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The dopamine D_3 receptor antagonist, (+)-S 14297, blocks the cataleptic properties of haloperidol in rats

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Abstract

In contrast to haloperidol, the selective dopamine D_3 receptor antagonist, (+)-S 11566 {(±)-[7-(*N*,*N*-dipropylamino)-5,6,7,8-tetrahydro-naphtho(2,3*b*)dihydro,2,3-furane]} and its active isomer, (+)-S 14297, induced neither catalepsy nor reduced conditioned avoidance responses in rats. (+)-S 11566 and (+)-S 14297 did, however, dose-dependently abolish the cataleptic actions of haloperidol. This action was expressed stereospecifically inasmuch as (−)-S 17777, the inactive distomer of (+)-S 14297, was ineffective. Further, the influence of haloperidol upon conditioned avoidance responses was not affected by (+)-S 14297. These data suggest that blockade of dopamine D_3 receptors may inhibit the extrapyramidal but not – as based on the conditioned avoidance response paradigm – antipsychotic actions of neuroleptics.

Keywords: Antipsychotic; Dopamine D_3 receptor; Catalepsy

Dopamine D_3 receptors differ to their D_2 counterparts in that they are more densely localized in limbic as compared to striatal tissues of rats and man (see Sautel et al., 1995). Further, although dopamine D_3 receptors and (tonically active) dopamine D_2 receptors may both function as inhibitory autoreceptors on dopaminergic neurones (Gobert et al., 1995), postsynaptic dopamine D_3 and D_2 receptors fulfill contrasting functional roles and may differentially affect motor behaviour. Thus, activation and blockade of dopamine D_3 receptor sites inhibits and stimulates motor behaviour, respectively, a pattern of actions opposite to that of dopamine D_2 receptors (Sautel et al., 1995; Waters et al., 1993). Indeed, mice lacking dopamine D_2 receptors display catalepsy-like behaviour whereas mice lacking dopamine D_3 receptors are hyperactive (Accili et al., 1996; Baik et al., 1995). These observations suggest that selective dopamine D_3 receptor antagonists may display a low potential for extrapyramidal side-effects in man. However, it has not, as yet, been evaluated whether blockade of dopamine D_3 receptors can modify the extrapyramidal (and/or antipsychotic) actions of neuroleptics such as haloperidol, which possesses a modest (approx. 6-fold) preference for dopamine D_2 receptors (Millan et al., 1995). In the present study, we addressed this issue employing the selective dopamine D_3 receptor antagonist, (+)-S 11566 {[7-(*N*,*N*-dipropylamino)-5,6,7,8-tetrahydro-naphtho(2,3*b*)dihydro,2,3-furane]} and its active eutomer, (+)-S 14297, in rats.

As previously (Millan et al., 1995), catalepsy was measured in male Wistar rats of 200–250 g by determining the duration of time they remained in a position with the hind paws placed over the ipsilateral front paws. The cut-off was 30 s and the mean of three determinations (separated by 1 min) was taken. The number of conditioned avoidance responses (max 10) was measured in trained rats during a 10-trial session in a two-compartment shuttle-box. A 30-s interval separated each trial from the next. Each trial consisted of a 10-s period (maximal duration) with the conditioning stimulus light on, followed or not, by a 5-s period (maximal duration) with electric shock (560 μA) through the grid floor depending upon the response of the animal to the stimulus light. The trial terminated once the rat had moved into the other compartment, either during

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the stimulus light-on period (avoidance response) or during the shock period (escape response). Drugs were dissolved in sterile water and injected s.c. 60 min before testing. In the antagonist studies, haloperidol was given 30 min pretesting. Doses are in terms of the base.

Haloperidol induced catalepsy with an effective dose$_{50}$ (95% confidence limits) of 0.15 (0.05–0.38) mg/kg, s.c. (+)-S 11566 and (+)-S 14297, up to 20.0 mg/kg, s.c., were inactive (Fig. 1 and not shown). Haloperidol reduced conditioned avoidance responses with an inhibitory dose$_{50}$ (95% confidence limits) of 0.08 (0.04–0.16) mg/kg, s.c. (+)-S 11566 and (+)-S 14297, up to 20.0 mg/kg, were ineffective (Fig. 1 and not shown). However, they blocked the cataleptic action of haloperidol (Fig. 1). In contrast, (−)-S 17777, the inactive distomer of (+)-S 14297, was ineffective (Fig. 1). In the presence of (+)-S 14297, the dose-response curve for haloperidol-induced catalepsy was displaced to the right. In distinction, (+)-S 14297 did not modify the dose-response curve for haloperidol in the conditioned avoidance response procedure (Fig. 1).

