefrontal cortex (Hertel et al. 1999) in a manner similar to that observed with clozapine (Moghaddam and Bunney 1990; Kuroki et al. 1999). In addition, the same study showed that idazoxan significantly potentiated the raclopride-induced suppression of the conditioned avoidance response (CAR) (Hertel et al. 1999), a classical sensitive, although not selective, preclinical screening test of antipsychotic activity (Arnt 1982; Wadenberg and Hicks 1999).

The goal of the present study was to examine whether this provocative hypothesis could hold out testing the above-mentioned pharmacological protocol in the behavioral paradigm of the prepulse inhibition (PPI) of startle. This approach has recently emerged as the most well validated tool for the study of agents with "atypical" antipsychotic properties versus "typical" antipsychotics (see Special Issue on PPI, Psychopharmacology 156, 2001). PPI is considered an operational paradigm for measuring abnormalities of gating in sensorimotor and cognitive domains which are shown to be impaired in the whole spectrum of psychotic disorders (McGhie and Chapman 1961; Braff et al. 1978, 1992, 2001). In addition, abnormalities of gating have also been observed in other neuropsychiatric disorders, such as Huntington's disease, Tourette's syndrome and obsessive-compulsive disorder that share some overlapping symptoms with schizophrenia-like disorders (Geyer et al. 2001). PPI is measured in rats and humans using near-identical stimulus parameters (Swerdlow and Geyer 1998) and changes in this paradigm can be induced in a highly sophisticated manner by using pharmacological tools, including noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists (Mansbach and Geyer 1989, 1991) such as phencyclidine (PCP), and DA direct and indirect agonists, such as apomorphine and amphetamine (Mansbach et al. 1988; Geyer et al. 2001). All antipsychotics, without distinction between "typical" and "atypical" profiles, are able to reverse PPI in rats treated with DA agonists (Swerdlow and Geyer 1993, 1998). On the contrary, it has been shown that PPI disruption induced by PCP is preferentially reversed by clozapine and other so-called "atypical" antipsychotic agents (Keith et al. 1991; Bakshi et al. 1994; Bakshi and Geyer 1995; Swerdlow et al. 1996).

Most interestingly, PCP can induce a psychotic state in humans (Sharp et al. 2001). This has been linked to the characteristics and pathophysiology of negative and cognitive symptoms in schizophrenia (Javitt 1987; Ellenbroek and Cools 2000). In addition, the effects of PCP in animals have been suggested to be a useful paradigm reflecting the gating disturbances in treatment-resistant psychosis based on the failure of most effective "typical" antipsychotics to block the effects of PCP on PPI of acoustic startle (Geyer and Swerdlow 1999).

On the basis of these premises and with the aim to provide insight into the challenging hypothesis of the involvement of α_2-adrenoceptor in the mode of action of clozapine, we investigated whether the effects of combining idazoxan and raclopride parallel those of clozapine in the PCP model of gating deficits in rats. We further studied the effect of this drug combination on PPI in apomorphine-treated rats.

Materials and methods

Subjects

A total of 250 male Sprague-Dawley rats (Harlan Laboratories, Milan, Italy) weighing 250–350 g were used in the present study. Methods for housing and all behavioral testing were consistent with the substantial literature of startle measures in rodents (Geyer and Swerdlow 1998). For example, animals were housed in groups of two and maintained on a reversed 12-h light/night cycle; all testing occurred between 9.00 a.m. and 5.00 p.m. Upon arrival and throughout the studies, rats were handled gently and daily to minimize stress during behavioral testing and were given access to food and water ad libitum except during behavioral testing. All efforts were made to prevent animal suffering and to reduce the number of animals used.

Experimental protocols were approved by the Ethical Committee (EC) at the University of Brescia and performed in strict accordance with the EC regulations for the care and use of experimental animals (CEE NE86/609).

Apparatus

Startle experiments used one startle chamber (SR-LAB; San Diego Instruments, San Diego, Calif., USA) housed in a sound-attenuated room. The startle chamber consisted of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5×25.5 cm Plexiglas frame within a ventilated enclosure. The delivery of acoustic stimuli was controlled by the SR-LAB microcomputer and interface assembly, which also digitized, rectified, and recorded stabilimeter readings, with 100, 1-ms readings collected beginning at stimulus onset. Startle magnitude was defined as the average of the 100 readings. Acoustic stimuli and background noise were presented via a Radio Shack Supertweeter mounted 24 cm above the Plexiglas cylinder. Startle magnitude was detected and recorded as transduced cylinder movement via a piezoelectric device mounted below the Plexiglas stand.

