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Assessment of the neuroleptic potential of some novel benzamide, butyrophenone, phenothiazine and indole derivatives

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A series of experimental models were used to determine the activity spectra of potential neuroleptic agents on extrapyramidal and/or mesolimbic dopamine systems: catalepsy induction by the drug alone or in the presence of the acetylcholine-like agent, RS86 [spiro-(*N'*-methylpiperidyl-4')-*N*-ethyl succinamide hydrogen fumarate], or α-methyl-*p*-tyrosine (α-MT), stereotypy antagonism (amphetamine) and hyperactivity antagonism (intra-accumbens and intrastriatal dopamine). Antiemetic potential was also considered. Whilst classical neuroleptics were active in all test situations, other neuroleptics including benzamide, phenothiazine, butyrophenone and indole derivatives exhibited novel activity spectra: clozapine failed to interact with α-MT, metoclopramide failed to antagonize a mesolimbic hyperactivity or interact with the acetylcholine-like agent. Other benzamide derivatives, clebopride, AHR6092, sultopride and tiapride also failed to interact with RS86, but whilst clebopride was active in all other test situations, AHR6092 was inactive in all but the antiemetic test, sultopride was only weakly cataleptogenic and tiapride only antagonized stereotypy and hyperactivity from the striatum. AHR6839, AHR6134, AHR6645, AHR6505B and AHR1709 were generally inactive in the catalepsy tests but exerted dopamine antagonistic potential in other test procedures. The antagonistic ability of AHR1709 was only revealed in the tests where dopamine function was specifically raised in the nucleus accumbens and caudate-putamen by intracerebral dopamine injections. Data are discussed in terms of a dissociation of drug effects on different cerebral dopamine systems.

Investigations using the classical behavioural tests for neuroleptic activity (inhibition of conditioned avoidance behaviour and self stimulation, catalepsy induction and stereotypy antagonism) have greatly increased knowledge on the mode of action of antipsychotic agents. However, used as screens, these tests have detected agents having essentially the same mode of action, which is primarily characterized by non-specific antagonism of all cerebral dopamine systems. Thus, neuroleptic agents in common use not only inhibit mesolimbic dopamine function (considered an essential prerequisite for antipsychotic potential) but also inhibit extrapyramidal dopamine mechanisms (causing Parkinson-like side effects) (Stevens, 1973; Waldmeier & Maitre, 1976; Hornykiewicz, 1977; Westerink, Lejeune & others, 1977). Recently, however, experimental models have been developed which use a more discrete stimulation of either mesolimbic or striatal dopamine systems, and these tests are considered to indicate, more specifically, an ability to antagonize a raised mesolimbic or striatal dopamine activity, for example, clozapine and metoclopramide respectively (Costall & Naylor, 1976a). The present studies further investigate the possibility of differentiating inhibitory drug action on dopamine systems using a series of novel benzamide, butyrophenone, phenothiazine and indole compounds.

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MATERIALS AND METHODS

Male Sprague-Dawley (CFE) rats, 250 ± 25 g, were used. For observation and measurement of catalepsy they were placed in individual, screened Perspex cages (25 × 15 cm and 15 cm high) in a sound-proofed, diffusely illuminated room maintained at a temperature of 21 ± 2°. Rats were placed in the observation/testing cages 30 min before drug treatment to allow adaptation to the new environment. All observations were made between 08.00 a.m. and 08.00 p.m.

Animals were tested for the presence of catalepsy by placing both front limbs over a 10 cm high horizontal bar, a cataleptic animal maintaining this position for a period of time dependent upon the degree of catalepsy. Animals were tested frequently after drug administration to determine the onset of catalepsy and the intensity of catalepsy

was then measured at 10–30 min intervals throughout the following 5 h. To account for animals maintaining the imposed position for an 'infinite' period the following scoring system was adopted for estimation of the intensity of catalepsy, 0 = no catalepsy, 1 = 0·1–2·5 min, 2 = 2·6–5·0 min, 3 = 5·1–10·0 min, 4 = 10·1–20·0 min, 5 = 20·1 min—∞.