The present observation that (+)-S 11566, and its active eutomer, (+)-S 14297, do not block conditioned avoidance responses in the rat suggests that selective blockade of dopamine D_3 receptors is not effective in classic models for the prediction of antipsychotic (antiproductive) activity. Nevertheless, clinical studies of the influence of dopamine D_3 receptor antagonists upon the positive, deficit and cognitive symptoms of schizophrenia will be required before their potential utility can be fully assessed. Although (+)-S 11566 and (+)-S 14297 did not modify the antipsychotic properties of haloperidol in the conditioned avoidance response procedure, they abolished its ability to induce catalepsy. Inasmuch as this interaction was specific to catalepsy, pharmacokinetic factors are unlikely to be involved. Thus, these anticataleptic actions of (+)-S 11566 and (+)-S 14297 likely reflect the opposite control of motor behaviour by postsynaptic dopamine D_3 versus D_2 receptors (Accili et al., 1996; Baik et al., 1995; Waters et al., 1993). Several other theoretical interpretations should, nevertheless, be briefly considered. First, inasmuch as inhibitory dopamine D_3 autoreceptors control postsynaptic dopamine release, (+)-S 14297 might counter haloperidol-induced catalepsy by enhancing dopamine release. However, dopamine D_3 autoreceptors are not tonically active and (+)-S 14297 does not increase extracellular levels of dopamine in the striatum or other tissues (Gobert et al., 1995). Second, muscarinic antagonists can inhibit neuroleptic-induced catalepsy (Lieberman, 1993) and (+)-S 14297 possesses weak – 20-fold lower than at dopamine D_3 receptors – affinity at muscarinic receptors. However, the action of (+)-S 14297 against haloperidol-induced catalepsy was expressed stereospecifically. Further, (+)-S 14297 does not manifest anticholinergic properties in vivo at the doses used herein, while an additional dopamine D_3 receptor antagonist, U 99194 (5,6-dimethoxy-indan-2-yl) dipropylamine (Waters et al., 1993),

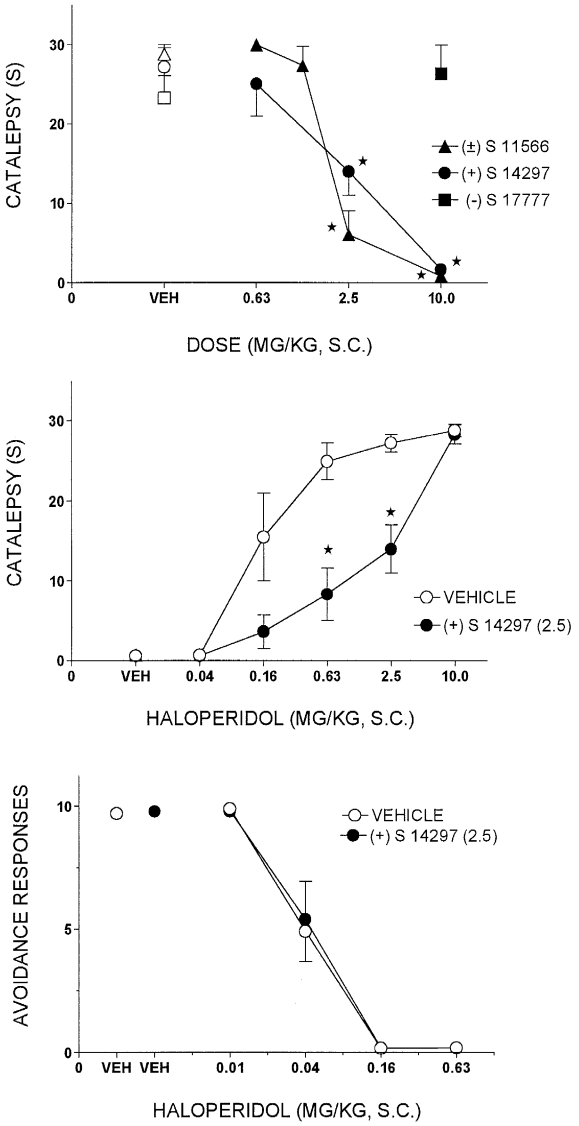

Fig. 1. Influence of the selective dopamine D_3 receptor antagonist, (+)-S 11566, and its active eutomer, (+)-S 14297, as compared to its inactive distomer, (−)-S 17777, upon the cataleptic and antipsychotic properties of haloperidol in rats. Upper panel: Reduction of haloperidol-induced catalepsy by (±)-S 11506 and (+)-S 14297. Middle panel: Displacement of the dose-response for haloperidol-induced catalepsy to the right by (+)-S 14297. Lower panel: Lack of influence of (+)-S 14297 upon the dose-response curve for haloperidol in the conditioned avoidance procedure. ANOVA as follows. Upper panel: (±)-S 11566, $F(4,25) = 34.4$, $P < 0.001$ and (+)-S 14297, $F(3,34) = 17.1$, $P < 0.01$. For (−)-S 17777, $P > 0.05$ in Student's two-tailed *t*-test. Middle panel: Influence of haloperidol, $F(4,55) = 28.4$, $P < 0.001$; influence of (+)-S 14297, $F(1,55) = 35.3$, $P < 0.001$ and interaction, $F(4,55) = 3.5$, $P > 0.01$. The slopes were 37.8 and 35.9 in the presence of vehicle and S 14297, respectively. Lower panel: Influence of haloperidol, $F(3,52) = 78.6$, $P < 0.001$; influence of (+)-S 14297, $F(1,52) = 0.2$, $P > 0.05$ and interaction, $F(3,52) = 0.1$, $P > 0.05$. The slopes were 82.3 and 81.3 in the presence of vehicle and (+)-S 14297, respectively. Asterisks indicate significance of differences between (+)-S 14297 and corresponding vehicle values in Dunnett's test ($P < 0.05$).

