LETTER TO THE EDITOR

Antagonism by propranolol of central dopamine receptor stimulation is not related to β-adrenergic blockade

G. LUSCOMBE, A. CLOW, P. JENNER, C. D. MARSDEN,* *University Department of Neurology, Institute of Psychiatry and King's College Hospital Medical School, Denmark Hill, London, SE5, UK*

The suggestion that (±)-propranolol might be valuable in treating schizophrenia (Yorkston et al 1974) has led to biochemical (Sullivan et al 1972; Fuxe et al 1976; Wiesel 1977) and behavioural studies (Costall et al 1978) into its effects on central catecholaminergic systems. Costall et al (1978) investigated the effects of a range of doses (2·5–40 mg kg^{-1}) of (±)-propranolol and its (+)- and (−)-isomers upon the following dopamine-dependent motor behaviours: the induction of dyskinetic phenomena in the guinea-pig by intrastriatal dopamine agonists, rat hyperactivity due to the injection of dopamine into the nucleus accumbens, and mouse climbing behaviour induced by apomorphine. Only the latter two behaviours were antagonized by propranolol, and the (−)-isomer, which is the potent β-receptor antagonist, was less effective than the relatively inactive (+)-isomer. That result suggested that the capacity of propranolol to antagonize some, but not all, dopamine-mediated behaviours was not due to its β-blocking actions. We have studied another model dependent upon enhanced dopamine-like activity, namely the apomorphine-induced circling behaviour observed in mice with unilateral 6-hydroxydopamine lesions of the striatum.

6-Hydroxydopamine (16 μg in 4 μl 0·9% saline) was injected directly into the right striatum according to the method of Pycock et al (1975). Two months after surgery, circling behaviour in mice was observed in individual boxes (12 cm × 12 cm). The number of net complete turns to the left was recorded within a 1 min period 15 min after apomorphine (0·5 mg kg^{-1} s.c.) administration. Mice were pretreated 60 min earlier with saline or a propranolol isomer ((±) 1–50 mg kg^{-1}; (+) and (−) 25 mg kg^{-1}, all i.p.).

The results are summarized in Table 1. (±)-Propranolol antagonized apomorphine-induced turning in a dose-dependent manner. (+)-propranolol (25 mg kg^{-1}) inhibited apomorphine-induced circling to the same extent as (−)-propranolol or (±)-propranolol given in the same dose. At this dose there were signs of sedation, muscular hypotonia (Leszkovszky & Tardos 1965) and hyporeactivity (Bainbridge & Greenwood 1971) which became more marked at 50 mg kg^{-1}. (All the mice given 100 mg kg^{-1} (±)-propranolol subsequently died.) Fuxe et al (1976), who injected 6-hydroxydopamine into the substantia nigra of rats, found (±)-propranolol (20 mg kg^{-1}) to significantly reduce the peak and overall number of turns per minute per rat induced by (+)-amphetamine (3·0 mg kg^{-1}), but they did not study its isomers in this model.

Costall et al (1978) found the (+)-isomer to be markedly more active than the (−)-isomer in antagonizing apomorphine-induced mouse climbing and dopamine-induced hyperactivity in the rat, but all three isomers have similar effects on apomorphine-induced circling. However, the finding that (−)-propranolol was the weakest isomer in all three models is of great interest in interpreting these results. That (−)-propranolol, the more potent β-receptor antagonist, was less potent or equally potent to (+)-and (±)-propranolol suggests that cerebral β-adrenergic antagonism plays a relatively unimportant role in the modulation of dopamine dependent responses. Horn & Phillipson (1976) found the (−)-isomer to be 100 times more potent than (+)-propranolol as an antagonist of mesolimbic noradrenaline-stimulated adenylate cyclase, and Nahorski (1976) showed (−)-propranolol to be almost 100 times more effective than the (+)-isomer in displacing [^{3}H] (±)-propranolol binding from cerebral β-adrenoceptors. Likewise it seems unlikely that propranolol is exerting a direct action upon apomorphine-sensitive receptors, since high concentrations of its isomers neither block the stimulation of striatal adenylate cyclase by dopamine (Forn

Table 1. Antagonism of apomorphine-induced circling behaviour by the isomers of propranolol. Circling behaviour was induced by apomorphine (0·5 mg kg^{-1} s.c.) and was measured 15 min later as the number of net complete turns to the left within 1 min. Each isomer of propranolol was given 60 min before apomorphine.

