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European Journal of Pharmacology 347 (1998) R1–R3

ejp

Rapid communication

# Atypical antipsychotic-like effects of the dopamine $D_3$ receptor agonist, (+)-PD 128,907 [1]

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Received 26 February 1998; accepted 27 February 1998

**Abstract**

Anti-schizophrenia agents with improved efficacy and side-effect profiles are required. A dopamine $D_3$ receptor agonist, *R*-(+)-trans-3,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-b]-1,4-oxazin-9-ol HCl ((+)-PD 128,907), displayed an atypical antipsychotic profile comparable to that of clozapine. (+)-PD 128,907 blocked stereotypy produced by dizocilpine (MK-801) at 12-fold lower doses than those affecting apomorphine-induced stereotypes in mice and did not produce catalepsy. These effects of (+)-PD 128,907 were stereospecific and were blocked by a $D_3$ antagonist. These data suggest a role for $D_3$ receptors in antipsychotic drug action. Published by Elsevier Science B.V.

*Keywords:* Dopamine $D_3$ receptor; Antipsychotic; (+)-PD 128,907

Pharmacological management of schizophrenia, a disorder affecting about 1% of the general population, is not well-advanced. Typical antipsychotics, like haloperidol, do not affect negative or cognitive symptoms and tend to produce chronic neurological sequelae upon repeated use. The atypical agent clozapine, while affecting a broader range of schizophrenic symptoms without inducing motor disorders, can result in lethal states of agranulocytosis. Although it is generally thought that antipsychotic agents act by functional blockade of dopamine receptors, the specific receptor subtype(s) mediating their antipsychotic effects have not been identified (Gerlach and Casey, 1996).

The localization of $D_3$ receptors in limbic brain structures underlying emotionality and their functional role as autoreceptors regulating the synthesis and release of dopamine (Gobert et al., 1995) has suggested that $D_3$ receptors may play a role in schizophrenia (Griffon et al., 1995; Sokoloff and Schwartz, 1995). Although research tools to investigate the function of $D_3$ receptors are imperfect, *R*-(+)-trans-3,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-b]-1,4-oxazin-9-ol HCl ((+)-PD 128,907) is the most selective $D_3$ receptor agonist presently available. (+)-PD 128,907 binds with high affinity to $D_3$ receptors, demonstrates at least an 18- to 200-fold selectivity over other dopamine receptor subtypes and does not bind with significant affinity to non-dopaminergic receptors (Pugsley et al., 1995; Sokoloff and Schwartz, 1995). In the present experiments, effects of (+)-PD 128,907 were compared to those produced by the atypical antipsychotic clozapine and the typical antipsychotic haloperidol. We now report the first evidence that (+)-PD 128,907 has the pharmacological profile of an atypical antipsychotic.

The blockade of stereotyped behaviors has long been employed as a preclinical model of antipsychotic drug efficacy (Hoffman, 1992; Gerlach and Casey, 1996). We used the stereotyped behaviors induced by the dopamine receptor agonist, apomorphine, and the *N*-methyl-D-aspartate (NMDA) antagonist, dizocilpine, to differentiate the

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[1] Animals used in these studies were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). In conducting the research described in this report, the investigators adhered to the 'Guide for the Care and Use of Laboratory Animals', as promulgated by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

0014-2999/98/$19.00 Published by Elsevier Science B.V.

