Selective affinities of bromocriptine and lergotrile for rat limbic dopamine binding sites

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The results of recent clinical studies with bromocriptine and lergotrile have stimulated interest in their pharmacological properties. Both are agonists of dopamine receptors (Corrodi, Fuxe, Hokfelt, Lidbrink & Ungerstedt, 1973), compete for dopamine binding sites (Burt, Creese & Snyder, 1976) and inhibit dopamine-stimulated adenylate cyclase (Schmidt & Hill, 1977). These results suggest that bromocriptine and lergotrile are capable of acting as both agonists and antagonists at dopamine receptors and a knowledge of the nature of the drug-receptor interactions in discrete brain areas would facilitate an understanding of their clinical profiles.

To gain insight into this, we have compared the effects of bromocriptine and lergotrile on the binding of [^{3}H]-dopamine (agonist ligand) and [^{3}H]-haloperidol (antagonist ligand) to limbic (T. olfactorium and N. accumbens) and striatal membranes. Freshly dissected tissues from male rats were homogenised in 50 vol ice-cold 50 mM tris-HCl buffer (pH 7.5 at 4°C) and centrifuged twice (50,000 *g*) for 10 minutes. The final pellet was re-homogenised in 100 vol 50 mM tris-maleate buffer (pH 7.1 at 4°C) containing, NaCl (120 mM), KCl (5 mM), $CaCl_2$ (2 mM), $MgCl_2$ (1 mM), ascorbate (0.1%) and pargyline (10 μM). Aliquots (400-500 μg protein) were incubated with 5 nM [^{3}H]-dopamine (15–17 Ci/mmol) or 2 nM [^{3}H]-haloperidol (8–20 Ci/mmol) for 30 min at 4°C. Specific binding was defined as that in excess of blanks determined in the presence of 100 μM dopamine for [^{3}H]-haloperidol and 1 μM dopamine for [^{3}H]-dopamine. Some 40–50% of total binding in the case of [^{3}H]-haloperidol and some 30–40% in the case of [^{3}H]-dopamine was specific, saturable and of high affinity. The apparent dissociation constants were similar in both membrane preparations (3 nM, [^{3}H]-haloperidol; 10 nM, [^{3}H]-dopamine) although there were differences in the number of binding sites. [^{3}H]-haloperidol had a B_{max} (pmoles/mg protein) of 0.53 for striatum and 0.24 for limbic areas; for [^{3}H]-dopamine and values were 0.44 for striatum and 0.18 for limbic areas.

Specific [^{3}H]-dopamine binding to limbic membranes was displaced by low concentrations of lergotrile (IC_{50} 13 nM), dopamine (IC_{50} 40 nM) and bromocriptine (IC_{50} 47 nM) whereas haloperidol (IC_{50} 6 μM) had lower affinity for these binding sites. The affinities of bromocriptine and lergotrile for striatal binding sites were much lower than those for limbic sites: lergotrile (IC_{50} 400 nM) and bromocriptine (IC_{50} 3.3 μM). Among a series of dopaminergic compounds only (3,4-dihydroxy-phenylamino)-2-imidazoline (DPI) also had greater affinity for limbic rather than striatal dopamine binding sites (IC_{50} limbic 20 nM; striatum 10 μM). More recent data from saturation studies with [^{3}H]-dopamine of higher specific activity (47 Ci/mmol) indicate more than one type of limbic dopamine binding site. However using [^{3}H]-haloperidol as the ligand no differences were apparent between striatal and limbic IC_{50} values: haloperidol (4 nM), lergotrile (40 nM), bromocriptine (200 nM), dopamine (1 μM) and DPI (10 μM).

The present demonstration of selectivity of bromocriptine, lergotrile and DPI for limbic as opposed to striatal dopamine binding sites adds to the possibility of different types of dopamine receptor (Cools & Van Rossum, 1976). In the cases of bromocriptine and lergotrile this selectivity may also be relevant to some of their clinical effects. However as both agents also interact with haloperidol binding sites, thus supporting their mixed agonist/antagonist potential, direct extrapolation of these findings to the clinical situation requires more detailed investigations.

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