Drugs

The following drugs were used: PCP hydrochloride (1.25 mg/kg SC); clozapine (7.5 mg/kg IP); idazoxan (1.5 mg/kg SC); raclopride (0.15, 0.05, 0.025 or 0.006 mg/kg, SC); apomorphine (0.25 mg/kg SC), all purchased from Sigma Milan. All drugs, excluding clozapine and apomorphine, were dissolved in 0.9% saline. Clozapine was dissolved in 0.5 vol 0.1 N HCL and diluted to full volume with saline (final pH 5.0–6.5). Apomorphine was dissolved in saline with 0.1 mg/ml ascorbic acid. Injection volume was 1 ml/kg. The doses of PCP and apomorphine were chosen, because they have been found previously to significantly disrupt PPI in rats (Bakshi et al. 1994; Swerdlow et al. 1996, 2000); dose of clozapine was chosen because it has been shown to reliably antagonize deficits in PPI induced by PCP (Swerdlow et al. 1996). Doses and time schedule of drug administration in the combined pretreatment with idazoxan and raclopride were based on the experimental protocol by Hertel et al. (1999). All experiments were conducted in separate groups of drug-naive and experimentally naive rats.

Testing procedures

Three days before drug testing each rat was placed into the startle chamber with 70 dB background noise and 5 min later was exposed to 18 pulse-alone (a 40 ms, 120 dB noise burst) trials and

six prepulse+pulse (a 20 ms, 82–12 dB over background – burst followed 100 ms later by the 120 dB burst) trials. The purpose of this initial session was to create equally matched treatment groups based on the mean startle magnitude data (from the pulse-alone trials) for each rat. In the PCP study, rats received the following pretreatments: saline, clozapine, idazoxan alone or idazoxan followed ten minutes later by raclopride. Five (idazoxan+raclopride) or 30 (clozapine) min after completion of pretreatment rats were treated with either PCP or saline. Ten minutes later, each rat was placed in the startle chamber for the test session. In the apomorphine study, rats were placed in the startle chamber immediately after apomorphine or saline injection. Rats were pretreated with either saline, idazoxan alone, one of the doses of raclopride alone, or with idazoxan followed 10 min later by one of the doses of raclopride. The test session used in both studies consisted of a background noise (70 dB) that was presented alone for 5 min and then continued for the remainder of the session, followed by several presentations in a pseudorandom order of pulse-alone trials, trials of pulse preceded by 3, 6 or 12 dB prepulses and no stimulus trials in which only the background noise was presented. There was a total of 50 trials (12 pulse-alone trials, ten each of the 3, 6 or 12 dB prepulse+pulse trials, eight no stimulus trials). In addition, five consecutive pulse-alone trials, which were not included in the calculation of PPI values, were presented at the beginning and at the end of the test session. Prepulse intensities were chosen to span a range of relatively weak (3 dB) and intense (12 dB) stimuli. Intertrial intervals averaged 15 s.

Data analysis

The initial and final five pulse alone trials were not included in the analysis, in order to ensure the calculation of PPI over a more stable range of startle responses. For each pulse-alone and prepulse+pulse trial, the startle response to the 120 dB burst was recorded. From these values, two measures were calculated for each rat for each of its pharmacological treatment conditions: first, the amount of PPI was calculated as a percentage score for each prepulse+pulse trial type: % PPI=100–{[(startle response for prepulse+pulse trial)/(startle response for pulse-alone trial)]×100}. Second, startle magnitude was calculated as the average response to all of the pulse-alone trials. PPI data were analysed with the general linear model univariate analysis of variance (ANOVA) using PPI values as dependent variable and treatment and prepulse magnitude as fixed factors (statistical package, SPSS vers.10). Startle magnitude data were analysed with one way ANOVA. The Bonferroni test was used as a post-hoc test for multiple comparisons with $P<0.05$ as threshold for significant difference.

