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Assessment of cocaine-like discriminative stimulus effects of dopamine D_3 receptor ligands

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Abstract

The highly selective dopamine D_3 receptor ligand, (+)-PD 128907 4*aR*10*bR*-(+)-*trans*-3,4,4*a*,10*b*-tetrahydro-4-*n*-propyl-2*H*5*H*[4,3-*b*]-1,4-oxazin-9-ol), and other dopamine D_3 receptor ligands, (±)-7-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin and (+)-7-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin, substituted for the discriminative stimulus effects of cocaine in rats, an animal model of subjective effects in humans. Substitution only occurred at doses that markedly decreased responding. These results suggest that dopamine D_3 receptors may be involved in the subjective effects of cocaine, and therefore may be a target for the discovery of treatments for cocaine dependence.

Keywords: Dopamine D_3 receptor; 7-OH-DPAT (7-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin); (+)-PD 128907 (4*aR*,10*bR*-(+)-*trans*-3,4,4*a*,10*b*-tetrahydro-4-*n*-propyl-2*H*,5*H*[4,3-*b*]-1,4-oxazin-9-ol)

Convergent experimental evidence suggests that behavioral effects of cocaine are related to the inhibition of dopamine reuptake, and the resulting potentiation of mesolimbic dopaminergic neurotransmission (Kuhar et al., 1991). When rats are trained to discriminate cocaine from saline, substitution for cocaine by a test drug is predictive of cocaine-like subjective effects, and compounds that substitute for the discriminative stimulus effects of cocaine in rats are generally those that increase dopaminergic neurotransmission (Witkin, 1994). Selective dopamine D_1 receptor agonists have not been shown to fully substitute for the discriminative stimulus effects of cocaine (Witkin et al., 1991). Likewise, dopamine D_2/D_3 receptor agonists do not fully substitute for cocaine (Witkin et al., 1991). Prior to the present report, the contribution of the D_3 dopamine receptor to the discriminative stimulus effects of cocaine has been hampered by the lack of selective ligands. The relative abundance of the dopamine D_3 receptor subtype in mesolimbic dopaminergic regions (Sokoloff et al., 1990) suggests that it may be involved in some of the behavioral effects of cocaine that are related to its abuse.

The dopamine D_3 receptor ligand, (+)-PD 128907 (4*aR*,10*bR*-(+)-*trans*-3,4,4*a*,10*b*-tetrahydro-4-*n*-propyl-2*H*,5*H*[4,3-*b*]-1,4-oxazin-9-ol), has recently been reported to bind to dopamine D_3 receptors with high affinity (K_i = 1.1 nM against [^{3}H]spiperone in Chinese hamster ovary (CHO-K1) cells), and with a selectivity ratio (K_i at D_2 dopamine receptors/K_i at D_3 dopamine receptors) of 1000 (DeMattos et al., 1993). (+)-PD 128907 is therefore more selective than either the prototypic, high affinity dopamine D_3 receptor ligand, (±)7-OH-DPAT (7-hydroxy-2-(*N*,*N*-di-*n*-propylamino)-tetralin), or its active (+) enantiomer. These compounds have K_i values of 0.78 nM (Lévesque et al., 1992) and 0.57 nM (Damsma et al., 1993), and selectivity ratios of approximately 80 and 220, respectively.

In order to determine if selective dopamine D_3 receptor ligands substitute for the discriminative stimu-

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lus effects of cocaine, drugs were administered to male Sprague-Dawley rats that had been trained to discriminate cocaine HCl from saline using food reinforcement. Training and testing took place in operant chambers equipped with two response levers, where rats reliably emitted 20 lever presses on one lever following 10 mg/kg cocaine (i.p.), or on the other lever following saline. During testing, procedures were identical except that following injection of a test compound, 20 consecutive responses on either lever produced food reinforcement. All compounds were administered 5 min prior to testing (see Witkin et al., 1991 for detailed methods).

