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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.

Bupropion, in contrast to DMI and nomifensine, significantly prevented 6-OHDA-induced depletion of brain DA but was ineffective against NA depletion. Dexamphetamine was effective against both DA and NA depletion (Table 1). In the rat striatal dopamine-sensitive adenylate cyclase preparation (Kebabian, Petzhold & Greengard, 1972) bupropion at 100 μM had no effect on the production of either basal or DA-stimulated (100 μM) C-AMP.

The results indicate that dopamine is involved in at least some of the central actions of bupropion. Although not a DA agonist on the adenylate cyclase preparation, the 6-OHDA model suggests that bupropion may inhibit DA uptake *in vivo* in the rat.

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## Changes in mesolimbic homovanillic acid content following discrete modulation of striatal dopamine systems


B. COSTALL & R.J. NAYLOR

*Postgraduate School of Studies in Pharmacology, University of Bradford*


Many authors have investigated the possibility of regional differences in the interaction of different neuroleptic agents (and many other drugs) with dopamine metabolism in the corpus striatum and mesolimbic structures (see Waldmeier & Maître, 1976; Westerink, Lejeune, Korf & van Praag, 1977). It is fundamental to these studies that the peripheral administration of neuroleptic agent to modify striatal or mesolimbic dopamine metabolism involves a discrete effect of the drug within the appropriate region. The present studies assess the validity of this assumption by directly stimulating and blocking striatal dopamine systems and determining the specificity of changes induced to the striatum by measuring alterations in dopamine metabolism both within the striatum and the mesolimbic structures.

Chronically indwelling cannulae were implanted in the brains of male Sprague-Dawley rats to allow drug or vehicle injection into the caudate-putamen (Ant. 9.0, Vert. +1.5, Lat. ±3.0, De Groot, 1959) (see Costall & Naylor, 1976, for details of the stereotaxic techniques). Fourteen days after surgery drug solutions (administered into the right hemisphere) and vehicle (administered into the left hemisphere) were injected simultaneously in volumes of 1 μl. Behavioural effects of circling and asymmetry were assessed for a 3 h period. Rats were then sacrificed, the brains rapidly removed and the striatum and tuberculum olfactorium dissected out over ice. Tissue from 6 animals was used for each extraction procedure. Homovanillic acid (HVA) concentrations were determined fluorometrically.

In 'control' non-cannulated rats HVA concentrations were 823 ± 97 ng/g (striatum) and 403 ± 73 ng/g (tuberculum olfactorium). In cannulated rats receiving intrastriatal vehicle the HVA concentrations were the same as those recorded for non-cannulated rats. The unilateral injection of dopamine into the striatum (1–100 μg) increased HVA levels in both the ipsilateral striatum *and* tuberculum olfactorium. Significant changes were not recorded for the other hemisphere. Whilst contralateral asymmetry and circling movements were apparently associated with the effects of dopamine (100 μg), lower doses of dopamine, although increasing HVA levels by 2× to 2× control values, failed to induce any obvious behavioural changes. The unilateral injection of fluphenazine (1–25 μg) also caused an increase (up to 7× control values) in HVA levels in the striatum *and* tuberculum olfactorium in *both* the ipsilateral and contralateral hemispheres. Ipsilateral asymmetry and circling were observed using the larger doses of fluphenazine but, although the lower doses of fluphenazine caused significant elevation in HVA levels, again these were not associated with any behavioural change.

The results indicate, firstly, that manipulation of