showed a faster onset and offset of apomorphine-induced contralateral rotation ($P < 0.05$) as previously described (Waddington, 1977), though mean rotations were unaltered. 5MeODMT induced a mild ipsilateral rotation in 6-OHDA-lesioned animals treated with nialamide; however, this response was more vigorous in 5,6-DHT-lesioned animals ($P < 0.05$). Nialamide alone failed to induce rotation in animals from either group.

The equivalence of DA depletions produced by either lesion procedure suggests that these results may be dependent upon the differing degrees of 5-HT depletion they produce. We are led to suggest that 5MeODMT-induced rotation may be due to a direct activation of forebrain 5-HT receptors on the lesioned side rendered supersensitive by denervation induced by 5,6-DHT and, to a much lesser extent, by a non-specific effect of 6-OHDA; these 5-HT receptors may be in opposition to striatal DA receptors with regard to determining the direction of movement. The relative roles of receptors in the striatum or limbic forebrain areas in mediating these effects, however, remain to be determined.

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5-HT antagonists inhibit neuroleptic and morphine antagonism of the hyperactivity induced by DA from the nucleus accumbens

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The injection of dopamine (DA) into the nucleus accumbens (ACB) of rats induces marked hyperactivity which is specifically antagonized by neuroleptic agents administered either peripherally or directly into the ACB (Pijnenburg, Honig & Van Rossum, 1975; Costall, Naylor & Pinder, 1976). This antagonism of the DA effect, which is also achieved using morphine (Fortune, unpublished data), has been interpreted almost exclusively in terms of DA receptor blockade (Costall & Naylor, 1976). However, injections of 5-hydroxytryptamine (5-HT) into the ACB also antagonizes the DA-induced hyperactivity (Costall, Naylor, Marsden & Pycock, 1976) and preliminary evidence indicates that the more enhanced effects of neuroleptic agents and morphine on motor function, namely catalepsy induction, involves an enhanced 5-HT action (Kostowski, Gumulka & Czlonkowski, 1972; Costall, Fortune, Naylor, Marsden & Pycock, 1975; Costall, Fortune & Naylor, 1977). In the present study we investigate the possibility that neuroleptic agents and morphine may antagonize the hyperactivity induced by DA from the ACB via a similar mechanism.

Animals were prepared for intracerebral injection into the ACB using the techniques of Costall & Naylor (1976) and drugs were injected in a volume of 1 µl. DA (5–50 µg) administered bilaterally into the ACB of chronically implanted rats pretreated with nialamide (100 mg/kg i.p., 2 h) induced a dose-dependent hyperactivity: this was recorded by placing rats in individual perspex cages fitted with photocells and measuring the number of interruptions of the light beam. The hyperactivity induced by 50 µg DA was antagonized by subsequent bilateral injections of 5-HT (6.3–25 µg), fluphenazine (6.3–25 µg) and morphine (0.5–5 µg) into the ACB. The antagonism of DA-induced hyperactivity by submaximal doses of 5-HT (12.5 µg), fluphenazine (12.5 µg) and morphine (1 µg) was significantly reduced or abolished by the administration of methysergide (0.063–1 mg/kg i.p.) or cyproheptadine (1–25 mg/kg i.p.). Both methysergide (1 mg/kg i.p.) and cyproheptadine (2.5 mg/kg i.p.) failed to modify the hyperactivity induced by 5 or 50 µg DA injected into the ACB.

It is concluded that the ability of morphine or of a neuroleptic agent such as fluphenazine to antagonize the hyperactivity induced by DA from the ACB may be associated with an enhancement of 5-HT function either concomitant or subsequent to a DA receptor blockade. The possibility that the locus of the 5-HT action may be within the mesolimbic circuits, suggested as possible substrates for the clinical

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