In experiments to determine the effects of α-methyl-*p*-tyrosine (α-MT) on catalepsy, it was administered at 250 mg kg^{-1}, i.p., 6 h before a threshold dose of neuroleptic/test agent. Animals were tested for catalepsy immediately before the administration of α-MT to establish that this compound did not in itself induce catalepsy, and animals were then tested at the usual 10–30 min intervals for a minimum of 5 h. To determine the effects of combining a threshold dose of neuroleptic/test agent with the acetylcholine-like agent RS86, both agents were administered at the same time. Preliminary experiments showed 5 mg kg^{-1}, i.p., RS86 induced a threshold cataleptic response (see also Costall & Naylor, 1973). This dose was, therefore, used in the combination studies.

Initial experiments indicated that 5 mg kg^{-1}, i.p., amphetamine was the lowest dose to reliably induce, in 100% animals, a stereotyped behaviour characterized by a continuous biting/gnawing/licking. This dose was used in all the antistereotypy experiments. The antistereotypic effects of the neuroleptic/test agents were determined by administering these drugs 30 min before amphetamine. Like catalepsy, stereotypy was initially assessed as a score before transposition to the simple system of assessment shown in Tables 1–3. The scoring system for stereotypy was 0 = no stereotypy, 1 = periodic sniffing, 2 = continuous sniffing, 3 = periodic biting, 4 = continuous biting.

In the hyperactivity experiments dopamine was injected directly into the nucleus accumbens (ACB) or caudate-putamen (CP). Bilateral guide cannulae (0·65 mm diameter) were stereotaxically implanted with their tips at Ant. 8·0, Vert. +3·0, Lat. ±3·0 (caudate-putamen) and Ant. 9·0, Vert. +2·5, Lat. ±1·6 (nucleus accumbens) (De Groot, 1959) 10–14 days before animals were used. Rats were then manually restrained and stylets removed from the guides and replaced by injection units (0·3 mm diam.) which terminated 1·5 mm (caudate-putamen) or 2·5 mm (nucleus accumbens) below the tips of the guides. 25 μg (2 μl) or 50 μg (1 μl) dopamine was delivered simultaneously to both hemispheres over 5 s with the injection units remaining in position for a further 55 s. Animals were used once only. On completion of the experiments, guide cannulae locations were determined histologically in every tenth rat: all locations were shown to be within the correct area.

Activity was measured in Perspex cages (30 × 20 cm and 15 cm high) fitted with photocells. The number of light beam interruptions occurring within each 5 min was recorded. Conditions were as previously described. Initial experiments established the reliability of the hyperactivity responses to injections of 25 μg dopamine into the caudate-putamen or 50 μg dopamine into the nucleus accumbens following a 2 h pretreatment with 100 mg kg^{-1}, i.p., nialamide (see Costall & Naylor, 1976a). Any animal showing stereotyped biting behaviour (caudate-putamen) or failing to exhibit a hyperactivity of at least 40 counts/5 min (nucleus accumbens) or 30 counts/5 min (caudate-putamen) were excluded. Neuroleptic/test agents were administered intraperitoneally when hyperactivity was established at maximum intensity (3 h after dopamine injection into the caudate-putamen or 2·5 h for the nucleus accumbens). Activity was then recorded for at least a further 4 h.

Dopamine HCl (Koch Light) was prepared for intracerebral administration immediately before use in nitrogen bubbled distilled water neutralized with sodium bicarbonate. All other agents were administered intraperitoneally and, where the solubility permitted, in a volume of 1 ml kg^{-1}, doses being expressed as the base.