Results

Effects of pretreatment with clozapine or the association idazoxan/raclopride on PCP-induced disruption of PPI and startle magnitude

In this series of experiments the effects on PPI using several prepulse intensitites (3, 6 or 12 dB) of PCP, PCP after clozapine pretreatment and PCP after idazoxan/raclopride pretreatment were studied. Significant main effects for treatment groups and prepulse intensities, and treatment group×prepulse intensity interaction were found (treatment groups: $F=58.9$, $P<0.001$, $df=3$; prepulse intensity: $F=86.2$, $P<0.001$, $df=2$; treatment groups×prepulse intensity: $F=3.55$, $P=0.003$, $df=6$] (Fig. 1). Post-hoc Bonferroni's test showed that PCP treatment significantly disrupted PPI ($P<0.001$ versus saline treatment). This effect was partially reversed by clozapine pretreatment ($P<0.001$ versus saline or PCP treatments), but not by idazoxan/raclopride pretreatment (NS versus PCP treatment; $P<0.001$ versus saline treatment). The combination of idazoxan and raclopride pretreatment significantly ($P<0.001$ versus all other treatment groups) increased startle magnitude, whereas no significant effects on startle magnitude were produced by any other pharmacological manipulation (data not shown).

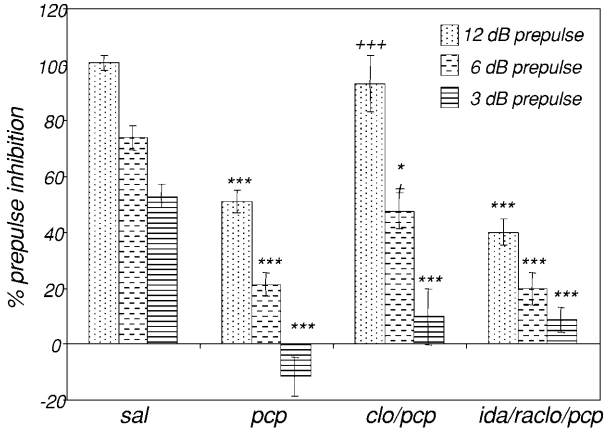

Fig. 1 Effects of clozapine (*clo*) or idazoxan/raclopride (*ida/raclo*) pretreatment on phencyclidine (*pcp*)-induced disruption of prepulse inhibition. Mean±SEM values are shown. Statistical analysis of PPI% at each prepulse intensity was performed by means of one way analysis of variance (ANOVA): 12 dB, $F=26.375$, $P<0.001$; 6 dB, $F=20.207$, $P<0.001$; 3 dB, $F=16.523$, $P<0.001$. Post-hoc analysis was performed by Bonferroni test for multiple comparisons: ***$P<0.001$, *$P<0.05$ versus saline-treated rats, +++$P<0.001$, +$P<0.05$ versus PCP-treated rats

In a separate experiment, the effects of saline or PCP on PPI were studied in the presence or absence of idazoxan pretreatment. In both cases, idazoxan pretreatment increased the startle magnitude but did not significantly alter PPI (not shown).

Effects of pretreatment with idazoxan and raclopride on apomorphine-induced disruption of PPI and startle magnitude

In this series of experiments, the effect of idazoxan pretreatment was studied on the capability of raclopride to reverse apomorphine-induced disruption of PPI. Several doses of raclopride as well as several prepulse intensities (3, 6 or 12 dB) were used. Significant main effects for treatment groups and prepulse intensities, but no significant treatment group×prepulse intensity interaction were found [treatment groups: $F=37.1$, $P<0.001$, $df=10$; prepulse intensity: $F=48.5$, $P<0.001$, $df=2$] (Fig. 2). Post-hoc Bonferroni's test showed that apomorphine treatment significantly disrupted PPI ($P<0.001$ versus saline treatment), while idazoxan pretreatment could not counteract apomorphine effect ($P<0.001$ versus saline, NS versus apomorphine treatment). All doses of raclopride could significantly ($P<0.001$ versus apomorphine treatment, NS versus saline treatment) counteract apomor-