The compound with greatest selectivity for dopamine D_3 receptors, (+)-PD 128907 (0.03–3.0 mg/kg), dose-dependently substituted for cocaine, producing a maximum of 87% (ED_{50} = 0.94 mg/kg, 95% C.L.: 0.57–1.54), and was similar in potency to cocaine itself (Fig. 1, upper panel). Unlike cocaine, the substitution of (+)-PD 128907 was accompanied by significant reductions in response rates (Fig. 1, lower panel). Similarly, (±)-7-OH-DPAT (0.03–1.0 mg/kg) dose-dependently substituted for cocaine (ED_{50} = 0.3 mg/kg, 95% C.L.: 0.27–0.38), and significantly reduced response rates. (+)-7-OH-DPAT (0.1–1.0 mg/kg) also produced dose-dependent cocaine-lever responding and was similar in potency to the racemate (ED_{50} = 0.23 mg/kg, 95% C.L.: 0.17–0.27), as described for other pharmacological actions (Damsma et al., 1993). In contrast, (−)-7-OH-DPAT (K_i = 42 nM, Damsma et al., 1993) produced substitution for cocaine that reached a maximum of only 48%, despite producing significant response rate reductions.

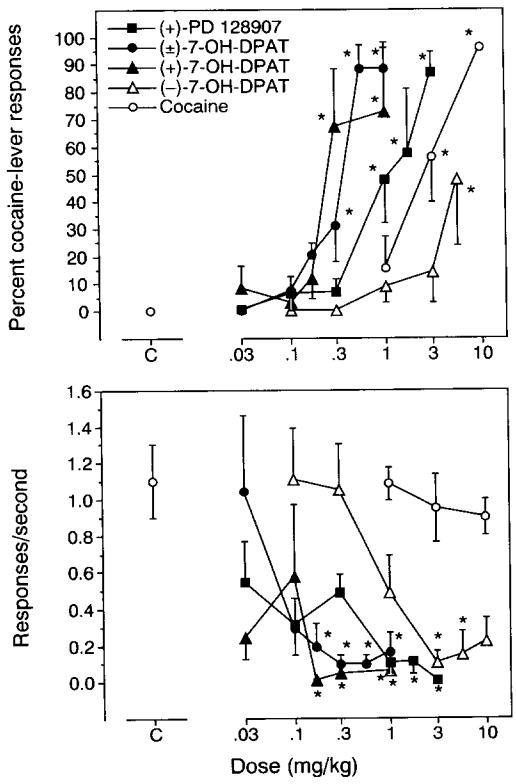

Fig. 1. Upper panel: Dose-dependent substitution of cocaine and dopamine D_3 receptor ligands in rats trained to discriminate 10 mg/kg cocaine from vehicle, shown as means and S.E.M.s. Asterisks indicate responding that was significantly different from saline control (points above C), as determined by Dunnett's test, (1-tailed, $P < 0.05$). Dose-effect functions, derived from mean values across subjects (n = 3–6 rats except for higher doses of (+)-PD 128907, where n = 4–10 rats), were analyzed with standard bioassay analysis of variance techniques, using data from the linear portions of the curves. Substitution data from individual subjects were not used when the corresponding response rate was lower than 0.02 responses/second, corresponding to the completion of one fixed-ratio or 20 responses. Lower panel: Dopamine D_3 receptor ligands significantly decreased response rates at doses that substituted for cocaine. Means and S.E.M.s are plotted as a function of dose, using data from all subjects (n = 6–12 rats).

These results suggest that high affinity dopamine D_3 receptor ligands may produce subjective effects that are similar to those of cocaine. However, binding at dopamine D_3 receptors results in behavioral depression and response rate reductions that are unlike the effects of cocaine itself (see Fig. 1, lower panel) and other drugs that have been reported to fully substitute for cocaine (cf. Witkin, 1994). Therefore, although dopamine D_3 receptors may be involved in the subjective effects of cocaine, this receptor subtype may mediate behavioral effects that are distinctly different from those of cocaine itself. Coupled with the finding that cocaine self-administration can be modulated by dopamine D_3 receptor ligands (Caine and Koob, 1993), results suggest that dopamine D_3 receptors may be an important target for the discovery of agents that may be used in the treatment of cocaine abuse.

Acknowledgments

Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Care (AAALAC), and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Division of Intramural Research, National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals, National Research Council, Department of Health, Education and Welfare, NIH Publication 85-23, revised 1985.

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