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Potent lipophilic substituted benzamide drugs are not selective D-1 dopamine receptor antagonists in the rat

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The substituted benzamide drugs YM 09151-2 and clebopride potently inhibited apomorphine-induced stereotyped behaviour in the rat and caused displacement of the specific binding of [^{3}H]spiperone to D-2 binding sites on striatal membranes in low nanomolar concentrations. Other substituted benzamide drugs including metoclopramide, sultopride and flubepride also inhibited stereotyped behaviour to a greater or lesser degree, but were less potent in displacing [^{3}H]spiperone from D-2 sites. YM 09151-2 and clebopride only weakly displaced specific binding of [^{3}H]piflutixol to D-1 sites on rat striatal membranes, and only weakly inhibited striatal dopamine stimulated adenylate cyclase activity, when compared with *cis*-flupenthixol. The other substituted benzamide drugs did not displace [^{3}H]piflutixol or inhibit dopamine stimulation of adenylate cyclase activity in the concentration range used. Clebopride and YM 09151-2 were highly lipophilic with apparent partition coefficient (log P′) values equivalent to those of classical neuroleptic compounds, such as *cis*-flupenthixol. In contrast, the other substituted benzamide drugs were markedly less lipophilic. A log P′ value of approximately 2 was required before inhibition of adenylate cyclase activity or displacement of [^{3}H]piflutixol binding occurred. However, in excess of this value there was no correlation between either inhibition of adenylate cyclase activity or displacement of [^{3}H]piflutixol binding and the lipophilicity of the various compounds. We conclude that potent lipophilic substituted benzamide drugs, like other members of the substituted benzamide series, are selective D-2 receptor antagonists. Inherent steric factors within the drug series would appear to dictate activity at D-1 and D-2 sites, although lipophilicity may contribute to actions in these environments.

Substituted benzamide drugs, such as sulpiride, are selective dopamine receptor antagonists since they do not interact with neuronal receptors in brain other than dopamine (Leysen 1982). Brain dopamine receptors are commonly divided into those linked to adenylate cyclase (D-1) and those which are apparently independent of stimulation of adenylate cyclase (D-2) (Kebabian & Calne 1979). D-1 and D-2 receptors may not be entirely independent of one another for some D-2 sites appear to be inhibitory on adenylate cyclase activity (Stoof & Kebabian 1981). Many substituted benzamide drugs are selective antagonists of the D-2 dopamine receptors (see Jenner & Marsden 1981). Thus, sulpiride inhibits the specific binding of [^{3}H]spiperone to D-2 binding sites on striatal membranes (Jenner et al 1978), but has little ability to inhibit dopamine stimulation of striatal adenylate cyclase activity or to inhibit the binding of [^{3}H]*cis*-flupenthixol or [^{3}H]piflutixol to D-1 receptors in striatal membranes (Hyttel 1978, 1980). Recently two new series of substituted benzamide drugs, namely the *N*-benzyl-4-piperidyl series, including clebopride (Prieto et al 1977), and the *N*-benzyl-3-pyrrolidinyl series, including YM 09151-2 and YM 08050 (Iwanami et al 1981), have been introduced. These compounds appear to resemble classical neuroleptic drugs more closely than previous substituted benzamide drugs such as sulpiride. Thus, clebopride and YM 09151-2 are potent in inducing catalepsy and in inhibiting apomorphine-induced stereotyped behaviour (Elliott et al 1977; Usuda et al 1979, 1981). In addition, Usuda and his colleagues (1981) have claimed that YM 09151-2 and YM 08050 are not selective for D-2 striatal dopamine receptors but are selective antagonists of D-1 adenylate cyclase linked dopamine receptors, at least in the dog. These observations obviously throw doubt on the concept that substituted benzamide drugs are selective D-2 antagonists.

