(0.06–0.25 mg/kg i.p.) or methysergide (10–40 mg/kg i.p.) decreased the cataleptic effect of haloperidol (4 mg/kg).

The results suggest that 5-HT function can modify the state of catalepsy relating to blockade of central DA mechanisms. Thus, increasing the level of 5-HT neurotransmission apparently enhances catalepsy, but only after blockade of DA receptors has been established.

The rather surprising result that potential DA agonists can, at certain doses, potentiate neuroleptic-induced catalepsy may be explained in terms of possible 5-HT mechanisms. It is known for example that amphetamine can release 5-HT (Fuxe & Ungerstedt, 1970), apomorphine increase 5-HT turnover (Grabowska, 1975), and that L-DOPA can displace 5-HT from central serotonergic nerve endings (Algeri & Cerletti, 1974).

In view of these findings one should perhaps be wary of interpreting various behavioural responses in rodents seen after the 'classical' DA agonists purely in terms of DA mechanisms.

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Interactions of substituted benzamide drugs with cerebral dopamine pathways

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Substituted benzamide drugs exhibit behavioural and biochemical properties consistent with a blockade of cerebral post-synaptic dopamine receptors (Peringer, Jenner, Donaldson, Marsden & Miller, 1976; Elliott, Jenner, Huizing, Marsden & Miller, 1976), thereby resembling classical neuroleptic compounds. However, in contrast to classical neuroleptics, substituted benzamides do not consistently inhibit the dopamine stimulated-adenylate cyclase system from rat striatum. We have examined other biochemical interactions of three substituted benzamide drugs, namely, metoclopramide (*N*-[diethylaminoethyl]-2-methoxy-4-amino-5-chlorobenzamide), sulpiride (*N*-[1'-ethyl-2'-pyrrolidinylmethyl]-2-methoxysulphamoylbenzamide) and clebopride (*N*-[*N'*-benzylpiperidin-4'yl]-4-amino-5-chloro-2-methoxybenzamide) with cerebral dopamine systems *in vivo* and *in vitro*.

Metoclopramide (100 mg/kg i.p.), sulpiride (100 mg/kg i.p.), clebopride (10 mg/kg i.p.) or haloperidol (0.1 mg/kg i.p.) elevated striatal and mesolimbic HVA and DOPAC in rats ($P < 0.001$). Pretreatment with gammahydroxybutyrolactone (GOBA; 750 mg/kg), an inhibitor of impulse flow, prevented the rise in the level of dopamine metabolites caused by all of these drugs.

Metoclopramide (20 mg/kg i.p.), sulpiride (50 mg/kg i.p.), clebopride (10 mg/kg i.p.) and haloperidol (0.1 mg/kg i.p.) raised striatal and mesolimbic HVA and DOPAC levels in the mouse ($P < 0.02$). The HVA elevation caused by haloperidol was partially blocked by atropine (50 mg/kg i.p.) pretreatment ($P < 0.005$); DOPAC levels were unaffected ($P > 0.05$). Metoclopramide and clebopride-induced increases in HVA were not affected by atropine pretreatment ($P > 0.05$) but the rise induced by sulpiride was reduced by atropine ($P < 0.02$). DOPAC levels were unaffected by atropine following clebopride and sulpiride administration but mesolimbic DOPAC in metoclopramide treated animals was reduced ($P < 0.01$).

Incorporation of metoclopramide, sulpiride and clebopride (10^{-10} to 10^{-6} M) into the [^{3}H]haloperidol (2×10^{-9} M) labelled dopamine receptor binding model from rat striatum (Creese, Burt & Snyder, 1976) caused displacement of haloperidol with IC_{50} values of 4.2×10^{-7} M, 3.6×10^{-7} M and 2.0×10^{-8} M respectively. These compare with values of 2.4×10^{-9} M and 7.9×10^{-9} M obtained for haloperidol and (+)-butaclamol respectively.

Uptake and release of [^{3}H]-dopamine by striatal synaptosomal particles was weakly affected by meto-

clopramide (IC_{50} 5×10^{-4} M and EC_{50} 2×10^{-5} M respectively), but was unaffected by sulpiride. Clebopride did not inhibit dopamine uptake, but had a marked effect on release (EC_{50} 1×10^{-7} M). These values compare with an uptake IC_{50} value of 9×10^{-9}M for nomifensine and a release EC_{50} value of 1×10^{-8} for amphetamine.

These data suggest that the substituted benzamides investigated do interact *in vitro* with dopamine receptors, although they have no consistent effect on dopamine-sensitive adenylate cyclase, nor do they consistently influence presynaptic dopamine uptake or release. They do cause an increase in cerebral dopamine metabolites, which is dependent on nerve impulse flow as judged by the effects of GOBA. Such an increase in HVA is sensitive to atropine in the case of sulpiride, but not in the case of metoclopramide and clebopride. Thus, substituted benzamides resemble classical neuroleptics in some respects, but differ in others.

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Antipodal central effects of dopamine and apomorphine

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Cohen & Berkowitz (1975) suggested there were two types of dopamine receptor, based on the response of rat aortic strips to dopamine and to apomorphine. Cools & van Rossum (1976) postulated that there were 'two types of dopamine site' in the central nervous system. Clear-cut differences (Table 1) in the effects of dopamine and apomorphine infused into the hypothalamus and the third cerebral ventricle were observed in young and adult chickens (*Gallus domesticus*).

Thus dopamine (0.1 μmol) infused into the hypothalamus of young chicks pretreated with mebanazine (10 μmol/100 g i.v. 18 h and 1 h previously) induced behavioural and electrocortical sleep, suppressed vocalization, body temperature declining up to 6°C at thermoneutrality and mean CO_2 elimination falling 55%, effects lasting 4–6 hours. In contrast, apomorphine (0.05 μmol) infused into the identical site evoked behavioural and electrocortical arousal, vocalization and pecking, accompanied by an 0.5°–1°C increase in body temperature at thermoneutrality, and a mean increase in CO_2 elimination of 70%. The effects on body temperature lasted about 40 min, and 20–30 min for other variables. Apomorphine (0.025 μmol/100 g i.v.) evoked behavioural and electrocortical arousal in chicken encéphale isolé preparations. Similar effects to the doses infused into the hypothalamus were elicited by dopamine (0.5 μmol) and apomorphine (0.25 μmol) given into the third cerebral ventricle of adult fowls at thermoneutrality.

Table 1 Effects of dopamine and apomorphine infused into the hypothalamus and third cerebral ventricle of chickens

	Dopamine	*Apomorphine*
Behaviour	Sleep	Arousal
Electrocortical activity	Slow wave, large amplitude	Fast frequency, small amplitude
Posture	Standing or squatting, wings lowered	Standing (wing abduction in adult only)
Vocalization	Decreased	Increased
Body temperature	Decreased	Increased
CO_2 elimination	Decreased	Increased
Effective antagonists	Phenoxybenzamine	Spiroperidol (encéphale isolé)
Ineffective antagonists	Spiroperidol, propranolol	Phenoxybenzamine, propranolol
Effects of amphetamines	Dissimilar to those of dopamine	Resembled those of apomorphine