antipsychotic action of the neuropleptic agents, may be relevant to an understanding of the action of an antipsychotic agent such as clozapine which, although having only weak blocking action on the DA receptor, is able to enhance 5-HT function (Ruch, Asper & Bürki, 1976).

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Possible importance of 5-hydroxytryptamine in neuroleptic-induced catalepsy in rats

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The state of catalepsy in rodents following systemic administration of neuroleptic agents has been closely associated with blockade of central dopamine (DA) receptors (Fog, 1972): the intensity of catalepsy presumably relating to the degree of inhibition of dopamine function. Conversely, stimulation of DA receptors by classical DA agonists such as apomorphine and amphetamine elicits hyperactivity and stereotypy. However the role of other neurotransmitters known to influence DA mechanisms are rarely considered in these behavioural states. In particular 5-hydroxytryptamine (5-HT) manipulation is known to modify DA-dependent behaviours, and blockade of central 5-HT mechanisms has been reported as reducing neuroleptic-induced catalepsy in rats (Costall, Fortune, Naylor, Marsden & Pycock, 1975; Maj, Mogilnicka & Przewlocka, 1975).

We have further investigated the effect of 'classical DA agonists' and a number of drugs known to modify central 5-HT mechanisms on catalepsy induced by neuroleptic drugs in rats. Rather contrary to present simplified concepts, we have shown that proposed DA agonists can in fact potentiate neuroleptic-induced catalepsy. Amphetamine (4 mg/kg i.p.) administered in combination with a variety of neuroleptic drugs (haloperidol, 1 mg/kg i.p., fluphenazine, 1 mg/kg i.p.; pimozide, 5 mg/kg i.p.) significantly enhanced the cataleptic response. Lower doses of amphetamine (1 and 2 mg/kg) had no significant effect on the neuroleptic-induced catalepsy, while a high dose (8 mg/kg) tended to reverse this behaviour and induce stereotypy. Similarly apomorphine (0.12–0.5 mg/kg s.c.) was shown to potentiate haloperidol (1 mg/kg) catalepsy significantly. Higher doses of apomorphine tended to reverse the cataleptic state. L-DOPA (80 and 160 mg/kg i.p.), when administered in combination with the dopamine uptake blocking agent nomifensine (10 mg/kg i.p.), also caused significant potentiation of the cataleptic response to haloperidol (1 mg/kg).

The proposed 5-HT agonists quipazine (5–40 mg/kg i.p.) and 5-methoxy-*N,N'*-dimethyltryptamine (1–4 mg/kg i.p.) and the 5-HT precursor 5-hydroxytryptophan (10–200 mg/kg i.p.) potentiated the cataleptic response of the neuroleptic haloperidol (1 mg/kg) as did the selective 5-HT uptake blocking compounds ORG 6582 (1.25–10 mg/kg i.p.) and FG 4963 (femoxetine, 5–40 mg/kg i.p.). Conversely, treatment with the 5-HT antagonists cyproheptadine

(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-