Woodruff & colleagues (1980) proposed that one reason for the specificity of sulpiride on D-2

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receptors is its poor lipid solubility compared with newer lipophilic substituted benzamide derivatives such as YM 09151–2 and YM 08050. The implication is that neuroleptic drugs might act on D–1 receptors only if sufficiently lipid soluble to penetrate some lipid barrier to reach the adenylate cyclase enzyme. On this basis drugs such as sulpiride may possess steric qualities to endow them with D–1 and D–2 activity when compared to other neuroleptic compounds, but poor lipid solubility.

Such arguments are of critical importance to our understanding of the mechanism of action of neuroleptic drugs and the classification of cerebral dopamine receptors. We have investigated, therefore, the role lipid solubility might play in the relative antagonism of D–1 and D–2 receptors by examining the relationship between lipid solubility and the potency of neuroleptic drugs to produce biochemical and behavioural changes associated with cerebral dopamine function.

MATERIALS AND METHODS

Drugs

The substituted benzamide drugs employed were: YM 09151–2 (*cis-N*-(1-benzyl-2-methyl-3-pyrrolidyl)-5-chloro-2-methoxy-4-methylaminobenzamide; Yamanouchi Pharmaceutical Co., Japan); clebopride (*N*-(*N*-benzyl-4-piperidinyl-4-amino-5-chloro-2-methoxybenzamide; Almirall Laboratories Ltd., Spain); Flubepride (*N*-(*N*-4-fluorobenzyl-2-pyrrolidylmethyl)-2-methoxy-5-aminosulphonyl-benzamide; Synthelabo, France); sultopride (*N*-(1-ethyl-2-pyrrolidyl-methyl)-2-methoxy-5-ethyl-sulphonyl benzamide; Delagrange, France); sulpiride (*N*-(1-ethyl-2-pyrrolidylmethyl)-2-methoxy-5-aminosulphonyl-benzamide; Delagrange, France); metoclopramide (*N*-(diethylaminoethyl)-2-methoxy-4-amino-5-chlorobenzamide hydrochloride; Beecham Research Laboratories, UK); tiapride (*N*-(diethylaminoethyl)-2-methoxy-5-methylsulphonyl benzamide; Delagrange, France); Tigan (*N*-(2-dimethylaminomethoxy) benzyl)-3,4,5-trimethoxybenzamide; Roche Products, UK).

As typical neuroleptic agents, *cis-* and *trans-*flupenthixol hydrochloride (Lundbeck, Denmark), spiperone and haloperidol (Janssen Pharmaceutica, Belgium), and thioridazine dihydrochloride (Sandoz, UK) were used.

For stereotypy experiments, clebopride, metoclopramide, sultopride, tiapride, tigan, *cis-* and *trans-*flupenthixol and thioridazine were dissolved in distilled water. YM 09151–2 was dissolved in a minimum quantity of 1M hydrochloric acid, diluted with distilled water and the pH of the final solution adjusted to pH 6–7 using dilute sodium hydroxide solution. Flubepride was dissolved in a minimum quantity of *N*-methyl-2-pyrrolidone and lactic acid and diluted to volume with distilled water. Sulpiride was dissolved in a minimum quantity of 2% sulphuric acid, diluted with distilled water, and the pH adjusted to between 5–6 using dilute sodium hydroxide solution. Haloperidol and spiperone were dissolved in a minimum quantity of glacial acetic acid and diluted to volume with distilled water.

For ligand binding assays the drugs were dissolved in 0.1% ascorbic acid. For adenylate cyclase assays the drugs were dissolved in incubation buffer at pH 7·4 using 2M sodium hydroxide solution.

Apomorphine-induced stereotyped behaviour

Rats (150 ± 10 g; Charles Rivers Ltd) were placed in individual Perspex cages (20 × 18 × 18 cm). Stereotyped behaviour was assessed 15 min following administration of apomorphine hydrochloride (0·5 mg kg^{-1} s.c.; Macfarlan Smith Ltd.). The following scoring system was used: 0 = animals indistinguishable from control animals; 1 = continuous locomotor activity, discontinuous sniffing; 2 = discontinuous locomotor activity, continuous sniffing; 3 = sporadic locomotor activity, discontinuous licking, gnawing or biting; 4 = only occasional locomotor activity, continuous licking, gnawing or biting.

