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[^{3}H]SCH 23390 identifies D-1 binding sites in rat striatum and other brain areas

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The specific in-vitro binding of [^{3}H]SCH 23390 has been characterized and its use in the identification of D-1 sites in various brain regions examined. At a single ligand concentration (0·4 nM) the specific binding of [^{3}H]SCH 23390 to striatal membranes was routinely 98% of total binding as defined using 10^{-5} M *cis*-flupenthixol. Specific binding at 37 °C reached equilibrium at 15 min and was reversible with a $t_{\frac{1}{2}}$ for dissociation of 14 min. Specific binding of [^{3}H]SCH 23390 over a range of concentrations (0·01–3·5 nM) was saturable (B_{max} 73 pmol g tissue^{-1}) of high affinity (K_d 0·36 nM) and to a single population of binding sites. Specifically bound [^{3}H]SCH 23390 (0·4 M) was stereo selectively displaced by the isomers of butaclamol and flupenthixol but not by the D-2 selective antagonist, sulpiride. 5-HT, noradrenaline and cinanserin caused little or no displacement. Specific binding of [^{3}H]SCH 22390 (0·4 nM; as defined using 10^{-5} M *cis*-flupenthixol) showed marked regional variation. Specific binding was highest in the striatum; high levels were also observed in the mesolimbic area and substantia nigra. Lower specific binding was found in the frontal cortex and superior colliculus with the lowest levels in cerebellar preparations. The inclusion of 3×10^{-7} M cinanserin did not alter the extent of specific binding observed in any brain region. The properties of [^{3}H]SCH 23390 suggest it to be an excellent ligand for identification of D-1 sites in a variety of brain regions.

Dopamine receptor populations are divided into those which stimulate the enzyme adenylate cyclase (D-1) and those which either inhibit or are not directly linked to this enzyme (D-2) (Stoof & Kebabian 1984). Until recently, all functional effects of dopamine action in the brain were attributed to the D-2 receptor. Thus, good correlations exist between the ability of dopamine agonist and antagonist drugs to elicit or inhibit dopamine-mediated behaviours, and their ability to act at D-2 sites as judged by displacement of [^{3}H]spiperone binding (Seeman 1980). The physiological role of the D-1 site remains unknown but Molloy & Waddington (1985) have now shown that selective behavioural responses may be evoked in the rat by D-1 stimulation.

Investigation of the D-1 site using ligand binding techniques has relied upon tritiated derivatives of the thioxanthene neuroleptics *cis*-flupenthixol and *cis*-piflutixol (Hyttel 1978a, b, 1981; Cross & Owen 1980; Leff et al 1984; Kilpatrick et al 1986). However, both these ligands show high non-specific binding components (30%) and both show an equal affinity for D-1 and D-2 sites. In addition, both ligands can potentially interact with 5-HT and noradrenaline receptors. In striatal tissue, careful definition of specific binding allows measurement of D-1 sites using [^{3}H]*cis*-flupenthixol or [^{3}H]*cis*-piflutixol. However, in other brain areas such as the nucleus accumbens or frontal cortex where the density of dopamine receptors is low and other monoamine transmitter receptors predominate, their use is limited.

The major problem in selectively identifying D-1 sites is related to the lack of compounds that selectively interact with this site. Recently, however, SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol) was described and appeared to be a selective D-1 antagonist (Cross et al 1983; Hyttel 1983; Iorio et al 1983; O'Boyle & Waddington 1984; Onali et al 1984; Boyce et al 1985). Subsequently, [^{3}H]SCH 23390 was prepared and shown to identify selectively D-1 sites in striatal membrane preparations, and to possess a low non-specific binding component (Billard et al 1984).

In the present study we set out to examine whether [^{3}H]SCH 23390 might be used to label dopamine D-1 sites in areas of rat brain with low receptor density. Since [^{3}H]SCH 23390 was only recently described as identifying D-1 sites, it has not been widely used. So it was important initially to confirm its ability to identify D-1 sites in striatum before assessing its use in identifying these sites in other brain regions.

