injected rats did not turn. This effect is consistent with inhibition of the nigrostriatal dopaminergic pathway by γ-acetylenic GABA.

For investigations of the limbic system, rats were injected bilaterally with GAG into the nucleus accumbens (10 μg/side in 2 μl) 3 h before the bilateral injection of dopamine (25 μg in 2 μl/side). All rats were dosed orally with isocarboxazid (100 mg/kg) 2 h before receiving dopamine. Motor activity was measured in an activity meter for 3 h following dopamine injection. GAG significantly reduced the dopamine-activated increase in motor activity, consistent with a GABA-mediated inhibition of the nucleus accumbens.

To verify the specificity of the effect of γ-acetylenic GABA on the two dopaminergic pathways a number of injections were made in various regions close to the substantia nigra and the nucleus accumbens. Injections more than 1 mm distal from the required area (verified histologically) were without effect on either turning or motor activity.

GABA-transaminase activity was estimated in samples obtained by micropuncture from regions in and close to the substantia nigra or nucleus accumbens. Injections of GAG into the substantia nigra and nucleus accumbens produced 88–90% inhibition in these areas. Fifty per cent or greater inhibition was found in areas approximately 1 mm from the site of injection suggesting a limited diffusion of γ-acetylenic GABA.

In conclusion the results suggest an inhibitory role for GABA in both the extrapyramidal and limbic systems.

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Rotational responses to the putative serotonin agonist 5MeODMT following unilateral 5,6-DHT lesions of the median forebrain bundle: a possible role for 5-HT in the control of rotational behaviour

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Asymmetric lesions of the medial raphé nucleus, which produce unilateral depletion of forebrain serotonin (5-HT), produce contralateral rotation in rats when treated with dopamine agonists (Costall, Naylor, Marsden & Pycock, 1976). Together with evidence indicating a serotonergic modulation of rotational responses to dopamine agonists in rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of ascending dopamine (DA) pathways (Milson & Pycock, 1976; Waddington, 1977), this suggests the possibility of inducing a rotational response to 5-HT agonists in rats with unilateral lesions of ascending 5-HT pathways. This was investigated using unilateral lesions of the median forebrain bundle (MFB) induced with the indolamine neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) in a comparison with lesions induced with 6-OHDA. For both types of lesions, rotational responses to the DA agonist apomorphine were compared with those following treatment with the putative 5-HT agonist 5-Methoxy-*N,N*-dimethyltryptamine (5MeODMT).

Male Sprague-Dawley rats, 150 ± 20 g, received unilateral stereotaxic injections of 6-OHDA (8 μg/4 μl saline; $n = 14$) or 5,6-DHT (5 μg/4 μl saline; $n = 14$) into the MFB. Eight days post lesion all animals received i.p. injections of apormorphine (1 mg/kg); on day 11 animals received 5MeODMT (2 mg/kg), 45 min after pretreatment with the monoamine oxidase inhibitor nialamide (75 mg/kg i.p.). Rotational behaviour was recorded in automated rotameter bowls for continuous recording of all rotations and these were assessed both with conventional statistical techniques and following orthogonal polynomial transformation. Rats were sacrificed 14 days post lesion and striata assayed spectrophotofluorimetrically for DA and 5-HT content.

6-OHDA and 5,6-DHT lesions produced 72.3% ($P < 0.001$) and 83.9% ($P < 0.001$) depletions of striatal DA respectively; there was no significant difference between DA depletions following the two lesion procedures ($P < 0.05$). 5-HT levels were reduced by 12.5% ($0.05 < P < 0.1$) and 52.5% ($P < 0.001$) following 6-OHDA and 5,6-DHT respectively; 5-HT depletion with 5,6-DHT exceeded that with 6-OHDA ($P < 0.001$).

6-OHDA animals showed the expected contralateral rotation to apomorphine; 5,6-DHT animals

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.

J.L.W. is an MRC Student.

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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