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Hallucinogen binding to dopamine/neuroleptic receptors

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Although previous work has established that the hallucinogenic drugs have a high affinity for 5-hydroxytryptamine and (+)-lysergic acid diethylamide receptor sites (Bennett & Snyder, 1976; Fillion, Fillion & others, 1976; Lovell & Freedman, 1976), it is known that the hallucinogen actions are blocked by neuroleptic drugs (Snyder, Faillace & Hollister, 1967; Lloyd, 1970) which are thought to act by dopamine receptor blockade (Andén, Roos & Werdinius, 1964; van Rossum, 1967; Andén, 1968).

In order to examine the suggestion (Pieri, Pieri & Haefely, 1974; Von Hungen, Roberts & Hill, 1974; Stone, 1974) that hallucinogenic drugs can act directly on brain dopamine receptors, we tested the effect of various hallucinogens on the binding of [^{3}H]haloperidol and [^{3}H]apomorphine to brain tissue. It is known that these two ligands bind to sites closely related to, if not identical with, the dopamine receptor (Seeman, Wong & Lee, 1974; Seeman, Chau-Wong & others, 1975; Burt, Creese & Snyder, 1976; Seeman, Lee & others, 1976a,b).

The experiments were done on crude homogenates of calf caudate, using procedures previously described (Seeman & others, 1976a, b). The final concentration in the incubation tube was 3·3 nM for [^{3}H]haloperidol and 1·5 nM for [^{3}H]apomorphine. The stereoselective component of binding was defined as that amount of [^{3}H]haloperidol or [^{3}H]apomorphine bound in the presence of (−)-butaclamol (inactive neuroleptic) minus that bound in the presence of (+)-butaclamol (active neuroleptic); 100 nM butaclamol was used for [^{3}H]haloperidol, and 1 μM butaclamol was used for [^{3}H]apomorphine.

The results (Table 1) indicate that *N,N*-dimethyl tryptamine (DMT), *N,N*-diethyltryptamine (DET) bufotenin and ibogaine were all rather active on the neuroleptic receptor ([^{3}H]haloperidol) in the nM region; methysergide and 2,5-dimethoxy-4-methylamphetamine (STP) were active in the 30–50 nM range, while mescaline and LSD blocked in the 100–500 nM region. The tryptamine derivatives which were potent in blocking the binding of [^{3}H]haloperidol were generally much weaker in blocking the binding of [^{3}H]apomorphine. In contrast (+)-LSD has a very low IC50 against [^{3}H]apomorphine binding (6 nM) but was less active against [^{3}H]haloperidol binding (500 nM).

Table 1. *The effect of hallucinogens on [^{3}H]haloperidol and [^{3}H]apomorphine binding**.

	Butaclamol-specific [^{3}H]haloperidol binding IC50 (nM)	Butaclamol-specific [^{3}H]apomorphine binding IC50 (nM)
DET	0·5	6000
Ibogaine	3	450 000
Bufotenin	4	5000
DMT	18	1000
Methysergide	30	70
Mianserin (GB-94)	30	900
STP	44	300 000
Mescaline	100	14 000
(+)-LSD	500	6
5-Methoxy-*NN*-dimethyltryptamine	—	3000
5-HT	—	6000

* The IC50 values are the concentrations of the drugs which reduced the stereospecific binding of [^{3}H]-haloperidol or [^{3}H]apomorphine by 50%.

The low IC50 for (+)-LSD on [^{3}H]apomorphine binding (6 nM) does suggest that there is a direct action of (+)-LSD on dopamine receptors. The crude relation in Fig. 1 further suggests that the tryptamine derivatives may reciprocally affect both the antagonist as well as the agonist state of the dopamine receptor, if such a two-state hypothesis is correct (Bennett & Snyder 1976).

* Correspondence.

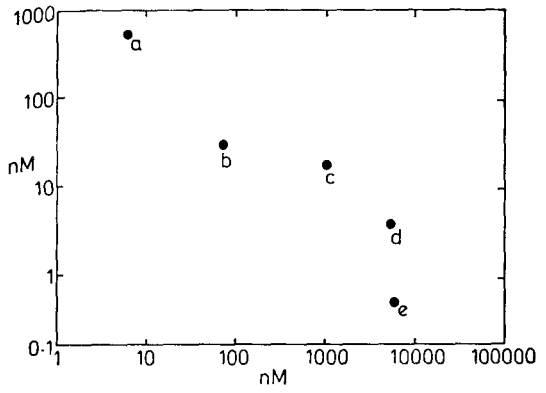

FIG. 1. Effects of various tryptaminergic drugs a—LSD, b—methylsergide, c—DMT, d—bufotenin, e—DET on specific [^{3}H] haloperidol and [^{3}H] apomorphine binding. The correlation suggests that haloperidol binding sites include both dopamine and tryptamine receptors. Ordinate—IC50 on butaclamol-specific [^{3}H] haloperidol binding (nM). Abscissa—IC50 on butaclomol-specific ^{3}H] apomorphine binding (nM).

More points will be necessary to test whether the qualitative relation in Fig. 1 is statistically valid, and many other 5-HT antagonists will have to be tested on [^{3}H]apomorphine and [^{3}H]haloperidol binding. It is already known that the hallucinogenic tryptamines have a conformation which match the conformation of dopamine (Kier, 1968; Falkenberg, 1972; Kang, Johnson & Green, 1973). The hydroxylated tryptamines (Szara & Axelrod, 1959; Szara & Hearst, 1961–2; Siddik, Barnes & others, 1975) would have an even better conformational match with dopamine, and this may explain the potent hallucinogenic properties of the hydroxylated tryptamines (Szara & Hearst, 1961–2). Thus, it is strange that the hallucinogenic tryptamines do not block the binding of the dopamine agonist ([^{3}H]apomorphine) more effectively than the antagonist ([^{3}H]haloperidol); it has also been noted by others (Burt & others, 1976), however, that bufotenin and *NN*-dimethyltryptamine are poor competitors for the binding of [^{3}H]dopamine.

In summary, there may be a tryptaminergic, as well as a dopaminergic, component of haloperidol binding.

We thank Mrs Joan Bowles for her excellent assitsance. We are grateful to Dr R. A. Graham of the Health Protection Branch, Department of National Health and Welfare, Canada, for supplying us with DMT, LSD, STP, DET and to Drs R. Deghenghi and L. Humber (Ayerst Research Laboratories, Montreal) for donating butaclamol. (Other drugs were obtained from Sigma Chemical Co.; Mianserin (GB94) was a gift from Dr E. Schönbaum, Organon Labs, The Netherlands; methysergide was donated by Sandoz, Montreal). The Canada Packers Hunisett plant generously donated calf brains. This work was supported by the Ontario Mental Health Foundation and the Medical Research Council of Canada (MT-2951).

February 3, 1977

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