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Blockade of phencyclidine-induced hyperlocomotion by clozapine and MDL 100,907 in rats reflects antagonism of 5-HT_{2A} receptors

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Abstract

Whereas haloperidol more potently blocked the locomotion elicited by amphetamine (2.5 mg/kg i.p.) than that elicited by phencyclidine (PCP) (20.0 mg/kg s.c.), with inhibitory $dose_{50}$s of 0.04 and 0.09 mg/kg s.c., respectively, clozapine more potently blocked the effect of PCP (0.04) than of amphetamine (8.8). Similarly, risperidone more potently blocked PCP (0.002) than amphetamine (0.2). In analogy to haloperidol, the selective dopamine D_2 receptor antagonist, raclopride, antagonised amphetamine (0.16) more potently than PCP (0.8) whereas the selective 5-HT_{2A} receptor antagonist, [$R(+)$-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol] (MDL 100,907), only antagonised PCP (0.001) as compared to amphetamine (> 10.0). The potency for inhibition of PCP correlated more highly to affinity at 5-HT_{2A} ($r = 0.97$, $P < 0.01$) than dopamine D_2 (0.57, $P > 0.05$) sites, while the potency for blockade of amphetamine correlated more highly with affinity at dopamine D_2 (0.94, $P < 0.01$) than at 5-HT_{2A} sites (0.37, $P > 0.05$). In conclusion, in contrast to amphetamine, induction of locomotion by PCP is dependent upon functional 5-HT_{2A} receptors, antagonism of which by 'atypical' antipsychotics underlies their ability to inhibit PCP-induced locomotion.

Keywords: 5-HT_{2A} receptor; Phencyclidine; Clozapine

Although antagonism of the actions of amphetamine is widely employed for the detection of antipsychotic activity, phencyclidine (PCP) is considered a more faithful model of schizophrenia as it reproduces both its positive and negative symptoms in man (Ögren and Goldstein, 1994). Whereas the motor actions of amphetamine are mediated primarily by dopaminergic mechanisms, there is evidence for an involvement of both dopaminergic and serotoninergic (5-HT_{2A}) mechanisms in the actions of PCP (Nabeshima et al., 1988). Further, the improved antipsychotic profile of atypical antipsychotics such as clozapine and risperidone, as compared to haloperidol, has been attributed to their higher activity at 5-HT_{2A} sites (Meltzer and Nash, 1991). Here, we examined the influence on PCP-as compared to amphetamine-induced hyperlocomotion of clozapine, risperidone and haloperidol. In addition, we examined the actions of [$R(+)$-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol] (MDL 100,907) and raclopride, selective antagonists at 5-HT_{2A} and dopamine D_2 receptors, respectively (Ögren and Goldstein, 1994).

Male Wistar rats weighing 250–350 g (Iffa Credo, Illskirchen, France) were used. The drugs were dissolved in distilled water and administered s.c. The rats were pre-treated with drug and placed in individual cages. Thirty minutes later, animals were challenged with amphetamine (2.5 mg/kg i.p.) or PCP (20 mg/kg s.c.) and the cages were placed in activity chambers (Lablink system, Coulbourn, USA). These were equipped with two infrared beams placed 24 cm apart and 4 cm from the floor. The consecutive interruption of two beams within 3 s was counted as a movement (ambulation), which was recorded over 60 min.

Amphetamine (0.16–2.5) and PCP (0.63–20.0) dose dependently elicited hyperlocomotion and the doses of 2.5 and 20.0, respectively, were selected as they induced equivalent hyperactivity with counts of 33 ± 7 ($n = 6$), 348 ± 49 ($n = 8$) and 285 ± 32 ($n = 7$), for saline, amphetamine and PCP, respectively: $F(2,19) = 19.2$, $P < 0.001$. Haloperidol more potently blocked

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amphetamine-than PCP-induced locomotion, whereas clozapine and risperidone more potently blocked the PCP effect (Fig. 1). While raclopride was more potent against amphetamine, MDL 100,907 more potently antagonised PCP. Correlation coefficients were more marked between potency for inhibition of PCP and affinity at 5-HT_{2A} than dopamine D_2 sites (Fig. 1). In contrast, antagonism of amphetamine was more powerfully correlated to affinity at dopamine D_2 than 5-HT_{2A} sites (Fig. 1).