(+)-Amphetamine SO_4 (Sigma), RS86 (Spiro-(*N'*-methylpiperidyl-4')-*N*-ethyl succinimide hydrogen fumarate (Sandoz), sultopride HCl (Delagrange), tiapride HCl (Delagrange), metoclopramide monohydrochloride (Beecham's), fluphenazine HCl (Squibb) and clebopride HCl (Almirall) were dissolved in distilled water, clozapine (Wander), sulpiride (Delagrange) and nialamide (Sigma) in the minimum quantity of HCl made up to volume with distilled water, haloperidol (Janssen), AHR6092 (*N*-(1-cyclohexyl-3-pyrrolidinyl)-2-methoxy-5-sulphamoyl benzamide), cloroperone (AHR6134) ([4-fluorophenyl] [1-(3-(5H-10,11-dihydrodibenz-[b,f]azepin-5-yl) propyl)piperidin-4-yl]methanone oxalate) (see Duncan, Helsley & others, 1970), AHR6839 (4-[4-(3,4-dichlorobenzoyl)piperidin-1-yl]-1-(4-fluorophenyl)-1-butanone), AHR6645 ([4-fluorophenyl]-[1-(3-(5-phenothiazinyl)propyl)-piperidin-4-yl]methanone fumarate hydrate (1:4)) (see Boswell, Welstead & others, 1978), AHR6505B ([1-(3-(2-chloro-10H-phenothiazin-10-yl)propyl)-piperidin-4-yl] [1-fluorophenyl]methanone fumarate)

(see Boswell & others, 1978) and AHR1709 (3,2-(4-phenyl-1,2,5,6-tetrahydropyridin-1-yl)ethyl)-1H-indole) (see Welstead, DaVanzo & others, 1967) were dissolved in the minimum quantity of *NN*-dimethylformamide made up to volume with distilled water and α-methyl-*p*-tyrosine (Sigma) prepared as a suspension in 2% carboxymethylcellulose.

RESULTS

The typical neuroleptic agents haloperidol and fluphenazine were shown to be potent cataleptogens producing a dose-dependent catalepsy which attained maximum intensity as defined by the scoring system in the Methods section. Threshold doses of both agents synergized in the production of catalepsy with the acetylcholine-like agent RS86 and with α-MT (Table 1). Subcataleptic doses of both haloperidol and fluphenazine antagonized the stereotyped behaviour induced by amphetamine in a dose-dependent manner, and achieving complete inhibition at the higher doses (Table 1). Subcataleptic doses of these typical neuroleptics similarly antagonized the hyperactivity caused by dopamine injected into the nucleus accumbens, and slightly larger doses also antagonized the

Table 1. *Effects of some typical and atypical neuroleptic agents in tests for dopamine antagonist activity.* Data were obtained in the different experimental paradigms using the techniques described in Metho s. The activity of the neuroleptic agents in the different test situations has been simplified to 0 = no effect, + = weak, ++ = moderate or +++ = marked effect (maximum effects shown).

Drug	Dose mg kg^{-1}, i.p.	Catalepsy: Drug alone	Catalepsy: Drug +RS86	Catalepsy: Drug +α-MT	Stereotypy antag.	Hyperactivity antagonism: (ACB)	Hyperactivity antagonism: (CP)	Antiemetic action*
Haloperidol	0·013				+			3·1*
	0·025				++			(i.m.)
	0·05	0			+++	++		
	0·125	0				+++		
	0·25	+	+++	+++		+++	0	
	0·2	++					++	
	1	+++					+++	
Fluphenazine	0·013				0			5·3*
	0·025				+	0		(s.c.)
	0·05				++	+		
	0·125				+++	+++	0	
	0·25	0				+++	++	
	0·5	+	+++	+++			+++	
	1	++						
	2	+++						
Clozapine	0·62					+		?
	1·25					+		
	2·5					+++	0	
	5					+++	+	
	10				0		+	
	20	0			+		++	
	40	+	+++	0	++		+++	
	80	+						
Sulpiride	1·25					0		1·8*
	2·5					+	0	(s.c.)
	5					++	+	
	10					+++	++	
	20	0					+++	
	40	+	+++	++	0			
	80	+			+			
	160	+			++			
Metoclopramide	0·5				+			30*
	1·25	0			++			(s.c.)
	2·5	+	0	+++	+++			
	5	+				0	0	
	10	++				0	++	
	20	+++				0	+++	
	30					0		