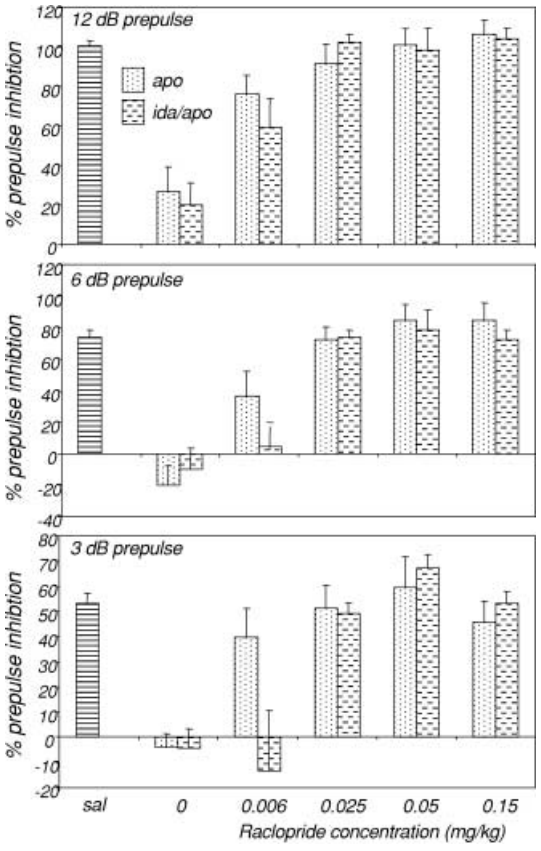

Fig. 2 Effects of idazoxan (*ida*) pretreatment on raclopride compensation of apomorphine-induced disruption of prepulse inhibition. Mean±SEM values are shown. Statistical analysis according to the general linear model univariate analysis of variance (ANOVA) using PPI values as dependent variable and treatment and prepulse amplitude as fixed factors, followed by Bonferroni test for multiple comparisons

phine-induced disruption of PPI. Idazoxan pretreatment did not modify raclopride effects, except at the lowest raclopride dose (0.006 mg/kg), where idazoxan pretreatment showed a trend towards a significant ($P<0.001$ versus saline treatment, $P=0.074$ versus apomorphine+raclopride 0.006 mg/kg, NS versus apomorphine or apomorphine/idazoxan treatment) attenuation of raclopride effect on apomorphine-induced PPI disruption. Thus, idazoxan did not show any positive effect on the antagonistic effect of a threshold dose of raclopride on apomorphine-induced PPI disruption.

One-way ANOVA followed by Bonferroni's test showed no significant change in startle magnitude for any single drug treatment in comparison with saline treatment. However, when comparing idazoxan/raclopride versus raclopride pretreatment groups, a significant ($P<0.034$) effect was observed (data not shown).

Discussion

The present data demonstrate that adding α_2-adrenoceptor blockade to a D_2 selective antagonist fails to reproduce the ability of clozapine to antagonize PCP-induced deficits in PPI, a paradigm of sensorimotor gating abnormalities, which currently appear to be the core of behavioral pathophysiology in the spectrum of schizophrenia-like disorders. In addition, the α_2-adrenoceptor antagonist idazoxan had no augmenting effect on the blockade of apomorphine-induced disruption of PPI by raclopride. Several important conclusions can be drawn from these results: first, the combined blockade of α_2 and D_2 receptors does not represent a critical component in the ability of clozapine to reverse sensorimotor gating abnormalities produced by PCP; second, in contrast to its enhancing effects in the CAR test (Hertel et al. 1999), α_2-blockade does not appear to enhance the potency of raclopride in reversing the apomorphine-induced disruption of PPI. The effects of concurrent α_2 and D_2 receptor antagonism on PPI can be dissociated from general effects on startle reactivity. In fact, an increase in startle magnitude was present whenever idazoxan alone or in combination was administered, irrespective of the fact that a change in PPI was detected or not. Therefore, a putative idazoxan-induced autonomic arousal seems to be neither a sufficient nor a necessary condition for changes in PPI. Taken together, these results indicate that the interpretation of the data and the hypothesis put forward by Hertel et al. could ultimately be an oversimplification, since the combination of the two compounds does not mimic the specific atypical profile of clozapine observed in PCP-induced disruption of PPI, presently the only behavioral preclinical test recognized to make potentially important distinctions between "typical" and "atypical" antipsychotics.

