(1–20 μg, $P<0.001$) and baclofen (5–25 ng, $P<0.001$) injections produced a vigorous dose-dependent contralateral rotation; these effects were mimicked by injections of muscimol (1 ng, $P<0.005$).

Considerable debate has centred on whether striatonigral GABA neurones are excitatory or inhibitory on nigrostriatal dopamine neurones (Dray & Straughan, 1976) whose asymmetric activity is presumed to underlay rotational behaviour; this demonstrated induction of contralateral rotation in the absence of any pretreatment suggests an excitatory process. Whether or not this is the case flurazepam produces effects identical to those produced by unilateral elevation of SNR GABA levels and SNR injections of both the GABA analogue baclofen, recently shown electrophysiologically to produce GABA-like depression of activity that is antagonized by the GABA antagonist bicuculline (Puil, Krnjevic and Werman, 1976), and the GABA agonist muscimol. These results suggest that baclofen may have some GABA agonist activity and further emphasize the GABA-like properties of benzodiazepines; whether this action is related to their clinical anxiolytic effect remains to be determined.

JLW is an MRC Scholar. Flurazepam, baclofen and muscimol were gifts from Roche Products Limited, Ciba Laboratories and Royal Dutch Shell respectively.

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Inhibition of dopaminergic activity in the extrapyramidal and limbic systems by γ-acetylenic GABA

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There is considerable evidence that γ-aminobutyric acid (GABA) acts as an inhibitory transmitter in the nigrostriatal pathway by inhibiting the ascending dopaminergic pathway at the level of the substantia nigra (Dray & Straughan, 1976). There is less evidence for a similar inhibitory role of GABA in the limbic system.

Using a new irreversible catalytic inhibitor of GABA-transaminase, γ-acetylenic GABA (GAG; RMI 71645; Jung, Lippert, Metcalf, Schechter, Böhlen & Sjoerdsma, 1977), we have examined inhibition of both the extrapyramidal and limbic dopaminergic pathways.

Three techniques were used to estimate catecholamine turnover in selected rat brain areas 4 h following GAG (100 mg/kg i.p.) administration: (a) α-methyl-*p*-tyrosine (AMPT)-induced disappearance of dopamine and noradrenaline, (b) homovanillic acid (HVA) concentrations, (c) [^{3}H]-dopamine formation following [^{3}H]-L-DOPA treatment. GAG decreased AMPT-induced dopamine disappearance in the striatum and olfactory tubercles ($P<0.005$). [^{3}H]-dopamine formation was also decreased in these regions (30 and 26% respectively, $P<0.05$) as was HVA concentration (61 and 49%, $P<0.005$). On the other hand, in the hypothalamus a small but significant ($P<0.02$) increase in dopamine turnover was found by the AMPT method and hypothalamic HVA was also increased (141%, $P<0.02$). Noradrenaline turnover was decreased in the olfactory tubercle and unchanged in the hypothalamus.

In a further series of experiments, rats received unilateral injections into the substantia nigra of 20 or 40 μg GAG in 2 μl saline or saline alone. Five hours later the rats were injected i.p. with either amphetamine (3–5 mg/kg) or apomorphine (2–6 mg/kg) and the number of rotations per minute were recorded for the following 2 hours. GAG-treated animals showed a consistent dose and time related ipsilateral turning with both amphetamine and apomorphine (e.g. 6.1 ± 0.7 turns/min after 6 mg/kg apomorphine; mean ± s.e., $n=8$), whereas saline

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