Drug	Dose (mg kg^{-1} i.p.)	Turns/minute*	Significance
(±)-Propranolol	0	8·91 ± 0·71	
	1	8·60 ± 9·60	NS
	10	8·39 ± 0·69	NS
	25	6·74 ± 0·53	0·01
	50	3·54 ± 0·85	0·0025
(+)-Propranolol	25	6·91 ± 0·57	0·025
(−)-Propranolol	25	7·30 ± 0·58	0·05

* Each value represents the mean (± 1 s.e.m.) of 24 mice. Significant differences between the results were determined using Student's *t*-test (NS = not significant).

* Correspondence

et al 1974), nor displace bound [^{3}H]apomorphine (Seeman et al 1976). Burt et al (1976) have shown propranolol to be a more potent displacer of haloperidol than dopamine but even so it still displays a very low affinity for the haloperidol binding site. The isomers of propranolol have been found to increase dopamine turnover in the olfactory tubercle and nucleus accumbens, but there was no such effect upon the striatum (Fuxe et al 1976; Wiesel 1977), although Sullivan et al (1972) found propranolol to increase striatal tyrosine hydroxylase activity in parallel to the dose-dependent behavioural depression which it caused.

Thus the isomers of propranolol do not seem to be acting through β-adrenergic mechanisms and only very weakly, if at all, through dopaminergic mechanisms in this behavioural model. Rather, the antagonism of apomorphine-induced circling behaviour by the propranolol isomers is best explained by their non-selective peripheral or cerebral action in producing sedation and muscular hypotonus which is in agreement with the conclusions of Anden & Strombom (1974) and Costall et al (1978).

December 4, 1978

REFERENCES

Anden, N.-E., Strombom, U. (1974) Psychopharmacologia 38: 91–103

Bainbridge, J. G., Greenwood, D. T. (1971) Neuropharmacology 10: 453–458

Burt, D. R., Creese, I., Snyder, S. H. (1976) Mol. Pharmacol. 12: 800–812

Costall, B., Naylor, R. J., Nohria, V., Owen, R. T. (1978) J. Pharm. Pharmacol. 30: 657–660

Forn, J., Krueger, B. K., Greengard, P. (1974) Science 186: 1118–1120

Fuxe, K., Bolme, P., Agnati, L., Everitt, B. J. (1976) Neurosci. Lett. 3: 45–52

Horn, A. S., Phillipson, O. T. (1976) Eur. J. Pharmacol. 37: 1–11

Leszkovszky, G., Tardos, L. (1965) J. Pharm. Pharmacol. 17: 518–520

Nahorski, S. R. (1976) Nature 259: 488–489

Pycock, C., Tarsy, D., Marsden, C. D. (1975) Psychopharmacologia 45: 211–219

Seeman, P., Lee, T., Chau-Wong, M., Tedesco, J., Wong, K. (1976) Proc. Natl. Acad. Sci. U.S.A. 73: 4354–4358

Sullivan, J. L., Segal, D. S., Kuczenski, R. T., Mandell, A. J. (1972) Biol. Psychiatry 4: 193–203

Wiesel, F.-A. (1977) Prog. Neuropsychopharmacol. 1: 83–89

Yorkston, N. J., Zaki, S. A., Malik, M. K. U., Morrison R. C., Havard, C. W. H. (1974) Br. Med. J. 4: 633–635