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MATERIALS AND METHODS

[^{3}H]SCH 23390 ([*N*-methyl-^{3}H]*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol; 80 Ci mmol^{-1}) was a gift from Dr L. Iorio (Schering Corporation, USA). Dopamine hydrochloride, noradrenaline bitartrate and 5-hydroxytryptamine creatinine sulphate (5-HT) were supplied by Sigma Chemical Co. The following drugs were used: (±)-2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN; Wellcome Research Laboratories), (+)- and (−)-butaclamol hydrochloride (Ayerst Laboratories), cinanserin hydrochloride (Squibb), *cis*- and *trans*-flupenthixol hydrochloride (Lundbeck), haloperidol (Janssen Pharmaceutica), SCH 23390 (Schering Corporation) and (±)-sulpiride (Delagrange).

Brain tissue preparation

Female Wistar rats (150 ± 10 g; Bantin & Kingman) were stunned, decapitated and the brains rapidly removed onto ice. The paired corpora striata, substantia nigra, superior colliculi, mesolimbic system (nucleus accumbens and tuberculum olfactorium) and the cerebellum and frontal cortex were dissected out and placed in 40 volumes of ice cold 50 mM Tris(hydroxyethyl)aminoethane buffer containing 120 mM NaCl, 5 mM KCl, 2·5 mM $CaCl_2$ and 1 mM $MgCl_2$ (Tris-salts buffer) which had been corrected to pH 7·4 (at 18–22 °C) using 6 M HCl. Pooled tissue from individual brain regions (usually from 10 animals) was homogenized using a Polytron homogenizer (setting 5) for 10 s. The resulting homogenate was centrifuged at 48 000*g* for 10 min in a Sorvall RC5B centrifuge at 4 °C. The tissue pellet formed was resuspended in 40 volumes of the Tris-salts buffer and the process repeated. In initial characterization studies, where only striatal tissue was used, the final pellet was resuspended in 270 volumes of the Tris-salts buffer. In all other experiments, where areas of low dopamine receptor density were expected, the final tissue pellet was resuspended in 90 volumes of this buffer.

[^{3}H]SCH 23390 binding to washed membrane preparations from regions of rat brain

Aliquots (900 μl) of the final tissue suspension were incubated with 50 μl of a solution of [^{3}H]SCH 23390. A final ligand concentration of 0·4 nM was used in most experiments. However, in equilibrium saturation studies, at least 6 ligand concentrations from 0·01–3·5 nM were employed. Non-specific binding was routinely defined by the inclusion of 50 μl of a solution of *cis*-flupenthixol so as to give a final concentration of 10^{-5} M. This concentration was shown in initial experiments to cause a maximal displacement of specific [^{3}H]SCH 23390 binding. For the assessment of total binding, 50 μl of the *cis*-flupenthixol vehicle (deionized water) was added. In some experiments, cinanserin was included in samples for the determination of both total and non-specific binding so as to assess the involvement of 5-HT sites. All samples were examined in triplicate at each ligand or displacing drug concentration. Samples were incubated for 20 min in a shaking water bath at 37 °C although in experiments to determine the association and dissociation rates of binding this time was varied from 1–60 min. The reaction was terminated by rapid vacuum filtration through Whatman GF/C filters over Millipore 3025 manifolds at 50 cm Hg vacuum. Filters were immediately washed twice with 5 ml of ice cold Tris salts buffer. Filters were then placed in 5 ml of Packard ES299 scintillation cocktail and left overnight before counting in a Packard 460C scintillation spectrometer at an efficiency of 45%–50%.

Data calculation

A computer curve fitting program (minimization of sum of squares by an iterative process) was used for calculating the parameters of equilibrium saturation studies by fitting to the equation:

$$b = B_{max}/1 + (K_d/F)$$

where b is the amount bound, K_d the affinity constant, B_{max} the amount bound at infinite ligand concentration and F the free (unbound) ligand.