Animals were pretreated with substituted benzamide drugs and other neuroleptic agents 1 h before the administration of apomorphine hydrochloride. A range of doses of each compound (according to potency) was used so as to establish the ID50 value for each agent.

Ligand binding assays

Ligand binding assays were carried out on pooled striatal tissue from 7 rats. Each individual experiment was carried out in triplicate at each concentration of displacing drug on at least two separate tissue pools.

Rats (150 ± 10 g; Charles Rivers Ltd) were killed by cervical dislocation and decapitation and paired corpus striata dissected out into ice-cold 50 mM Tris HCl buffer (pH 7·7). Pooled tissue was homogenized in 100 volumes of 50 mM Tris HCl buffer, pH 7·7, using an Ultraturrax homogenizer and then centrifuged at 45 000 *g* for 25 min. Tissue pellets were then resuspended in 200 volumes of the incubation buffer 50 mM tris HCl containing sodium chloride 120 mM, calcium chloride 2·5 mM, magnesium chloride 1 mM,

potassium chloride 5 mM, 0·1% ascorbic acid (pH 7·4), centrifuged as before, followed by final re-suspension in 500 volumes of the incubation buffer. Tissue preparation was carried out at 4 °C throughout.

In experiments to determine the IC50 values for substituted benzamide drugs and other neuroleptics, aliquots (1·0 ml) of the washed tissue preparations were pre-incubated on ice with either 50 µl 0·1% ascorbic acid to determine total binding or with 50 µl 0·1% ascorbic containing the displacing drug for 10 min. [^{3}H]Spiperone (16 or 21 Ci^{-1} mmol; Amersham International) was added in 50 µl 0·1% ascorbic acid to give a final concentration of 0·2 nM. Specific binding to D–2 sites was defined by the incorporation of 3×10^{-5} M sulpiride. [^{3}H]Piflutixol (11·7 Ci^{-1} mmol; Lundbeck) also was added in 0·1% ascorbic acid to give a final concentration of 0·3 nM. Specific binding to D–1 sites was defined by the incorporation of 10^{-6} M *cis*-flupenthixol in the presence of 3×10^{-5} M sulpiride. Incubations were carried out at 37 °C for 15 min in the case of [^{3}H]spiperone binding and for 25 min for [^{3}H]piflutixol binding. Incubates were filtered using Millipore 1225 filtration manifolds over GF/C Whatman filters under vacuum and washed twice with 5 ml ice-cold 50 mM Tris HCl buffer, pH 7·7. Filter papers were placed in 4 ml ES 299 scintillation cocktail (Packard), allowed to stand overnight and counted at 45% efficiency using a Packard 460C scintillation counter.

Displacing drugs were added to the incubates in concentrations ranging between 10^{-10} – 10^{-4} M. The concentration required to produce 50% inhibition of specific binding was determined from the pooled results of determinations made on two separate tissue pools.

Adenylate cyclase assay

Basal and dopamine (100 µM) stimulated striatal adenylate cyclase activity was assayed according to the technique of Miller et al (1974) using the saturation assay of Brown et al (1972). Rats (150 ± 10 g) were killed by cervical dislocation and decapitation and the brain rapidly removed onto ice. Paired striata from 3 animals were dissected out and pooled. Basal and dopamine stimulated adenylate cyclase were determined in triplicate in pooled striatal tissue homogenates on at least two separate occasions. Substituted benzamide drugs and other neuroleptics were incorporated into tissue incubates in concentrations between 10^{-10}–10^{-4} M. The results from each experiment were pooled and the concentration response curve for inhibition of cyclic AMP formation examined to determined the IC50 value for each drug.

