possible that the receptors are the same as are involved in inhibiting PGE_1- and VIP-induced secretion, since the antisecretory effect of morphine against these secretagogues, measured by the same experimental method, is also blocked by naloxone. Additionally, the range of morphine doses that causes inhibition of PGE_1- and VIP-induced secretion is the same (Coupar 1978: Lee & Coupar 1980a).

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Influence of classical and atypical neuroleptics on apomorphine-induced behavioural changes and on extinction of a conditioned avoidance response

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Acquisition and extinction of conditioned avoidance behaviour are used as animal models to determine the activity of potential antipsychotic drugs. Thus, neuroleptics inhibit acquisition and facilitate extinction of conditioned avoidance behaviour. These drugs are also potent antagonists of dopamine (DA) action. Particularly, the antagonism of behavioural responses induced by apomorphine, a DA receptor stimulant, is considered as an important pharmacological test for showing blockade of DA action. Apomorphine causes a biphasic effect in rate: at low doses it decreases motor activity and induces sedation, while at high doses it increases motor activity and elicits stereotypy (see Di Chiara & Gessa 1978).

The present studies were carried out to determine a possible relation between the ability of haloperidol (a classical neuroleptic drug) and of sulpiride and clozapine (atypical neuroleptics) to antagonize the behavioural responses to apomorphine and their capacity to facilitate extinction of pole-jumping avoidance behaviour in rats.

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Materials and methods

Male Wistar rats of an inbred strain (CPB-TNO, Zeist, The Netherlands), 130–140 g, were housed 5–6 per cage, kept on a standard illumination schedule (light on between 5.00 a.m. and 17.00 p.m.) and had free access to food and water. Experimentation was carried out between 9.00 a.m. and 2.00 p.m. in a sound-proof room. Drugs were administered subcutaneously in the neck. Each rat was used once.

The behavioural effects elicited by apomorphine were observed as described before (Van Ree & Wolterink 1981; Van Ree et al 1982). Briefly, locomotor activity and rearing were measured for 3 min, starting 5 min after apomorphine injection, in a rectangular perspex observation cage. Subsequently, locomotor activity, rearing and stereotypy (duration of sniffing the cage floor) were measured for 4 min, starting 20 min after apomorphine treatment in a small open field.

Table 1. Effect of haloperidol, sulpiride and clozapine on apomorphine-induced behavioural changes. Locomotion was measured for 3·5 min after subcutaneous injection of placebo or apomorphine (125 μ kg^{-1}). The same rats were tested for stereotypy for 4 min, 20 min after treatment. Rats were subcutaneously pretreated with placebo or graded doses of neuroleptics 1 h before placebo or apomorphine.

pre-treatment (mg^{-1}kg)		Locomotion (Mean score ± s.e.m.) Placebo		Apomorphine		Stereotype sniffing (mean time s ± s.e.m.) Placebo	Apomorphine
Placebo		15·8 ± 0·4[1]	(18)	7·5 ± 0·4***	(18)	4 ± 1	68 ± 4**
Haloperidol	0·0005	16·0 ± 1·1	(6)	6·6 ± 1·2***	(6)	4 ± 2	65 ± 6***
	0·001	16·3 ± 0·6	(6)	12·1 ± 0·8**,†††	(6)	6 ± 1	41 ± 4***,†
	0·005	15·8 ± 1·1	(6)	15·7 ± 1·1†††	(6)	4 ± 1	37 ± 2***,††
Placebo		16·8 ± 0·4	(30)	8·5 ± 0·5***	(30)	6 ± 1	59 ± 3***
Sulpiride	0·25	17·6 ± 1·2	(6)	13.3 ± 1·2*,†	(6)	6 ± 2	45 ± 7***
	0·5	15·2 ± 0·5	(6)	13·8 ± 1·5†	(6)	6 ± 1	61 ± 6***
	1·0	15·7 ± 1·2	(6)	14·0 ± 1·3†††	(6)	7 ± 1	61 ± 6***
	5·0	19·7 ± 1·3	(6)	17·2 ± 0·8†††	(6)	6 ± 1	50 ± 6***
	35·0	11·0 ± 1·2**	(6)	13·2 ± 0·8†	(6)	16 ± 3	29 ± 5*,†††
Placebo		18·1 ± 0·9	(12)	11·4 ± 0·8***	(12)	11 ± 2	82 ± 5***
Clozapine	0·10	13·1 ± 1·7*	(6)	8·6 ± 1·0*	(6)	7 ± 2	59 ± 2***,††
	0·25	14·3 ± 1·3*	(6)	9·2 ± 1·5*	(6)	8 ± 2	34 ± 6**,†††

( ) number of animals.
* Different from placebo-placebo or neuroleptic-placebo treated rats (* $P < 0·05$, ** $P < 0·01$, *** $P < 0·001$).
† Different from placebo-apomorphine treated rats († $P < 0·05$, †† $P < 0·01$, ††† $P < 0·001$).