IC50 values were calculated graphically from displacement curves. Hill numbers were calculated by regression analysis of displacement data after plotting log % bound/(100% bound) vs log drug.

Association and dissociation rate constants of binding were calculated according to Weiland & Molinoff (1981). Association rates were calculated by the integrated rate equation of a second order reaction. Results are presented as mean ± s.e.m. if n = 3 or mean ± range if n = 2. Statistical significance was determined using an unpaired, two-tailed Student's *t*-test.

In all calculations the free ligand concentration was corrected for the total amount of ligand bound.

RESULTS

Equilibrium analysis of [^{3}H]SCH 23390 (0·4 nM) binding to washed homogenates of rat striatum

The association of specific [^{3}H]SCH 23390 (0·4 nM) binding to washed striatal homogenates (300 volume

dilution) appeared to reach equilibrium after 15 min at 37 °C. The association rate constant of binding was $2{\cdot}67 \times 10^6 \text{M}^{-1} \text{s}^{-1}$. In subsequent experiments a time of 20 min was used. [3H]SCH 23390 binding was slowly reversible. Dissociation initiated by addition of 10^{-5} M *cis*-flupenthixol after 30 min incubation at 37 °C occurred with a half life of 14 min. The dissociation rate constant of binding was $6{\cdot}73 \times 10^{-4} \text{s}^{-1}$. Calculation of the affinity constant (K_d) of binding from the association and dissociation rates (K_{-1}/K_{+1}) gave a value of 0·25 nM.

Equilibrium saturation analysis of specific [3H]SCH 23390 (0·01–3·5 nM) binding revealed saturable (B_{max} = 72·7 ± 3·6 pmol g tissue^{-1}; n = 3) and high affinity (K_d = 0·36 ± 0·07 nM; n = 3) binding. Eadie-Hofstee analysis of the saturation data was linear. The regression coefficient was greater than 0·99 in each of the three experiments performed, suggesting the involvement of a single binding site. Specific binding ranged between 98–91% of total binding. At the concentration of [3H]SCH 23390 routinely used, namely 0·4 nM, specific binding was never less than 95%. Displaceable binding (by incorporation of 10^{-5} M *cis*-flupenthixol into tissue blanks) of [3H]SCH 23390 (0·4 nM) to the GF/C filters was not evident.

Drug displacement of [3H]SCH 23390 (0·4 nM) binding to rat striatal membranes (Fig. 1, Table 1)

Total binding of [3H]SCH 23390 (0·4 nM) was displaced to a similar extent (95%) by nanomolar concentrations of SCH 23390, (+)-butaclamol and *cis*-flupenthixol; [3H]SCH 23390 (0·4 nM) binding was only weakly displaced by (−)-butaclamol or *trans*-flupenthixol. Dopamine and ADTN displaced [3H]SCH 23390 binding in micromolar concentrations. The order of potency for displacement of binding was SCH 23390, (+)-butaclamol, *cis*-flupenthixol, haloperidol, ADTN, dopamine.

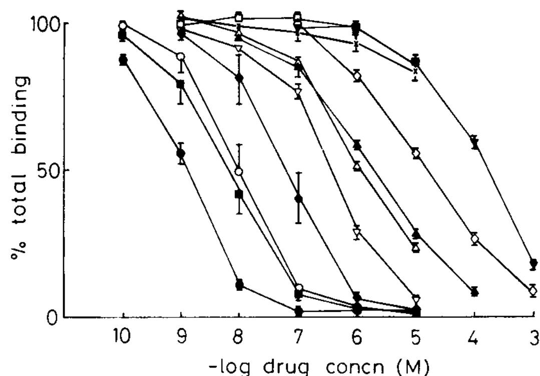

FIG. 1. The drug displacement profile of [3H]SCH 23390 (0·4 nM) binding to homogenates of rat striatum (300 volume dilution). Points represent mean ± s.e.m. of three separate experiments except noradrenaline, 5-HT and (−)-butaclamol where points are mean ± range of two separate experiments. Each individual experiment was performed in triplicate at each drug administration. ● SCH 23390; ■ (±)-butaclamol; ○ *cis*-flupenthixol; ◆ *trans*-flupenthixol; ▽ haloperidol; △ ADTN; ▲ dopamine; ◇ noradrenaline; ▼ 5-HT; × sulpiride; □ (−)-butaclamol.

