Stereoselective blockade of cerebral dopamine receptors by sulpiride and sultopride

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The enantiomeric substituted benzamide drugs sulpiride and sultopride are cerebral dopamine receptor antagonists (Justin-Besançon, Laville, Margarit & Thominet, 1974; Laville, 1972; Elliott, Jenner, Huizing, Marsden & Miller, 1977). We have investigated their stereoselectivity using a number of behavioural and biochemical indices of cerebral dopamine receptor activity.

Locomotion induced by apomorphine hydrochloride (2 mg/kg i.p.) in reserpine (10 mg/kg i.p.; 18 h previously) pretreated mice was partially inhibited by (−)-sulpiride (4–64 mg/kg i.p.) and (−)-sultopride (2.5-40 mg/kg i.p.). The (+)-enantiomers of both drugs were inactive. Stereo-typed behaviour induced in rats by apomorphine hydrochloride (0.5 mg/kg sc; 15 min previously) or (+)-amphetamine sulphate (5 mg/kg i.p. 30 min previously) was completely inhibited by (−)-sultopride (16–128 mg/kg i.p.; ID_{50} 10.5 and 7.5 mg/kg respectively). (+)-Sultopride was only partially effective in inhibiting stereotyped behaviour at 128 mg/kg. The enantiomers of sulpiride (4–128 mg/kg i.p.) were only effective in inhibiting apomorphine or amphetamine-induced stereotyped behaviour at the highest dose used.

Striatal and mesolimbic HVA and DOPAC levels in the rat were elevated by the (−)-enantiomers of sulpiride (2–100 mg/kg i.p.) and sultopride (2–50 mg/kg i.p.). While (+)-sulpiride was without effect, high doses of (+)-sultopride (25 and 50 mg/kg) elevated striatal and mesolimbic DOPAC levels. [^{3}H]-Spiperone (0.5 nM; 20 Ci/mmole) bound to rat striatal preparations was displaced in a concentration dependent manner by (−)-sulpiride and (−)-sultopride (10^{-10}–5×10^{-6} M) (IC_{50} value 3.5×10^{-7} M and 6.6×10^{-8} M respectively). The (+)-enantiomers caused only a small displacement at the highest concentration employed being approximately 6 and 15 times less potent respectively. Similarly, (−)-sulpiride (10^{-10}– 5×10^{-6} M) was 10 times more effective than (+)-sulpiride in displacing [^{3}H]-sulpiride (15 nM; 26 Ci/mmole) from its striatal binding site (IC_{50} values 9.3×10^{-8} M and 9.8×10^{-7} M respectively), while (−)-sultopride (10^{-10}–5×10^{-6} M) was 53 times more effective than (+)-sultopride (IC_{50} values 1.9×10^{-8} M and 1.0×10^{-6} M respectively).

In contrast the inclusion of either (+)- or (−)-sultopride or sulpiride (10^{-8}–10^{-4} M) into rat striatal preparations did not inhibit the dopamine (10^{-4} M) stimulation of adenylate cyclase activity.

In conclusion, it would appear that the central pharmacological action of such substituted benzamide drugs resides in the (−)-enantiomer, in agreement with previous findings for sulpiride (Garau, Govoni, Stefanini, Trabucchi & Spano, 1978; Andrews & Woodruff, 1978). In addition this action would appear to be mediated via non-adenylate cyclase dependent dopamine receptors.

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