* ED50 (μg kg^{-1}) using 100 μg kg^{-1}, s.c. apomorphine in dogs. Route of administration is shown in parentheses.

hyperactivity caused by dopamine from the caudate-putamen (Table 1). Clozapine and sulpiride were shown to be only weakly cataleptogenic, and although rats treated with clozapine exhibited marked motor depression/sedation, those given sulpiride appeared alert even during the period of the catalepsy response. Both agents synergized markedly with RS86 in the production of catalepsy, but synergism was less marked when sulpiride was combined with α-MT and α-MT plus clozapine failed to synergize in the production of catalepsy (Table 1). Stereotyped behaviour was antagonized by both clozapine and sulpiride, but the doses required were large in comparison to those of the typical neuroleptics and a complete inhibition of the amphetamine stereotypy was not observed at the doses used. In contrast to the generally weak cataleptogenic and antistereotypic actions of clozapine and sulpiride, both these agents were highly effective as antagonists of the hyperactivity states induced by dopamine from either the nucleus accumbens or caudate-putamen. Again, the hyperactivity induced from the nucleus accumbens was most susceptible to antagonism, and the effects of clozapine and sulpiride against both hyperactivity responses was dose-dependent and complete at the larger doses (Table 1). Metoclopramide exhibited an activity spectrum unique from those of the typical and atypical agents selected for this study. Thus, metoclopramide caused a dose-dependent catalepsy attaining maximum intensity, and synergized in the production of catalepsy with α-MT. However, in contrast to both the typical and atypical agents, metoclopramide did not synergize with RS86. In further contrast, metoclopramide also failed to antagonize the hyperactivity induced by dopamine from the nucleus accumbens, even in supramaximal cataleptic doses (Table 1). However, the hyperactivity resulting from intrastriatal dopamine injections was antagonized by metoclopramide, as was amphetamine stereotypy (Table 1). All agents shown in Table 1 are potent antiemetic drugs.

Of the benzamide derivatives shown in Table 2, both AHR6092 and tiapride failed to induce catalepsy in dose ranges of 10–160 mg kg^{-1}. Further, other than a weak response recorded for tiapride in combination with α-MT, both this pretreatment and RS86 failed to reveal a cataleptic potential for either AHR6092 or tiapride. Indeed, animals

Table 2. *Effects of some benzamide derivatives in tests for neuroleptic activity.* Data were obtained in the different experimental paradigms using the techniques described in Methods. The activity of the benzamide derivatives in the different test situations has been simplified to 0 = no effect, + = weak, ++ = moderate or +++ = marked effect (maximum effects shown).

Drug	Dose mg kg^{-1}, i.p.	Catalepsy: Drug alone	Catalepsy: Drug +RS86	Catalepsy: Drug +α-MT	Stereotypy antag.	Hyperactivity antagonism: (ACB)	Hyperactivity antagonism: (CP)	Antiemetic action*
Clebopride	0·25				0		0	2·5*
	0·5				+	0	++	(s.c.)
	1·25				+	++	+++	
	2·5	+	0	+++	++	+++		
	5	++			+++			
	10	++						
	20	++						
AHR6092	20	0			0	0	0	13·8*
	40	0			0	0	0	(s.c.)
	80	0			0	0	0	
	160	0	0	0	+	0	0	
Sultopride	10	0			0	0	+	2·3*
	20	+	0	++	+	+	++	(s.c.)
	40	+			+++	++	+++	
	80	+			+++	+++		
	160	++						
Tiapride	10	0			0	0	0	42·0*
	20	0			0	0	++	(s.c.)
	40	0	0	+	+	0	+++	
	80	0			+++	0		
	160	0			+++	0		

* ED50 (μg kg^{-1}) using 100 μg kg^{-1}, s.c. apomorphine in dogs. Route of administration is shown in parentheses.