Table 1. The affinity of monoamine neurotransmitters and drugs to displace [3H]SCH 23390 (0·4 nM) binding to washed homogenates of rat striatum (300 volume dilution).

	IC50 (nM)	Hill number
Dopamine	1 780 ± 120	0·59 ± 0·06
ADTN	1 090 ± 110	0·66 ± 0·33
Noradrenaline	14 100 ± 1 600*	0·56 ± 0·01
5-HT	168 000 ± 10 000*	0·77 ± 0·02
SCH 23390	1·10 ± 0·16	0·88 ± 0·01
(+)-Butaclamol	8·40 ± 3·0	0·92 ± 0·01
(−)-Butaclamol	>10 000*	—
cis-Flupenthixol	9·40 ± 3·3	0·96 ± 0·08
trans-Flupenthixol	56·00 ± 10	0·95 ± 0·15
Haloperidol	311·00 ± 44	0·92 ± 0·02
Sulpiride	>10 000	—
Cinanserin	>10 000*	—

Results are the mean (± s.e.m.) of three experiments or * mean (± range) of 2 experiments. The IC50 was defined as the concentration of drug displacing 50% of specific binding (determined by the inclusion of 10^{-5} M *cis*-flupenthixol). In these experiments total binding was 25 600 ± 1100 d min^{-1} and non-specific binding was 470 ± 30 d min^{-1}.

The selective D-2 antagonist (±)-sulpiride did not displace [3H]SCH 23390 binding in concentrations up to 10^{-5} M. The 5-HT antagonist cinanserin did not displace SCH 23390 binding at concentrations of up to 10^{-5} M. Noradrenaline was 8 times weaker than dopamine in displacing [3H]SCH 23390 binding. 5-HT only caused displacement at high micromolar concentrations.

Hill numbers for the displacement of [3H]SCH 23390 (0·4 nM) binding were near unity for the antagonists SCH 23390, (+)-butaclamol, *cis*- and *trans*-flupenthixol and haloperidol (0·88–0·96). Hill numbers for displacement by dopamine, ADTN, noradrenaline and 5-HT ranged between 0·56–0·77.

Regional specific binding of [3H]SCH 23390 (0·4 nM) to washed membrane preparations of rat brain

Specific [3H]SCH 23390 (0·4 nM; defined using 10^{-5} M *cis*-flupenthixol) binding showed regional variation (Table 2). Specific binding was highest in washed membrane preparations of the striatum, substantia nigra and mesolimbic system (nucleus accumbens plus tuberculum olfactorium). Specific

Table 2. Regional specific binding of [^{3}H]SCH 23390 (0·4 nM) to washed membrane preparations of rat brain.

Brain region	Bound (pmol g^{-1})	% specific binding
Striatum (a)	16·9 ± 1·0	98
(b)	17·4 ± 1·1	98
Mesolimbic (a)	13·0 ± 0·4	97
(b)	12·4 ± 0·3	97
Substantia nigra (a)	10·3 ± 0·2	96
(b)	9·7 ± 0·1	96
Frontal cortex (a)	1·8 ± 0·2	85
(b)	1·5 ± 0·2	82
Superior colliculus (a)	1·5 ± 0·1	82
(b)	1·3 ± 0·2	79
Cerebellum (a)	0·5 ± 0·1	60
(b)	0·5 ± 0·1	57

(a) In absence of 30 nM cinanserin.
(b) In presence of 300 nM cinanserin.
Results are the mean (± s.e.m.) of three experiments. Total and non-specific samples were examined in triplicate on each experiment. Non-specific binding was defined by the inclusion of 10^{-5} M *cis*-flupenthixol.

binding was considerably lower in membranes from the frontal cortex and superior colliculus and lowest in homogenates of the cerebellum. The inclusion of the 5-HT antagonist cinanserin (300 nM) displaced small amounts of specific [^{3}H]SCH 23390 (0·4 nM) binding in homogenates of the frontal cortex. This displacement did not reach the level of significance in the grouped results but within individual experiments specific binding to this area was significantly lower (10–15%) in the presence of 300 nM cinanserin.