which is devoid of affinity at muscarinic sites, likewise inhibits haloperidol-induced catalepsy (unpublished observations). Third, haloperidol might elicit catalepsy by acting as an inverse agonist at dopamine D_2 receptors whereas (+)-S 14297 might be acting as a neutral antagonist (Nilsson et al., 1996). However, this theory cannot accommodate the observation that mice with null mutations of the dopamine D_2 receptor gene display catalepsy (Baik et al., 1995). Further, (+)-S 14297 shows no antagonist properties at dopamine D_2 receptors in the conditioned avoidance response test or in other in vivo models over the dose range employed herein (Fig. 1, Millan et al., 1995).

Collectively, thus, blockade of haloperidol-induced catalepsy likely reflects the opposite influence of postsynaptic dopamine D_3 versus D_2 receptors upon motor behaviour, actions presumably mediated in the striatum. In contrast, in models of antipsychotic activity, mediated in limbic structures, dopamine D_3 receptor blockade does not interfere with the actions of dopamine D_2 receptor antagonism (Sautel et al., 1995; Waters et al., 1993). This conclusion, based upon results in the conditioned avoidance response procedure, would clearly be of interest to extend to other models of antipsychotic activity. In this light, it is of note that, in mice, (+)-S 14297 likewise does not interfere with the inhibition of apomorphine-induced climbing by haloperidol (unpublished observation).

In conclusion, selective antagonism of dopamine D_3 receptors by (+)-S 14297 interferes with the cataleptic but not, as based on the conditioned avoidance response paradigm, antipsychotic properties of the neuroleptic, haloperidol, in rats. These findings suggest that it may be possible to optimize ratios of dopamine D_3 to D_2 receptor blockade whereby the therapeutic actions of antipsychotic drugs would be maintained, yet their extrapyramidal actions minimized.

References

Accili, D., Fishburn, C.S., Drago, J., Steiner, H., Lachowicz, J.E., Park, B.-H., Gauda, E.B., Lee, E.J., Cool, M.H., Sibley, D.R., Gerfen, C.R., Westphal, H., Fuchs, S., 1996. A targeted mutation of the dopamine D_3 receptor gene is associated with hyperactivity in mice. Proc. Natl. Acad. Sci. USA 93, 1945–1949.

Baik, H., Picetti, R., Salardi, A., Thiriet, G., Dierich, A., Depaulis, A., Le Meur, M., Borrelli, 1995. Parkinsonian-like locomotor impairment in mice lacking dopamine D_2 receptors. Nature 377, 424–428.

Gobert, A., Rivet, J.-M., Audinot, V., Cistarelli, L., Spedding, M., Vian, J., Peglion, J.-L., Millan, M.J., 1995. Functional correlates of dopamine D_3 receptor activation in the rat in vivo and their modulation by the selective antagonist, (+)-S 14297: II. Both D_2 and 'silent' D_3 autoreceptors control synthesis and release in mesolimbic, mesocortical and nigrostriatal pathways. J. Pharmacol. Exp. Ther. 275, 899–913.

Lieberman, J.A., 1993. Understanding the mechanism of action of atypical antipsychotic drugs. A review of compounds in use and development. Br. J. Psychiatry 163, 7–18.

Millan, M.J., Peglion, J.-L., Vian, J., Rivet, J.-M., Brocco, M., Gobert, A., Newman-Tancredi, A., Dacquet, C., Bervoets, K., Girardon, S., Jacques, V., Chaput, C., Audinot, V., 1995. Functional correlates of dopamine D_3 receptor activation in the rat in vivo and their modulation by the selective antagonist, (+)-S 14297: I. Activation of postsynaptic D_3 receptors mediates hypothermia, whereas blockade of D_2 receptors elicits prolactin secretion and catalepsy. J. Pharmacol. Exp. Ther. 275, 885–898.

Nilsson, C.L., Ekman, A., Hellstrand, M., Eriksson, E., 1996. Inverse agonism at dopamine D_2 receptors. Haloperidol-induced prolactin release from GH_4C_1 cells transfected with the human D_2 receptor is antagonized by *R*(−)-*n*-propylnorapomorphine, raclopride and phenoxybenzamine. Neuropsychopharmacology 15, 54–61.

Sautel, F., Griffon, N., Sokoloff, P., Schwartz, J.-C., Launay, C., Simon, P., Costentin, J., Schoenfelder, A., Garrido, F., Mann, A., Wermuth, C.G, 1995. Nafodotride, a potent preferential dopamine D_3 receptor antagonist, activates locomotion in rodents. J. Pharmacol. Exp. Ther. 275, 1239–1246.

Waters, N., Svensson, K., Haadsma-Svensson, S.R., Smith, M.W., Carlsson, A., 1993. The dopamine D_3 receptor: a postsynaptic receptor inhibitory on rat locomotor activity. J. Neural Transm. 94, 11–19.