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

P. JENNER, C.D. MARSDEN & C. REAVILL

University Department of Neurology, Institute of Psychiatry & King's College Hospital School, Denmark Hill, London, SE5, U.K.

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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The involvement of dopamine in the central actions of bupropion, a new antidepressant

H. CANNING, D. GOFF, M.J. LEACH, A.A. MILLER, J.E. TATESON & P.L. WHEATLEY

Pharmacology Laboratory, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS

Bupropion (d, 1-2-t-butylamino-3-chloropropiophenone HCl), a new antidepressant, possesses a pharmacological profile intermediate between that of the tricyclic antidepressants and the amphetamine-like stimulants. In comparison with the tricyclics, bupropion was weaker in inhibiting noradrenaline (NA) uptake *in vitro* but was more potent against dopamine (DA) uptake. Bupropion, like dexamphetamine, increased locomotor activity of rodents (Soroko, Mehta, Maxwell, Ferris & Schroeder, 1977).

To investigate the possible involvement of dopamine in the central actions of bupropion we have now compared bupropion with dexamphetamine, desipramine and nomifensine in rats on: (i) EEG studies of drugs alone and in interaction with pimozide, a dopamine antagonist known to block dexamphetamine-induced EEG arousal (Baxter, Miller & Wheatley, 1976) (ii) inhibition of monoamine uptake *in vivo* using a modification of the 6-hydroxydopamine (6-OHDA) method of Goodlet, Mireylees & Sugrue (1977), and (iii) dopamine-sensitive adenylate cyclase preparation *in vitro*.

EEG studies were undertaken in conscious unrestrained rats ($n \geqslant 3$ per treatment). Drugs were administered (s.c.) at multiple doses of their ED_{50} values against tetrabenazine-induced depression, except for bupropion which is ineffective against tetrabenazine in rats. Bupropion (5 and 10 mg/kg) was similar to dexamphetamine (0.3 mg/kg, $ED_{50} \times 0.25$) and nomifensine (1.2 mg/kg, $ED_{50} \times 1$) in inducing EEG arousal which was reduced or blocked by pre-treatment with pimozide at 1.7 mg/kg (ED_{95} against apomorphine-induced stereotypy), whereas DMI (5 mg/kg, $ED_{50} \times 2$) induced arousal was not reduced.

Table 1 Blockade of 6-OHDA induced depletion of rat brain noradrenaline (NA) and dopamine (DA)

		Noradrenaline		*Dopamine*	
Drug	*Dose i.p. mg/kg*	*Mean % Block*	*ID_{50} mg/kg (+95% limits)*	*Mean % Block*	*ID_{50} mg/kg (+95% limits)*
Desipramine	10	23.7		4.2	
(DMI)	20	44.3	24.9	−4.9	—
	40	67.7	(14.1–43.8)	4.8	
D-amphetamine	2.5	39.7		35.4	
	5	33.0	6.6	64.5	3.0
	10	53.8	(4.2–10.2)	75.9	(1.6–5.7)
Bupropion	20	12.0		18.6	
	40	−16.2	—	45.4	54.4
	80	−11.1		64.8	(32.0–92.3)
Nomifensine	4	9.3		−15.3	
	8	14.5	38.9	−14.8	—
	16	30.9	(14.7–102.6)	14.0	

Bupropion, or other test drugs, were administered (i.p.) to rats (Wistar, male, 250 to 300 g) 30 min prior to injections, made under halothane anaesthesia of 6-OHDA (125 μg in 10 μl : solution in 0.9% saline containing ascorbic acid 1 mg/ml) into each lateral ventricle (0.9 mm posterior and ±1.5 mm lateral to the bregma at a depth of 5 mm). After 3 days the rats were killed and brains removed for estimation of NA (von Euler & Lishajko, 1961) and DA (Anton & Sayre, 1964) after extraction by the method of Brownlee & Spriggs (1965). Each dose value is the mean of at least 8 determinations. Brain NA levels of vehicle treated control rats were 361 ± 22 ng/g ($n = 24$) and for DA 751 ± 49 ng/g ($n = 36$). After 6-OHDA, brain NA levels declined to 101 ± 9 ng/g ($n = 24$) and for DA, 358 ± 25 ng/g ($n = 36$), equivalent to 72% and 52% depletion respectively. ID_{50} values were determined by computer data fitting to a non-linear equation (Riddall & Leavens, 1978) for action on a single receptor.