effects of haloperidol from those of clozapine and (+)-PD 128,907. Haloperidol potently inhibited apomorphine-induced gnawing (Fig. 1a, open circles) with an $ED_{50}$ of 0.07 mg/kg (95% confidence limits: 0.05–0.09) but blocked dizocilpine-induced forepaw treading (filled circles) only at a dose of 3 mg/kg ($ED_{50}$: 0.72 mg/kg; 95% conf. limits: 0.31–1.64). In contrast, clozapine blocked dizocilpine-induced stereotypy (Fig. 1b) ($ED_{50}$: 0.90 mg/kg; 95% conf. limits: 0.41–1.9) at significantly lower doses than those required to block apomorphine-induced stereotypy ($ED_{50}$: 5.7 mg/kg; 95% conf. limits: 3.7–9.0). Like clozapine, (+)-PD 128,907 blocked dizocilpine-induced stereotypy ($ED_{50}$: 0.96 mg/kg; 95% conf. limits: 0.37–2.5) (Fig. 1c) at lower doses than required to block stereotypy induced by apomorphine ($ED_{50}$: 11.2 mg/kg; 95% conf. limits: 0.02–59.4). The dizocilpine-blocking effect of (+)-PD 128,907 was stereospecific as its enantiomer ($K_i$ at $D_3$ receptors > 2000 nM) was devoid of effect up to a dose of 100 mg/kg. NGB 2900 (*N*-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyl}-2-antrhacenecarboxamide HCl) is a highly selective $D_3$ receptor antagonist with a 1500-fold selectivity over $D_2$ receptors ($D_3$ = 0.69 nM; $D_2$ = 1089 nM; $D_4$ = 4276 nM; $D_1$, $D_5$ > 10 000 nM; $5HT_{1A}$ = 786 nM; $5HT_2$ = 548 nM). NGB 2900 dose-dependently reversed the inhibition of dizocilpine-induced stereotypy produced by (+)-PD 128,907 (Fig. 1d). This is the first report on the selective binding of this novel $D_3$ receptor antagonist and its ability to block effects of a $D_3$ receptor agonist.

Catalepsy, a preclinical predictor of extrapyramidal side-effects (Gerlach and Casey, 1996), was evaluated by placing the forepaws of mice upon a 2-mm diameter wire suspended 5 cm above the floor. Mice remaining on the wire for ≥ 30 s were considered cataleptic.Haloperidol produced catalepsy at the doses required to block stereotypy induced by dizocilpine ($ED_{50}$: 1.7 mg/kg; 95% conf. limits: 1.1–2.9). Around 81% (13/16) of the mice were cataleptic at 3 mg/kg haloperidol. Neither clozapine (30 mg/kg) nor (+)-PD 128,907 (100 mg/kg) produced catalepsy.

$D_3$ receptors are implicated in the pharmacological effects of (+)-PD 128,907 presented above. (+)-PD 128,907 demonstrated stereospecificity. Consistent with the negligible affinity of its enantiomer, the (+)- but not the (−)-isomer of PD 128,907 was active in blocking dizocilpine stereotypy. Further, a selective $D_3$ receptor