Determination of lipophilicity

The apparent n-octanol/water partition coefficients at pH 7·4 were determined by the shake flask method using concentration of solutes in the range $5–8 \times 10^{-5}$ M. Between 6–8 independent assays were made in phosphate or carbonate buffers pH values ranging from 6–9 and of ionic strength 0·1. The temperature was 20 ± 1 °C. As far as possible the volume of the two phases was chosen to leave approximately 30–60% of the solute in the aqueous phase. The tubes were submitted to gentle mechanical shaking for 1 h then centrifuged for 20 min at 8000 rev min^{-1}. The aqueous phase was analysed for the solutes by u.v. spectroscopy. The pH was measured before and after each experiment using a Polymetron 5101 pH meter. From the experimentally determined partition coefficients at the various pH values, the log P′ values at pH 7·4 were calculated using the pK_a values of these compounds. The standard deviations of the log P′ values are in the range 0·02–0·10.

RESULTS

The results of the behavioural and biochemical examinations are summarized in Table 1.

Table 1. Comparison of the ability of substituted benzamide drugs and other neuroleptic compounds to inhibit [^{3}H]spiperone ([^{3}H]SPI) or [^{3}H]piflutixol ([^{3}H]PIF) binding to rat striatal preparations, to inhibit striatal dopamine-stimulated adenylate cyclase (AC) and to inhibit apomorphine-induced stereotyped behaviour.

Drug	IC50 (nM) AC	[^{3}H]PIF	[^{3}H]SPI	ID50 (mg kg^{-1}) Stereotypy
YM 09151-2	20 000	22 000	0·4	0·017
Clebopride	19 000	100 000	18	0·34
Flubepride	>100 000	>100 000	290	24
Sultopride	>100 000	>100 000	260	41
Sulpiride	>100 000	>100 000	570	>128
Metoclopramide	>100 000	>100 000	680	5·4
Tiapride	>100 000	>100 000	1000	48
Tigan	>100 000	>100 000	8000	>250
cis-Flupenthixol	24	3·2	1·3	0·25
trans-Flupenthixol	850	89	56	>128
Spiperone	3360	1400	0·6	0·028
Haloperidol	1800	1000	6	0·16
Thioridazine	7600	40	120	10·4

Adenylate cyclase activity was stimulated by the incorporation of 100 µM dopamine. Specific binding of [^{3}H]spiperone (0·2 nM) to D-2 receptors was defined using 3×10^{-5} M sulpiride. Specific binding of [^{3}H]piflutixol (0·3 nM) to D-1 receptors was defined using 10^{-6} M *cis*-flupenthixol in the presence of 3×10^{-5} M sulpiride. Drugs were incorporated into binding assays into concentrations between 10^{-10}–10^{-5} M and into adenylate cyclase assays between 10^{-10}–10^{-4} M. Each drug concentration was examined in triplicate on at least two separate occasions.

Stereotypy was assessed following administration of apomorphine hydrochloride (0·5 mg kg^{-1}) 15 min previously. Drugs were administered 1 h before apomorphine administration.

Apomorphine-induced stereotyped behaviour

Apomorphine (0·5 mg kg^{-1} s.c. 15 min previously) -induced stereotyped behaviour was potently inhibited by clebopride and YM 09151-2. Flubepride, sultopride, metoclopramide and tiapride also inhibited stereotyped behaviour but were less potent. Sulpiride and Tigan did not inhibit stereotyped behaviour in the dosage range used. *cis*-Flupenthixol but not *trans*-flupenthixol, spiperone, haloperidol and thioridazine also markedly inhibited stereotyped behaviour.

Ligand binding assays

YM 09151-2 and clebopride displaced [^{3}H]spiperone (0·2nM) from its specific striatal D-2 binding site in low nanomolar concentrations. Flubepride, sultopride, sulpiride and metoclopramide were less potent in displacing [^{3}H]spiperone while tiapride and tigan only caused displacement in micromolar concentrations.

cis-Flupenthixol was approximately 4 times more potent than *trans*-flupenthixol in displacing [^{3}H]spiperone. Spiperone, haloperidol and thioridazine also caused displacement of [^{3}H]spiperone from its specific binding site.