treated with both small and large doses of these drugs exhibited alert appearances. This alert and responsive attitude also occurred in animals treated with all doses of clebopride (0·25–20 mg kg^{-1}) and with sultopride (doses up to 40 mg kg^{-1}) even though a weak to moderate intensity catalepsy was recorded. As observed with AHR6092 and tiapride, clebopride and sultopride both failed to synergize with RS86 to produce catalepsy, although both agents synergized with α-MT (Table 2). The ineffectiveness of AHR6092 in the catalepsy tests was generally reflected in all experimental paradigms: AHR6092 caused only a weak antagonism of amphetamine stereotypy at 160 mg kg^{-1}, and failed to antagonize the hyperactivity states induced by dopamine from the nucleus accumbens or caudate-putamen (20–160 mg kg^{-1}) (Table 2). However, like the other benzamide derivatives, and the agents shown in both Tables 1 and 3, AHR6092 has been found to exert potent antiemetic properties.

In contrast to AHR6092, clebopride, sultopride and tiapride were each shown to cause dose-dependent (and eventually complete) antagonism of amphetamine stereotypy and the hyperactivity resulting from intrastriatal dopamine. However, although clebopride and sultopride were also effective antagonists of the accumbens hyperactivity, tiapride was completely inactive in this model (Table 2). In contrast to the effects of the typical and atypical neuroleptic agents shown in Table 1, clebopride and sultopride showed a tendency to greater antagonistic activity against intrastriatal dopamine (Table 2).

The activity spectra of the AHR compounds

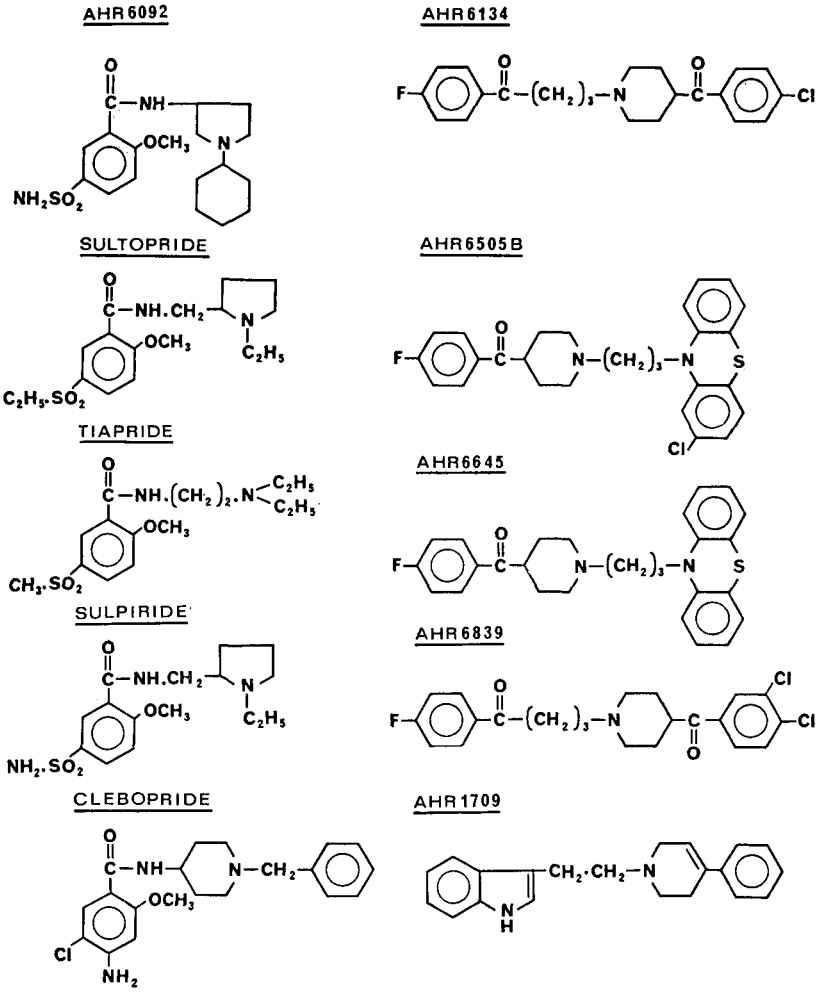
Table 3. *Effects of some AHR compounds in tests for neuroleptic activity.* Data were obtained in the different experimental paradigms using the techniques described in Methods. The activity of the AHR compounds in the different test situations has been simplified to 0 = no effect, + = weak, ++ = moderate or +++ = marked effect (maximum effects shown).

