Polyethylene cannulae were inserted into a femoral vein and retrogradely into the right carotid artery for i.v. and i.a. injection respectively. Blood pressure was recorded from a femoral artery. Sulphasalazine was administered by continuous slow infusion (1 ml every 30 minutes).

Prostaglandins E_1, E_2 and A_2 were vasodepressor in the anaesthetized rat, and the potencies of PGE_2 and PGA_2 relative to PGE_1 (set as 100%) were 40% and 1.6% respectively. PGD_2 produced inconsistent effects, being either pressor (3 experiments) or depressor (2 experiments). However, as a depressor PGD_2 was of equivalent potency to PGA_2. PGs of the E series had much greater effect if injected i.a. than i.v., whereas vasodepressor responses to PGA_2 were similar regardless of the route of administration. The difference between the i.a. and i.v. responses is a measure of the pulmonary metabolism of these prostaglandins and indicates that PGA_2 is not inactivated in the lungs. Our data show that there is extensive pulmonary metabolism of both PGE_1 (97.0 $\pm$ 8.2%, $n = 5$) and PGE_2 (92.3 $\pm$ 6.8%, $n = 5$).

Sulphasalazine (5–50 μg) had no direct effect on blood pressure when injected into the femoral vein, and did not influence the vasodepressor response to injected PGE_1 (4 experiments). During continuous infusion of sulphasalazine (3.1–16.3 μg $kg^{-1}min^{-1}$) the vasodepressor effect of PGE_1 injected i.v. was potentiated, causing a shift in the i.v. dose-response curve to the left towards the i.a. dose-response curve (5 experiments). The response to i.a. administration of PGE_1 was unchanged. The potentiation of i.v. PGE_1 observed in these experiments must be due to decreased inactivation of the prostaglandin in the pulmonary circulation. When the sulphasalazine infusion was stopped the i.v. response to PGE_1 declined rapidly to reach pre-treatment values some 20–40 min later, indicating that the effect of the drug on pulmonary PG breakdown is readily reversible, or that it is itself rapidly metabolized in the body.

These experiments show that sulphasalazine inhibits PG metabolism *in vivo* and, together with previous *in vitro* evidence showing the same effect, support our proposal that this action may underly the therapeutic benefit of sulphasalazine in ulcerative colitis.

P.K.M. was supported by a CASE award (S.R.C. and May & Baker Ltd, Dagenham).

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Prostaglandin and noradrenaline interactions in rat brain synaptosomes

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In the peripheral nervous system, the suggestion that prostaglandins of the E series, released as a consequence of noradrenergic action, operate a negative feedback control of noradrenaline release, has become generally accepted (see Brody & Kadowitz, 1974). It is tempting to assume a similar action in the central nervous system, but evidence for this is far less convincing. We have, therefore, studied the effects of noradrenaline on prostaglandin synthesis, and of prostaglandin E_2 (PGE_2) on noradrenaline release from rat brain synaptosomes.

Synaptosomes were prepared from whole brains of 250 g female Wistar rats by the method of Gray & Whittaker (1962). Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and PGE_2 release was estimated by radioimmunoassay. As reported previously (Hillier, Roberts & Woollard, 1976) addition of noradrenaline (0.1 mM–1 mM) to incubates increased the release of PGE_2 and $PGF_{2\alpha}$ in a dose dependent manner. Typically, noradrenaline, (0.5 mM) increased PGE_2 levels from approximately 40 pg mg $protein^{-1}$ 10 min^{-1} to approximately 70 pg mg $protein^{-1}$ 10 min^{-1} and $PGF_{2\alpha}$ levels from approximately 225 pg mg $protein^{-1}$ 10 min^{-1} to approximately 340 pg mg $protein^{-1}$ 10 $minutes^{-1}$.