YM 09151-2 and clebopride caused only weak displacement of [^{3}H]piflutixol (0·3 nM) binding to D-1 sites on striatal preparations in high micromolar concentrations. Flubepride, sultopride, sulpiride, metoclopramide, tiapride and tigan were inactive in displacing [^{3}H]piflutixol in the concentrations used in these experiments.

cis-Flupenthixol caused displacement of [^{3}H]piflutixol in low nanomolar concentrations, and was approximately 30 times more active than *trans*-flupenthixol. Thioridazine also potently displaced [^{3}H]piflutixol from its specific binding site but spiperone and haloperidol were active only in micromolar concentrations.

Dopamine stimulated adenylate cyclase activity

YM 09151-2 and clebopride inhibited dopamine (100 μM)-stimulated adenylate cyclase activity but only in micromolar concentrations. Flubepride, sultopride, sulpiride, metoclopramide, tiapride and tigan were inactive in the concentrations employed in these experiments.

cis-Flupenthixol inhibited dopamine stimulated adenylate cyclase activity in low nanomolar concentrations and was approximately 40 times more effective than *trans*-flupenthixol. Spiperone, haloperidol and thioridazine, however, were only effective in micromolar concentrations.

Lipid solubility

The apparent partition coefficients of the substituted benzamide drugs and other neuroleptics are shown in Table 2 in comparison to their ability to inhibit parameters associated with D-1 receptors (dopamine stimulated adenylate cyclase activity and specific [^{3}H]piflutixol binding sites).

Table 2. Potency order of substituted benzamide drugs and other neuroleptic compounds in inhibiting dopamine-stimulated adenylate cyclase (AC) and [^{3}H]piflutixol ([^{3}H]PIF) binding in rat striatal preparations, ranked according to increasing lipid solubility (log P′ at pH 7·4).

Compound	log P′	IC50 (nM) AC	IC50 (nM) [^{3}H]PIF
Sulpiride	−1·15	>100 000	>100 000
Tiapride	−1·08	>100 000	>100 000
Sultopride	−0·62	>100 000	>100 000
Metoclopramide	0·46	>100 000	>100 000
Tigan	0·89	>100 000	>100 000
Flubepride	1·17	>100 000	>100 000
Spiperone	2·34[a]	3360	1400
Clebopride	2·99	19 000	100 000
Haloperidol	3·03[a]	1800	1000
Thioridazine	3·29[a]	7600	40
YM 09151-2	3·51	20 000	22 000
cis-Flupenthixol	3·96[a]	24	3·2
trans-Flupenthixol	3·96[a]	850	89

[a] Data taken from Tollenaere et al (1977).

Sulpiride, sultopride and tiapride showed very low lipid solubility. Metoclopramide, tigan and flubepride also were only weakly lipophilic. In contrast, YM 09151-2 and clebopride showed high lipophilicity equivalent to that of spiperone, haloperidol, thioridazine and *cis*- and *trans*-flupenthixol.

Comparison of the apparent partition coefficient with the ability of substituted benzamide drugs and other neuroleptics to inhibit dopamine stimulated adenylate cyclase activity and displace [^{3}H]piflutixol binding showed that log P′ values of less than 2 resulted in no inhibition of these parameters. Compounds with log P′ values greater than 2 inhibited both adenylate cyclase activity and displaced [^{3}H]piflutixol from its specific binding site but there was no correlation between the ability of compounds to inhibit these parameters and their apparent partition coefficient.

DISCUSSION

We have compared the ability of substituted benzamide drugs and classical neuroleptic agents to act on D-1 and D-2 receptors as judged by their capacity to inhibit ligand binding assays and dopamine