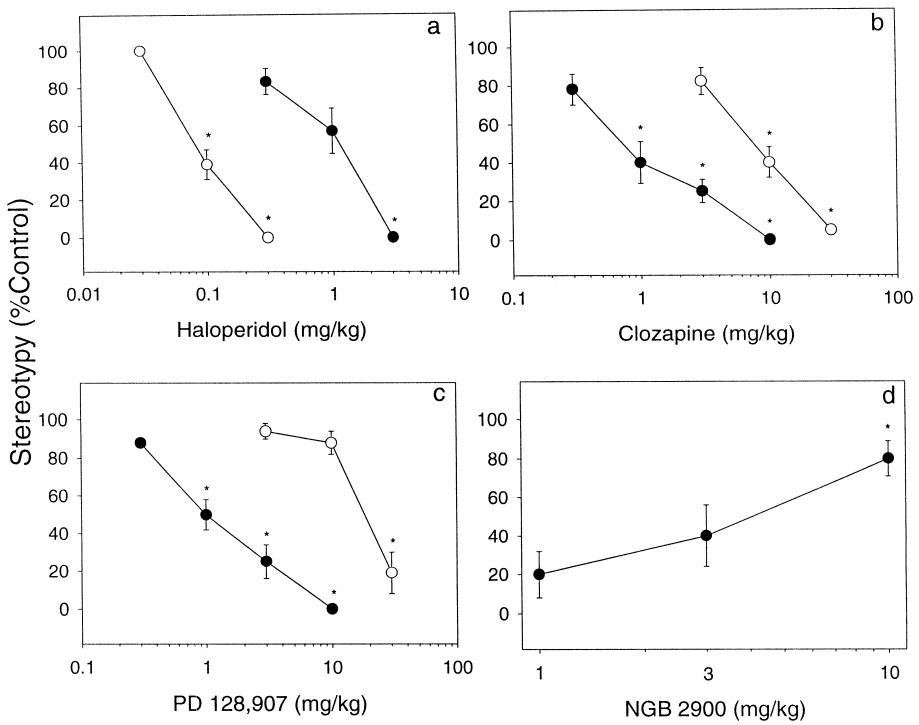


Fig. 1. (a–c) Comparison of effects of haloperidol, clozapine and (+)-PD 128,907 on apomorphine-induced stereotyped gnawing (○) or dizocilpine-induced stereotyped forepaw treading (●). Gnawing was assessed in wire-mesh cages (1 cm mesh, 15 × 15 × 26 cm high) in Swiss Webster mice (Taconic Farms, Germantown, NY). Forepaw treading was observed in clear Plexiglas chambers (14 × 25 × 36 cm high). Drugs were given i.p. in conjunction with either apomorphine (10 mg/kg i.p.) or dizocilpine (0.3 mg/kg s.c.). Mice were scored for the presence or absence of the stereotypy over 5 min, 30 min post injection. Data are means ± S.E.M. of three experiments ($n$ = 12). Control values were 93 ± 2.1% (apomorphine) and 92 ± 1.4% (dizocilpine). * denotes effects significantly different from control, Fisher's Exact Probability test ($P < 0.05$). (d) The $D_3$ receptor antagonist, NGB 2900, dose-dependently reversed the inhibition by (+)-PD 128,907 of the stereotyped forepaw treading produced by dizocilpine. Dizocilpine (0.3 mg/kg s.c.), 3 mg/kg (+)-PD 128,907 (i.p.) and NGB 2990 (s.c.) were given 30 min prior to behavioral evaluation. Control experiments in the absence of NGB 2900 confirmed the dizocilpine blocking effects of (+)-PD 128,907 (3 mg/kg) which reduced dizocilpine-induced forepaw treading from 94 ± 2.1% to 20.0 ± 8.6% ($P < 0.05$). Other details as in panels (a–c).

antagonist, NGB 2900, blocked the effects of (+)-PD 128,907.

The present findings are the first to document an antipsychotic pharmacological profile for a $D_3$ receptor ligand. The fact that no catalepsy was produced by (+)-PD 128,907 suggests that, like clozapine (Gerlach and Casey, 1996), (+)-PD 128,907 may demonstrate a low propensity for the induction of extrapyramidal side-effects. These results encourage research into the discovery and evaluation of $D_3$ receptor agonists for the pharmacological management of schizophrenia. A potential role for dopamine agonists in the treatment of schizophrenia has been suggested (Benkert et al., 1995; Gerlach and Casey, 1996). The ability of both clozapine and (+)-PD 128,907 to block dizocilpine-induced stereotypy suggests that a common mechanism for these preclinical findings may be through the dynamic interplay between dopaminergic and glutamatergic neuronal pathways. Such a mechanism is in alignment with the hypothesis that NMDA receptor hypofunction and its impact upon dopaminergic transmission in corticolimbic structures underlies the clinical and pathophysiological symptoms of schizophrenia (Olney and Farber, 1995). The dizocilpine blocking effects of clozapine and (+)-PD 128,907 provide further confirmation that this animal model may be useful for the evaluation of novel antipsychotic agents with improved efficacies and side-effect profiles (cf., Hoffman, 1992). Further, the ability of (+)-PD 128,907 to block dizocilpine-induced stereotypy implicates $D_3$ receptors as targets for agents that may be useful in the modulation of effects (e.g., abuse, toxicity) of phencyclidine (PCP), another blocker of the NMDA-receptor ion channel.

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