Rats were trained for pole jumping avoidance behaviour, as described previously (De Wied et al 1978). Briefly, rats were trained in 10-trial daily sessions for 4 days to jump into a pole during 5 s presentation of a light signal (conditioned stimulus) to avoid an electric footshock of 0·25 mA (unconditioned stimulus), presented immediately after the conditional stimulus. The day after the last acquisition session rats were subjected to three 10-trial extinction sessions, separated by 2 h. Treatment was performed immediately after the first extinction session.

Apomorphine-HCl was freshly dissolved in 0.9% NaCl (saline). Haloperidol (Haldol) and sulpiride (Dogmatil) were used in the commercially available solution. Clozapine was dissolved in acetic acid, the solution brought to pH 5 with NaOH and adjusted to a final volume with saline.

Student's *t*-test was used to analyse the statistical significance of the data.

Results and discussion

In saline-pretreated animals, apomorphine (125 μg kg^{-1} s.c.) decreased locomotor activity as assessed 5 min after its injection in a small test box (Table 1). Also the rate of rearing was suppressed 5 min after apomorphine treatment (data not shown). When the rats were tested again in the small open field 20 min after apomorphine treatment a significant increase in locomotor activity and rearing compared with control animals was observed (data not shown). In addition, the rats showed stereotyped sniffing for about a quarter of the observation time (Table 1).

The decrease in locomotor activity induced by apomorphine was counteracted by haloperidol in a dose-dependent fashion, while these doses of the neuroleptic failed to affect locomotor activity itself (Table 1). Haloperidol also dose-dependently antagonized the apomorphine-induced stereotypy. However, a dose of 5 μg kg^{-1}, which completely antagonized apomorphine-induced hypoactivity, reduced the drug-induced stereotypy by about 50% only. Also the apomorphine-induced increase in locomotor activity was attenuated

Table 2. Effect of haloperidol, sulpiride and clozapine on extinction of pole-jumping avoidance behaviour.

Treatment	Extinction (10 trials) 0 h	2 h	4 h	
Haloperidol				
0.2 μg kg^{-1}[a]	9·4 ± 0·4[b]	6·2 ± 1·8	3·8 ± 1·3*	(5)
0·7 μg kg^{-1}	9·0 ± 0·4	3·2 ± 0·4**	2.0 + 0.7***	(4)
Saline 0·5 ml	9·7 ± 0·2	9·0 ± 0·5	7·2 ± 1·2	(4)
Sulpiride				
0·2 mg kg^{-1}	9·5 ± 0·5	7·0 ± 2·1	7·0 ± 2·3	(4)
Saline 0·5 ml	9·2 ± 0·2	6·7 ± 2·3	6·7 ± 2·3	(4)
Sulpiride				
2 mg kg^{-1}	9·7 ± 0·2	7·5 ± 0·6	6·5 ± 1·1	(4)
7 mg kg^{-1}	9·6 ± 0·3	6·3 ± 1·2	6·0 ± 0·5	(3)
Saline 0·5 ml	9·0 ± 0·5	7·0 ± 0·0	6·5 ± 0·6	(4)
Sulpiride				
10 mg kg^{-1}	9·5 ± 0·2	7·2 ± 1·2	6·7 ± 0·8	(4)
Saline 0·5 ml	8·6 ± 0·3	8·3 ± 0·3	7·3 ± 0·8	(3)
Sulpiride				
35 mg kg^{-1}	9·4 ± 0·3	4·1 ± 1·1*	2·3 ± 0·7***	(9)
Saline 0·5 ml	9·5 ± 0·3	7·7 ± 0·7	7·2 ± 0·9	(8)
Clozapine				
30 μg kg^{-1}	9·0 ± 0·5	7·0 ± 0·5	6·3 ± 1·3	(4)
Placebo 0·5 ml	9·2 ± 0·4	8·0 ± 0·4	8·0 ± 0·7	(4)
Clozapine				
150 μg kg^{-1}	10 ± 0·0	9·2 ± 0·4	7·5 ± 0·9	(4)
300 μg kg^{-1}	9·2 ± 0·4	7·0 ± 0·4	3·0 ± 0·8**	(4)
Placebo 0·5 ml	9·2 ± 0·4	8·0 ± 0·5	7·0 ± 0·7	(4)