Drug	Dose mg kg^{-1}, i.p.	Catalepsy: Drug alone	Catalepsy: Drug +RS86	Catalepsy: Drug +α-MT	Stereotypy antag.	Hyperactivity antagonism: (ACB)	Hyperactivity antagonism: (CP)	Antimetic action*
AHR6839	2·5					0	0	N.T.
	5	0				++	+	
	10	0			0	+++	++	
	20	0			+	+++	+++	
	40	0	++	+++	++			
	80	0			++			
AHR6134	1·25				0	0	0	77*
	2·5				+	++	++	(i.m.)
	5				++	+++	+++	
	10				++	+++		
	20	0			++			
	40	0			++			
	80	+	+++	0	+++			
AHR6645	5	0			0	+	0	N.T.
	10	0			+	+++	+++	
	20	0			+	+++	+++	
	40	0	+	+++	+	+++		
	80	0			++			
AHR6505B	0·5				0		0	14·1*
	1·25				++	0	++	(i.m.)
	2·5	0			++	+++	+++	
	5	+	0	0	++	+++		
	10	+			++			
	20	+			+++			
	40	+						
AHR1709	2·5					0	0	≪5·0**
	5	0			0	+++	+++	(p.o.)
	10	0			0	+++	+++	
	20	0			0			
	40	0	0	0	0			
	80	0			0			

ED50 (μg kg^{-1}),* (mg kg^{-1})** using 100 μg kg^{-1}, s.c. apomorphine in dogs. Route of administration is shown in parentheses. N.T. not tested.

shown in Table 3 were unique. All agents exhibited powerful effects in certain of the experimental situations, but with the exception of the weak catalepsy recorded for AHR6505B, all agents failed to induce catalepsy in doses up to 40 or 80 mg kg^{-1} (AHR6839, AHR6134, AHR6645 and AHR1709). In contrast, animals treated with up to 40 mg kg^{-1} AHR6134, 80 mg kg^{-1} AHR6645 and 80 mg kg^{-1} AHR1709 appeared alert, the latter animals being reactive to handling and exhibiting periods of increased locomotion. However, animals treated with AHR6839 and AHR6505B were quiet and muscular hypotonia was apparent at the larger doses (20–80 mg kg^{-1}).

Although AHR6839 and AHR6645 failed to induce catalepsy alone, a cataleptic potential was revealed for both these agents by combination with RS86 and α-MT. Further, both agents were shown to antagonize amphetamine stereotypy and both were capable of completely antagonizing the dopamine hyperactivity responses from the nucleus accumbens and caudate-putamen. AHR6134 was similarly effective against stereotypy and the two hyperactivity states but, although a cataleptic potential was revealed for this agent in combination with RS86, α-MT and AHR6134 failed to cause catalepsy (Table 3). AHR6505B was also effectively anti-stereotypic and antagonized the hyperactivity responses: however, the weak cataleptic effect of this drug was not enhanced by either RS86 or α-MT (Table 3). The activity spectrum of AHR1709 differed even further from those of control neuroleptic agents: AHR1709 failed to induce catalepsy when administered alone or in combination with RS86 and α-MT, and failed to antagonize stereotypy. However, when dopamine



function was artificially raised by injection of the neurotransmitter into the nucleus accumbens or caudate-putamen, the resultant hyperactivity states could be abolished by AHR1709 (Table 3).

DISCUSSION

The present studies analysed the activities of classical neuroleptic agents and some novel potential neuroleptics to cause effects consistent with an action on both the extrapyramidal and mesolimbic systems, or a more specific action on one system.