stimulation of striatal adenylate cyclase in rat tissue preparations. All the substituted benzamide drugs including YM 09151-2 and clebopride caused displacement of [^{3}H]spiperone from its specific striatal binding site but these compounds had little or no activity in inhibiting adenylate cyclase activity or in displacing [^{3}H]piflutixol from D-1 binding sites. This contrasts with the effects of *cis*-flupenthixol, a drug equiactive at D-1 and D-2 receptors. Most substituted benzamide drugs were inactive in the D-1 systems in the highest concentrations employed. However, YM 09151-2 and clebopride did cause some inhibition of dopamine stimulated adenylate cyclase activity and specific [^{3}H]piflutixol binding. Nevertheless, neither of the latter compounds was a selective D-1 active drug. They were both at least 1000 times more potent in inhibiting [^{3}H]spiperone binding to D-2 receptors than acting on the D-1 test systems. This would suggests that substituted benzamide drugs as a whole are selective antagonists of the D-2 dopamine receptor binding site. In contrast to the assertions of Usuda and colleagues (1981) the more potent lipophilic substituted benzamide drugs such as clebopride or YM 09151-2 did not exert a powerful action on D-1 receptors compared with their actions on D-2 receptors; certainly, they were not selective antagonists at the D-1 receptor. The biochemical experiments suggested that although clebopride and YM 09151-2 were not selective D-1 antagonists, they did cause some inhibition of D-1 receptor systems. This may be correlated with their greater lipid solubility compared with other substituted benzamide drugs. To investigate this possibility we have examined the effects of increasing lipid solubility, as judged by log P′, on the ability of the drugs to inhibit dopamine stimulated adenylate cyclase activity and to displace [^{3}H]piflutixol from its binding site on rat striatal preparations (Table 2).

A log P′ value of less than 2 was associated with no activity in inhibiting dopamine sensitive adenylate cyclase or in displacing [^{3}H]piflutixol from its specific binding site. Log P′ values above 2 were associated with inhibition of both systems. These findings are consistent with the hypothesis of Woodruff & colleagues (1980) that the interaction of neuroleptic drugs with D-2 receptors is at least partially dependent of high lipid solubility. However, there was no direct correlation between lipid solubility and the selectivity of drugs for D-1 as opposed to D-2 receptors. This suggests that although lipid solubility is a limiting factor, steric factors also contribute significantly to the action of neuroleptic drugs at D-1 receptors. We suggest that substituted benzamide drugs are selective for D-2 receptors, an effect which is not merely a function of lipid solubility. These molecules contain inherent steric factors which dictate their activity at the D-2 site but not at the D-1 receptor site. Activity at D-1 receptors appears dependent to some extent on lipid solubility but within a wide range of lipid solubilities steric factors also dictate the interaction of neuroleptic drugs with these receptor sites. This conclusion is strengthened by the fact that functional neuroleptic activity is associated with the activity of these drugs at D-2 sites (Seeman 1980; Leysen 1982). Indeed, in the present study, correlation matrix analysis showed a high degree of correlation between the ability of neuroleptic drugs to displace [^{3}H]spiperone and their ability to inhibit apomorphine-induced stereotyped behaviour (Table 3). As might be expected, a good correlation existed also between the two parameters associated with D-1 receptor function, namely [^{3}H]piflutixol binding and dopamine stimulated adenylate cyclase. This confirms the original finding of Hyttel (1978). However, there was no such correlation between [^{3}H]piflutixol binding or dopamine stimulated adenylate cyclase activity and [^{3}H]spiperone binding or stereotyped behaviour. In conclusion, substituted benzamide drugs do appear to be selective D-2 receptor antagonists and this selectivity does not appear to be due entirely to their variable lipid solubility.

Table 3. Correlation matrix for the ability of the neuroleptic drugs examined to inhibit apomorphine-induced stereotypy, to inhibit striatal dopamine stimulated adenylate cyclase (AC) and to inhibit specific binding of [^{3}H]spiperone and [^{3}H]piflutixol to rat striatal preparations

	pIC50 stereotypy	pIC50 AC	pIC50 [^{3}H]-piflutixol
pIC50 stereotypy	—		
pIC50 AC	−	—	
pIC50 [^{3}]piflutixol	−	+	—
pIC50 [^{3}H]spiperone	+	−	−

+ Significant ($P < 0{\cdot}01$).
− No correlation ($P > 0{\cdot}1$)

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