An inhibitory influence of (high doses of) risperidone upon the locomotion elicited by PCP in rats, as well as an inhibitory influence of clozapine upon PCP-induced locomotion in mice, has been previously reported (Jackson et al., 1994; Kitaichi et al., 1994). However, the current study revealed, in a direct comparison, that clozapine and risperidone can be distinguished from haloperidol as they preferentially block (with remarkable potency) PCP-as compared to amphetamine-induced locomotion, respectively. The pre-

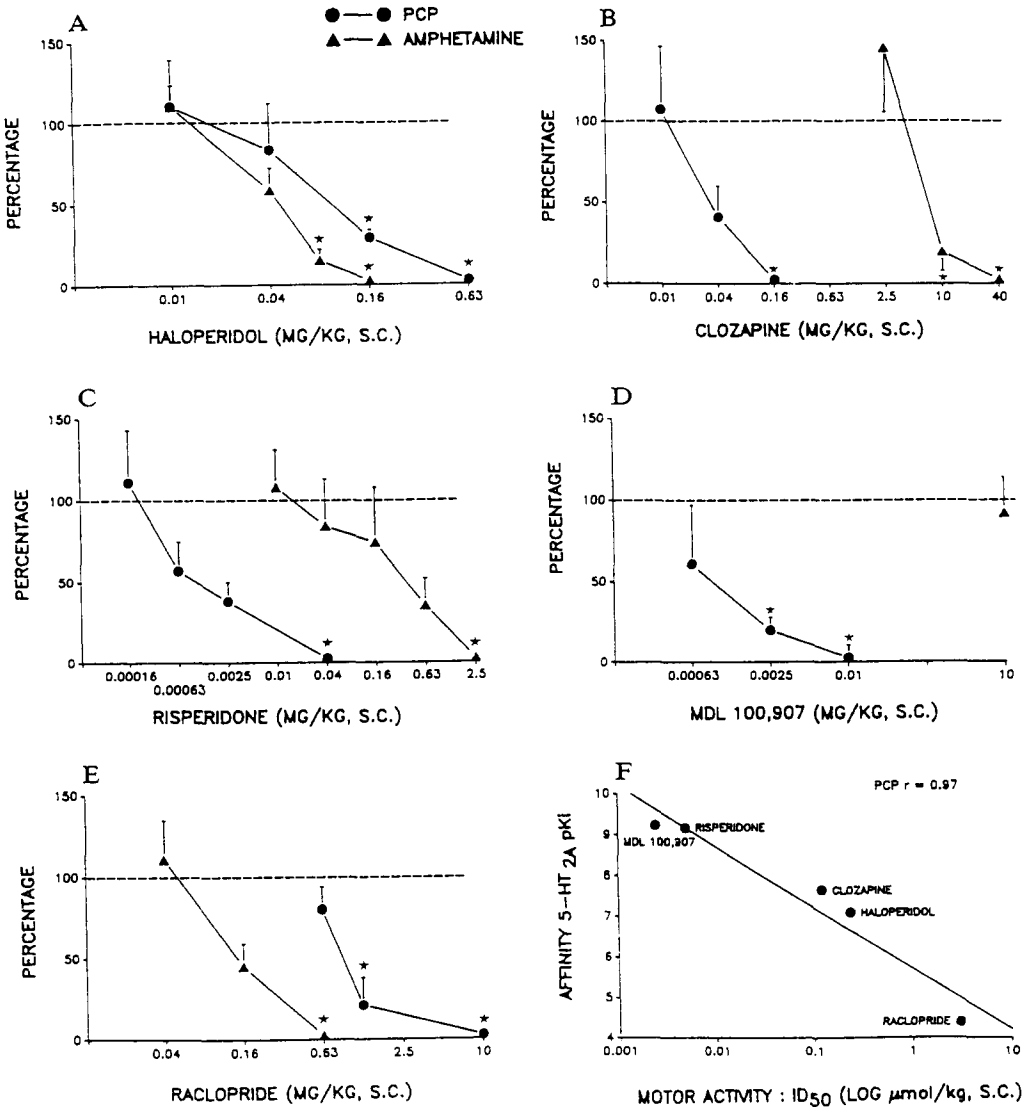

Fig. 1. Influence of antipsychotic drugs on the induction of hyperlocomotion by PCP as compared to amphetamine. The broken line corresponds to ambulation counts in control, vehicle-treated rats. These values were highly consistent and (typical) control values for panel A were 290 ± 29 and 266 ± 38 for amphetamine and PCP, respectively. For panels A–E, the data are means ± S.E.M. $n > 5$ per value. Amphetamine: haloperidol, $F(4,67) = 13.4$, $P < 0.01$; clozapine, $F(3,62) = 8.3$, $P < 0.05$; risperidone, $F(5,46) = 4.6$, $P < 0.01$ and raclopride, $F(3,64) = 11.0$, $P < 0.01$. PCP: haloperidol, $F(4,41) = 9.1$, $P < 0.01$; clozapine, $F(3,27) = 8.2$, $P < 0.01$; risperidone, $F(3,22) = 6.2$, $P > 0.01$; MDL 100,907, $F(3,17) = 15.8$, $P > 0.01$ and raclopride, $F(3,30) = 17.1$, $P < 0.01$. Asterisks indicate significance of differences from vehicle in Dunnett's test; $^*P < 0.05$. Inhibitory $dose_{50}$s (95% confidence limits). Amphetamine: haloperidol, 0.04 (0.03–0.06); clozapine, 8.8 (6.4–12.1); risperidone, 0.2 (0.1–0.4) and raclopride, 0.16 (0.1–0.2). PCP: haloperidol, 0.09 (0.06–0.14); clozapine, 0.04 (0.02–0.08); risperidone, 0.002 (0.0008–0.007); raclopride, 0.8 (0.5–1.4) and MDL 100,907, 0.0009 (0.0003–0.003). For panel F, correlation analyses are for inhibition of PCP-induced locomotion. The 'r' value to D_2 sites was 0.57 ($P > 0.05$). Correlation coefficients for inhibition of amphetamine-induced locomotion were 0.94 ($P < 0.05$) and 0.37 ($P > 0.05$) for D_2 and 5-HT_{2A} affinities, respectively (affinities are from V. Audinot, unpublished observations).