Capitalising on the data of Hertel et al. (1999), Lindström (2000), in a high-impact commentary, proposed that the combination of a "typical" antipsychotic with an α_2-adrenoceptor antagonist might represent a treatment strategy in many cases. It must be underlined, however, that the significance itself of augmentation strategies remains to be clarified, given the weakness of most of the pertinent studies which are open-label and uncontrolled clinical trials (Lindenmayer 2000). In preclinical studies with the CAR test, on the other hand, an adjunctive antipsychotic potential has been found for a variety of combinations of drugs acting at other brain neurotransmitter receptors in addition to DA D_2 receptor blockade (Wadenberg and Hicks 1999). This includes α_2-adrenoceptor antagonists (Hertel et al. 1999), 5-HT receptor antagonists (Wadenberg and Ahlenius 1991; Prinssen et al. 1996; Wadenberg et al. 1996, 1998) or α_1-adrenoceptor antagonists (Wadenberg and Hicks 1999).

The present data clearly failed to support the heuristic value of knowledge on antipsychotic potential or augmentation derived from the CAR experiment. This apparent discrepancy, at least in part, may be explained by differences in face validity and predictive validity between the CAR test and the PPI paradigm. Unlike the CAR test, the PPI paradigm shows face validity, since PCP and apomorphine-induced startle gating deficits in

rats mimic the abnormalities of gating that are thought to underlie sensory flooding and cognitive fragmentation in the spectrum of schizophrenia (McGhie and Chapman 1961; Swerdlow et al. 1994; Swerdlow and Geyer 1998; Braff et al. 2001). In addition, the predictive validity of the CAR test for the detection of atypical antipsychotic potential has been challenged, because the CAR behavior, like positive symptoms, but unlike negative symptoms, is inhibited by all antipsychotics (Arnt 1982). In this regard it is worth mentioning that clozapine is superior to "typical" antipsychotics in normalizing PPI in patients with schizophrenia (Kumari et al. 1999), and that in the experimental setting, the loss of PPI in PCP-treated rats can be preferentially reversed not only by clozapine (Bakshi et al. 1994) but also by olanzapine (Bakshi and Geyer 1995) and quetiapine (Swerdlow et al. 1996).

Most relevant to the discussion of the present paper, clozapine indeed affects a great variety of receptors, and mechanisms other than a combined antagonism of a non-DA receptor and DA D_2 receptor blockade have been proposed to generate its unique antipsychotic profile. One interesting mechanism, that deserves further investigation, could even involve DA agonist-like properties. A number of behavioral experiments indicated, in fact, that clozapine may exert partial agonistic effects at both D_1 and D_2 receptors (Jackson et al. 1995, 1998; Salmi et al. 1996). Another intriguing hypothesis is based on the fact that clozapine exerts a unique selective agonistic property at the muscarinic M_4 receptor, while inhibiting all the other muscarinic receptors (Zorn et al. 1994). The potential relevance of the cholinergic agonistic profile to atypical antipsychotic action may find support in the recent observation that drugs enhancing central cholinergic transmission substantially reduce psychotic-like features in Lewy body dementia (McKeith et al. 2000).

A consistent number of laboratory and neuroimaging clinical experiments, on the other hand, tend to support an alternative hypothesis; that the single most powerful predictor of atypical antipsychotic activity is the fast dissociation from the DA D_2 receptor, without any relevant contribution of other receptors (Kapur and Seeman 2001). Indeed, clozapine has a more rapid and transient D_2 occupancy than "typical" antipsychotics and it is hypothesized that repeated transient blockade at D_2 receptor sites, also dependent on endogenous DA levels, drives atypicality in a manner that allows appropriate modulation of the DA system (Saller and Salama 1993; Kapur and Seeman 2001). However, according to the same authors, this hypothesis does not imply that partial agonistic properties or action at other receptors cannot make relevant contributions to the added efficacy of clozapine in the treatment of refractory symptoms (Kapur and Seeman 2001).

In conclusion, challenging the hypothesis that simple α_2/D_2 blockade is sufficient to produce clozapine-like "atypical" antipsychotic activities, the results presented in this work indicate that combining idazoxan, a specific α_2-adrenoceptor antagonist, with raclopride, a selective $D_{2/3}$ receptor antagonist, does not mimic the abilities of clozapine to reverse PCP-induced disruption of PPI and fails to show an augmentation effect in the animal model of deficient sensorimotor gating produced by apomorphine. Insights drawn from our results may help to consider the need to design new experimental pharmacological protocols in order to improve the development of strategies in antipsychotic treatment.

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