[a] dose per rat, s.c., injected just after the first extinction session (0 h).
[b] mean response ± s.e.m.
( ) number of rats.
* $P < 0·05$, ** $P < 0·01$, *** $P < 0·001$, compared with placebo-treated rats.

by haloperidol (5 μg kg^{-1}) for about 50% (data not shown). Relatively low doses of sulpiride, which failed to affect locomotor activity, antagonized the apomorphine-induced decrease in locomotor activity (Table 1). This antagonism was about 50% when a dose of 0·25 mg kg^{-1} was used. The high dose of sulpiride (35 mg kg^{-1}) decreased locomotor activity of the rats, but attenuated the apomorphine-induced hypoactivity. Doses of sulpiride, that antagonized apomorphine-induced hypoactivity, failed to prevent apomorphine-induced stereotypy. Only the high dose (35 mg kg^{-1}) of sulpiride significantly attenuated apomorphine-induced stereotyped sniffing. Although clozapine (100 or 250 μg kg^{-1}) induced a decrease in locomotor activity, it failed to antagonize apomorphine-induced hypoactivity (Table 1). However, these doses antagonized apomorphine-induced stereotypy in a dose-dependent manner. Similar effects as described for apomorphine-induced decrease of locomotor activity and drug-induced stereotyped sniffing, were observed on apomorphine-induced decrease of rearing and increase of locomotor activity respectively (data not shown).

These data indicate that haloperidol antagonizes the sedative as well as the stimulant effects of apomorphine, that sulpiride preferentially prevents the sedative response to apomorphine and, only at relatively high doses, antagonizes apomorphine-induced stereotypy, and also that clozapine preferentially prevents apomorphine-induced stereotyped sniffing. It has been suggested that the sedative effects of apomorphine are mediated by DA autoreceptors (or presynaptic DA receptors or self-inhibitory DA receptors) (see Di Chiara et al 1978; Van Ree & Wolterink 1981), while the stimulant effects (stereotypy and hyperactivity) are considered to be due to stimulation of postsynaptic DA receptors (Kelly et al 1975). Thus, the present data suggest that low doses of haloperidol block pre- as well as postsynaptic DA receptors, that sulpiride is more active on presynaptic than postsynaptic DA receptors, and that clozapine is more active on postsynaptic DA receptors. However, although low doses of haloperidol may be active on both pre- and postsynaptic receptors, the present data suggest differences between these receptor sites. The dose of haloperidol needed to antagonize apomorphine-induced stereotypy for 50% was approximately five time higher than that to block apomorphine-induced hypoactivity. In fact, the slope of the dose response curves of haloperidol is different, suggesting that different types of receptor sites are involved.

Haloperidol (0·2 and 0·7 μg kg^{-1}) facilitated extinction of pole-jumping avoidance behaviour (Table 2), as reported before (Kovács & De Wied 1978). Sulpiride was much less active. Only the high dose of this drug (35 mg kg^{-1}) facilitated extinction. The same was found for clozapine which facilitated extinction of the avoidance response in a dose of 300 μg kg^{-1}. The doses of the atypical neuroleptics that facilitated extinction were in the same range as those needed to attenuate apomorphine-induced stereotypy for about 50%. This suggests that the influence of neuroleptics on extinction of pole jumping avoidance behaviour is mediated by DA receptors, particularly involved in apomorphine-induced stereotypy. However, haloperidol was more potent in facilitating extinction of pole-jumping avoidance behaviour that in reducing apomorphine-induced stereotypy. Moreover, γ-type endorphins, which appear to be at least as potent as haloperidol on extinction of pole-jumping avoidance behaviour (De Wied et al 1978; Kovács & De Wied 1978), antagonized apomorphine-induced hypoactivity and did not affect apomorphine-induced stereotypy (Van Ree et al 1982). It is possible therefore that other actions of neuroleptics (e.g. on cholinergic, adrenergic, or 5-hydroxytryptaminergic systems) contribute to or even determine their effect on extinction of avoidance behaviour. In conclusion, the action of neuroleptics on extinction of pole-jumping avoidance behaviour may be mediated by certain dopamine receptor systems, although another mode of action cannot be excluded.

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