sent data also suggest a *mechanistic* basis for the inhibition of PCP in terms of involvement of 5-HT_{2A} receptors. This is clearly indicated in the antagonism of PCP by the highly selective 5-HT_{2A} receptor antagonist, MDL 100,907, a putative atypical antipsychotic (Schreiber et al., 1994). The potency of MDL 100,907 was close to that required for blocking two further behavioural responses mediated by 5-HT_{2A} sites: induction of head-twitches (0.005 mg/kg s.c.) and of a drug discriminative stimulus (0.0006 mg/kg s.c.), by the 5-HT_{2A} receptor agonist, [1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane] (DOI) (Schreiber et al., 1994). Further, the potency to block PCP correlated very highly to the affinity at 5-HT_{2A} but not D_2 sites (Fig. 1). Blockade of PCP-induced locomotion by clozapine and risperidone thus reflects antagonist actions at 5-HT_{2A} receptors. In contrast, in line with results of studies suggesting an involvement of mesolimbic dopamine D_2 receptors in the hyperlocomotion provoked by amphetamine, amphetamine-induced locomotion was potently antagonised by the selective D_2 antagonist raclopride (Jackson et al., 1994; Moore and Kenyon, 1994). Further, there was a good correlation between drug affinity at D_2 sites and potency for blockade of amphetamine.

It has been suggested that certain of the behavioural actions of PCP may be related to an allosteric modulation of activity at 5-HT_{2A} receptors, whereas other actions may depend upon the release of 5-HT (Hernandez et al., 1988; Nabeshima et al., 1988). PCP possessed low affinity at rat 5-HT_{2A} sites ($pK_i < 5.0$) and did not occupy central 5-HT_{2A} receptors under ex vivo conditions (Audinot, V., unpublished observation). Further, in dialysis studies, PCP increases the release of 5-HT in the accumbens (Hernandez et al., 1988; Maurel-Remy, S., unpublished observation). In addition, lesions of serotoninergic terminals in the nucleus accumbens abolish PCP-induced locomotion, while microinjection of PCP in the nucleus accumbens elicits hyperlocomotion (Maurel-Remy, S., unpublished observation). These observations suggest that an indirect activation of 5-HT_{2A} receptors via the release of accumbens 5-HT may be involved in the induction of locomotion by PCP. Although PCP behaves as a non-competitive antagonist at the ion channel coupled to NMDA receptors, and as a further blocker of this channel, dizoicipine, also elicits locomotion (Ögren and Goldstein, 1994), a role of these sites seems unlikely. Thus, dizolcipine-induced locomotion is expressed via mechanisms different from those underlying PCP-induced locomotion, and the action of dizolcipine is insensitive to MDL 100,907 and clozapine (Ögren and Goldstein, 1994; Maurel-Remy, S., unpublished observation). Finally, the present data do *not* exclude a role of dopaminergic mechanisms in the induction of locomotion by PCP (Jackson et al., 1994) and it remains to be seen whether activation of 5-HT_{2A} sites is sufficient, as well as necessary, for the locomotor action of PCP. Further, an evaluation of other doses of PCP would be of interest.

In conclusion, these data distinguish the locomotion elicited by PCP (20.0 mg/kg s.c.) and by amphetamine (2.5 mg/kg i.p.) based on their dependence on functionally intact 5-HT_{2A}, as compared to dopamine D_2, receptors, respectively. Correspondingly, the action of PCP is potently antagonised by atypical antipsychotics possessing marked activity at 5-HT_{2A} receptors. Comparison of PCP-to amphetamine-induced locomotion may provide a model for the detection of novel antipsychotic drugs. Finally, the present data reinforce the hypothesis that blockade of 5-HT_{2A} receptors contributes to the distinctive profile of atypical antipsychotic agents.

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