Neuroleptic catalepsy was assumed, with certain reservations (see Jenner, Elliott & others, 1978), to be a behavioural effect in rats which is broadly analogous to the Parkinson-like side effects induced by neuroleptic agents in the clinic. Catalepsy was assessed in normal rats and in those treated with either an acetylcholine-like agent, RS86, or α-MT to optimize conditions for catalepsy induction (see Costall & Naylor, 1973). It was shown that the potential of the classical neuroleptic agents, haloperidol and fluphenazine, to induce a marked catalepsy could not be extended to other butyrophone and phenothiazine test compounds. Thus, AHR6839, AHR6645 and AHR6134 failed to induce catalepsy in normal rats, and required RS86 and/or α-MT to facilitate a response. Similarly, in the benzamide series, metoclopramide was shown to induce an intense cataleptic state, and the weaker actions of clebopride, sultopride and particularly sulpiride were exaggerated by RS86 and/or α-MT. In contrast, the benzamide derivative tiapride and the indole compound ARH1709 failed to induce consistent catalepsy in any of the experimental paradigms. However, although tiapride, AHR6839 and AHR6645 failed to induce catalepsy when administered alone, and AHR6134 had only a weak effect, these agents all exhibited some inhibition of the stereotyped behaviour induced by (+)-amphetamine, indicating that they do have some ability to inhibit cerebral dopamine function (although this ability does not compare with the incisive antistereotypic actions of haloperidol and related agents).

The ability of neuroleptic agents to induce catalepsy and to antagonize stereotypy probably reflects an action within the mesolimbic and extrapyramidal dopamine systems (Costall & Naylor, 1974; 1976b; Pijnenburg, Honig & van Rossum, 1975). Although the precise relevance of these two behavioural indices to an antischizophrenic action remains speculative, drug action in the mesolimbic system is considered to more closely relate to an antipsychotic action, whereas the extrapyramidal effect is thought to relate to an ability to induce Parkinson-like side effects (see Introduction). In an attempt to obtain a further index of drug action in these two major dopamine-containing systems, assessments were made of the ability of the agents to antagonize the locomotor hyperactivity induced by intra-accumbens and intrastriatal dopamine. The hyperactivity responses were inhibited by haloperidol and related agents and, more important, also by the atypical agents, clozapine, sulpiride and thioridazine, which are generally inactive in tests for neuroleptic activity. These observations were extended to all of the novel agents investigated in the present studies. Thus agents such as AHR6839 and AHR6645 can dissociate an antagonistic action against raised dopamine function in the extrapyramidal and mesolimbic systems from a cataleptic potential in normal rats. The ability to dissociate antagonistic effects on different cerebral dopamine systems was emphasized by a number of observations. Firstly, AHR1709 failed to induce catalepsy (indeed, this drug appeared to have an alerting effect on normal animals) and failed to antagonize stereotypy, and yet inhibited the hyperactivity induced by dopamine from the nucleus accumbens and caudate-putamen. Secondly, an ability to antagonize the extrapyramidal hyperactivity was differentiated from antagonism of the mesolimbic hyperactivity by tiapride and metoclopramide which selectively inhibited the former. Further, AHR6092 was found to be a selective antiemetic agent, which may be indicative of a specific dopamine receptor inhibitory effect in the area postrema, although an inability to penetrate the blood brain barrier may be an associated factor.

In the above interpretation of dissociative drug effects, the differentiations should be cautiously regarded as relative rather than absolute since 'inactive' drugs may be effective at higher dosage. Also, many of the compounds used have received restricted pharmacological investigation and it is possible that they may modify other neurotransmitter systems apart from dopamine. Drug effects on 5-HT, GABA and acetylcholine may clearly influence dopamine function, and the interpretation of data is carefully considered in terms of dopamine 'systems' or 'mechanisms' rather than dopamine 'receptors'. Nevertheless, using a series of butyrophenone, phenothiazine, benzamide and indole compounds, an ability to differentially induce or antagonize behavioural effects indicating a modified dopamine function has been shown. Most interesting,

the present studies have delineated compounds which fail to induce catalepsy and yet are able to modify cerebral dopamine function: such agents may present novel and valuable activity spectra for the treatment of schizophrenia.

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