Specific binding of [^{3}H]SCH 23390 (0·4 nM) was readily and reproducibly measurable in homogenates of all the brain areas used in this study. Low non-specific binding of [^{3}H]SCH 23390 was observed in all brain areas except the cerebellum. Specific binding of [^{3}H]SCH 23390 was approximately 80% or more of total binding in known dopamine containing brain regions. For example, in the frontal cortex homogenates the total binding of [^{3}H]SCH 23390 (0·4 nM) was 4100 ± 250 d min^{-1} whilst binding remaining in the presence of 10^{-5} M *cis*-flupenthixol was 617 ± 94 d min^{-1}. The non-specific component of [^{3}H]SCH 23390 binding was the same in all areas studied amounting to between 0·28 and 0·37 pmol g $tissue^{-1}$.

DISCUSSION

In membrane preparations of rat striatum [^{3}H]SCH 23390 interacts with a limited population of binding sites. The specific component of binding (as defined by incorporation of 10^{-5} M *cis*-flupenthixol) was high, being routinely 98% of total binding. Kinetic analysis showed the association of the ligand with its binding site to reach equilibrium rapidly and to be reversible. Equilibrium analysis revealed that binding was of subnanomolar affinity and apparently involved a single population of binding sites. Stereoselective displacement by the isomers of butaclamol and flupenthixol showed involvement of a pharmacologically select site.

The specific binding of [^{3}H]SCH 23390 was displaced with high affinity by nanomolar concentrations of SCH 23390 (+)-butaclamol and *cis*-flupenthixol. However, haloperidol displaced specific binding only at high nanomolar concentrations and the selective D-2 antagonist sulpiride (Jenner & Marsden 1981) was inactive in displacing binding at concentrations of up to 10^{-5} M. Drug displacement of [^{3}H]SCH 23390 binding to striatal membranes was similar to that reported for the thioxanthene ligands [^{3}H]*cis*-flupenthixol (Hyttel 1978a, b, 1981; Cross & Owen 1980; Leff et al 1984) and [^{3}H]*cis*-piflutixol (Hyttel 1981; Kilpatrick et al 1986). Again, binding was inhibited potently by (+)-butaclamol and *cis*-flupenthixol. Haloperidol was less active and sulpiride caused only partial displacement. The low ability of butyrophenone compounds such as haloperidol, and of substituted benzamides such as sulpiride, to displace these ligands related to the D-2 selectivity of such drugs.

Ligands such as [^{3}H]*cis*-flupenthixol and [^{3}H]*cis*-piflutixol identify D-1 and D-2 sites with equal affinity. However, in the presence of sulpiride to prevent interaction with D-2 sites, some 80% of specific binding remains (Fleminger et al 1982). This component of specific binding represents that due to D-1 receptor interaction. The drug displacement profile of [^{3}H]SCH 23390 strongly suggests it specifically interacts with D-1 sites with little or no D-2 involvement. This is most clearly shown by the failure of sulpiride to displace the ligand. The ability of drugs other than structural analogues of the ligand to cause displacement suggests a pharmacologically relevant binding site is involved. The low displacing effect of 5-HT and noradrenaline compared with dopamine suggests selectivity of the ligand for dopamine receptors, at least in the striatum. The failure of cinanserin to cause displacement supports this argument.