Noradrenaline release was studied in synaptosomes preloaded with [^{3}H]-noradrenaline. After 20–30 min perfusion, at 37°C with Krebs, spontaneous overflow of [^{3}H]-noradrenaline was relatively stable. An increased release could be obtained with 30 mM K^+ Krebs; as expected, this release was calcium dependent. We could not reproduce previous work of Roberts & Hillier (1976) in which PGE_2 (1 μg/ml) was shown to increase [^{3}H]-noradrenaline overflow. To the contrary, PGE_2 (0.5–4 μg/ml) had no effect on the spontaneous outflow or on the K^+stimulated release of [^{3}H]-noradrenaline. The reasons for this discrepancy are not readily apparent. Further, in low calcium (0.25 mM) conditions (normal was 2.57 mM), which render PGE_2 more effective in peripheral systems (Hedqvist, 1974), PGE_2 (1 μg/ml) was still without effect on [^{3}H]-noradrenaline release. The prostaglandin synthesis, inhibitor, indomethacin (10 μg/ml), also did not alter [^{3}H]-noradrenaline overflow.

We conclude that if prostaglandins do possess a

role as noradrenergic regulators in rat central nervous system, that role is more complex than would appear in peripheral systems.

W.W.T. is an M.R.C. student. We thank the Upjohn Company for prostaglandins.

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Evidence for metabolite involvement in bromocryptine-induced circling behaviour

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Bromocryptine is believed to be a potent post-synaptic dopamine agonist. However, some central actions (i.e. stimulation of locomotion or provocation of turning behaviour in rodents with unilateral nigral lesions) are inhibited by reserpine and α-methyl-p-tyrosine (AMPT) suggesting the involvement of presynaptic events (Corrodi, Fuxe, Hokfelt, Lidbrink & Ungerstedt, 1973; Johnson, Loew & Vigouret, 1976). We now report the action of bromocryptine in a double lesion circling rodent model designed to rigorously distinguish pre- and post-synaptic dopamine receptor action.

Male Wistar rats (150 g) were injected with 6-hydroxydopamine (8 μg/3 μl 0.9% saline containing 2 μg ascorbic acid) into the medial forebrain bundle at the level of the rostral hypothalamus on one side and the lateral hypothalamus on the opposite side (Pycock & Marsden, 1978). Such animals have destruction of dopamine pathways to one striatum and both mesolimbic areas. Animals were selected 20 days after lesioning that showed strong rotation to apomorphine (0.5 mg/kg sc 15 min previously) but negligible circling to amphetamine sulphate (3 mg/kg ip 30 min previously).

Administration of bromocryptine mesylate (10 mg/kg ip 1 h previously) produced brisk turning (20 ± 5 turns per min) contralateral to the denervated striatum, identical to that produced by apomorphine, thus suggesting a post-synaptic site of action on dopamine receptors. However, AMPT methyl ester hydrochloride (200 mg/kg ip 1 h previously) still inhibited bromocryptine induced circling in this double lesion model (50%; $P<0.01$) but not that produced by apomorphine. Accordingly we wondered if bromocryptine's central actions might be dependent on some metabolite related to hydroxylation.

Therefore we investigated the effect of an inhibitor of hepatic drug metabolism SKF 525A (β-diethylaminoethyldiphenylpropylacetate hydrochloride; 75 mg/kg ip 30 min prior to bromocryptine). SKF 525A inhibited bromocryptine-induced turning (60%; $P<0.025$) but did not reduce apomorphine-induced circling. This data is compatible with the involvement of an active metabolite of bromocryptine in the mediation of circling behaviour. In view of the AMPT effect we also studied the effect of inhibition of noradrenaline re-uptake by desipramine hydrochloride and dopamine re-uptake using nomifensine hydrogen maleate (both 25 mg/kg ip 30 min prior to bromocryptine). Both desipramine and nominfensine inhibited bromocryptine-induced circling (by 74 and 84% respectively; $P<0.0125$) but neither affected apomorphine-induced circling. The data may indicate the importance of intact function in presynaptic catecholamine terminals in the mediation of circling behaviour by bromocryptine (or its metabolites). However, both desipramine and nomifensine enhanced hexobarbital (100 mg/kg ip)-induced sleeping times in female Swiss S mice (20–25 g) ($P<0.005$) while desipramine (but not nomifensine) potentiated zoxazolamine (150 mg/kg ip) paralysis time ($P<0.0025$). This would suggest that the effects observed with these re-uptake blockers could also be associated with inhibitory effects on drug metabolising mechanisms. However, AMPT methyl ester hydrochloride (200 mg/kg ip) was without effect on either hexobarbital or zoxazolamine-induced parameters.

The data would suggest that bromocryptine causes rotation in rodents by a post-synaptic action involving metabolite formation. The role of presynaptic events remains unclear.

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