The similarity between the site identified by [^{3}H]SCH 23390 and that identified by the thioxanthene ligands in the presence of sulpiride is shown also by the similarity of number of sites labelled. Thus, for [^{3}H]*cis*-flupenthixol and [^{3}H]*cis*-piflutixol

the apparent B_{max} values are 78 and 76 pmol g tissue^{-1}, respectively (Hyttel 1978b, 1981), compared with 73 pmole g tissue^{-1} for [3H]SCH 23390 binding. However, the data presented suggest [3H]SCH 23390 possesses advantages over both thioxanthene ligands. Thus, in striatal membranes, the binding of [3H]SCH 23390 appears to be solely to D-1 sites with no involvement of D-2, 5HT and noradrenaline binding sites. The non-specific component of [3H]SCH 23390 binding is small (routinely 2% at 0·4 nM). In contrast, non-specific [3H]*cis*-flupenthixol and [3H]*cis*-piflutixol binding is between 30 and 70% of total binding (Hyttel 1978a, b 1981; Cross & Owen 1980; Fleminger et al 1982; Murrin 1983; Leff et al 1984; Kilpatrick et al 1986).

Striatal tissue is routinely used for dopamine ligand binding studies because of its high density of dopamine receptors and relatively low concentrations of 5-HT and noradrenaline receptors. However, in other brain regions receiving dopamine neuron innervation this is not the case. Specific problems arise with widely used D-2 ligands such as [3H]spiperone. For example, in mesolimbic tissue a significant component of specific binding is to 5-HT receptors in contrast to striatum. Also in frontal cortex, the identification of D-2 receptors is almost impossible due to their low density, and to the high density of 5-HT sites also labelled by [3H]spiperone. Similar problems also exist in the identification of D-1 receptors outside the striatum. Thus, both [3H]*cis*-flupenthixol and [3H]*cis*-piflutixol are potentially capable of labelling both 5-HT and noradrenaline sites although this has not been extensively investigated. In addition, the relatively low specific binding of these ligands increases the difficulties of reliably and accurately measuring small D-1 receptor populations in extrastriatal regions.

The properties of [3H]SCH 23390 as a ligand for identifying D-1 sites in striatum suggests it to be potentially useful in other brain areas. Indeed, potentially specific [3H]SCH 23390 binding could be routinely and reliably measured within both the frontal cortex and mesolimbic regions. The minor effect seen on inclusion of cinanserin suggests little if any of the binding to involve 5-HT receptors (Leysen et al 1981) although other sites have yet to be excluded. Clearly in brain areas such as the frontal cortex where the dopamine innervation is sparse and dopamine receptor density is low, [3H]SCH 23390 may be useful in providing an accurate and reproducible measure of D-1 sites.

The use of [3H]SCH 23390 to identify D-1 sites in other areas outside the striatum is shown by some of the results in this initial study. In contrast to a relatively low density of D-2 sites found in the substantia nigra (Hall et al 1983), specific [3H]SCH 23390 binding suggests a high density of D-1 sites in this area. Also the data show specific binding of [3H]SCH 23390 to the superior colliculus, an area where we have recently identified D-2 sites (Chivers et al 1984) and which may represent a previously unknown region of dopamine innervation. However, careful pharmacological characterization of such sites is necessary before the interaction of [3H]SCH 23390 can be reliably attributed to D-1 receptors and this is presently being undertaken.

In conclusion, this study confirms and extends the observation of Billard et al (1984) that [3H]SCH 23390 binds to dopamine D-1 sites in homogenates of rat striatum. The low non-specific component of binding and high selectivity for D-1 sites suggest [3H]SCH 23390 to be superior to other ligands previously used to identify these sites. Similarly, these properties allow the ligand to be used to label D-1 sites in brain areas with a low receptor density and where other monoamine transmitter receptors predominate. Indeed, very recently [3H]SCH 23390 has been found to be useful for the labelling of D-1 receptors in brain slices using autoradiography (Dawson et al 1985). Similarly, [3H]SCH 23390 may be appropriate for the identification of D-1 sites in human post-mortem studies (Raisman et al 1985) and in a brominated form as a ligand for D-1 sites in positron emission tomography (PET) studies in man (Friedman et al 1985).

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