oxypertine on spontaneous locomotor activity and blood pressure during various light schedules. *Ann. Med. exp. Biol. Fenn.*, **51**, 93-103,

ZANOBONI, A. & ZANOBONI-MUCIACCIA, W. (1967). Experimental hypertension in pinealectomized rats. *Life Sci.*, **6**, 2327-2331.

BRL 13776: a novel antihypertensive agent with interesting noradrenaline-depleting properties

JOANNE MELROSE, M.G. PALFREYMAN*
R.H. POYSER & R.L. WHITING

Beecham Pharmaceuticals, Research Division, Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD

Whilst studying a series of 4-(4-pyridyl)-chroman-5-ols which were being evaluated for activity in the central nervous system, a compound BRL 13776 (7-n-pentyl-4-[1-(2-naphthylmethyl)-1, 2, 5, 6-tetrahydro-4-pyridyl]-2, 2-dimethylchroman-5-ol) was found to have antihypertensive activity yet be devoid of behavioural properties. The antihypertensive activity was assessed in deoxycorticosterone acetate/NaCl-treated hypertensive rats (Sprague-Dawley) and renal hypertensive cats (cellophane perinephritis model, see Poyser, Shorter & Whiting, 1974). In both models, BRL 13776 (suspended in 1% w/v methylcellulose) caused a significant lowering ($P < 0.05$) of blood pressure at doses of 30 mg/kg p.o. and above. The antihypertensive response was evident 4-6 h after dosing and blood pressure had almost returned to pre-dose values at 24 hours. No behavioural changes nor adverse symptoms were observed in either species.

Studies on the mechanism of action of BRL 13776 revealed that the compound depleted noradrenaline in various peripheral organs of both normotensive and hypertensive rats. Noradrenaline was measured by the method of Shellenberger & Gordon (1971), and animals receiving BRL 13776 were compared with vehicle-dosed controls. Six or more rats were used in each group and all animals were killed 6 h after dosing. In the normotensive rats, a single dose of BRL 13776 (100 mg/kg p.o.) reduced the noradrenaline content of heart, spleen and adrenals by 78%, 80% and 82% respectively ($P < 0.001$). A similar depletion occurred in hypertensive rats (e.g. 65% in the heart, $P < 0.001$).

In contrast to the depletion in peripheral tissues, BRL 13776 did not affect the noradrenaline content of whole brain. Nevertheless, more detailed studies revealed a significant reduction ($P < 0.01$) in the hind-brain region (pons/medulla) of both normotensive and hypertensive rats. This was in the order of 37-40% at 6 h following the 100 mg/kg single p.o. dose. No concomitant decrease in the noradrenaline concentration of the cerebral hemispheres, mid-brain or hypothalamus was observed. In this respect BRL 13776 differed from reserpine. Even on repeated dosage with BRL 13776 (100 mg/kg p.o. twice daily for 14 days) the cerebral hemispheres were not depleted of their noradrenaline whereas the reduction in the hind-brain was still apparent (18%, $P < 0.01$). However, in the repeated-dose study there was also some depletion of the hypothalamus (28%, $P < 0.01$). Throughout the 14 day study no gross toxicity, behavioural changes or side effects were observed.

In conclusion, BRL 13776 is a novel structure displaying antihypertensive and noradrenaline-depleting properties. Noradrenaline depletion in the brain of rats is restricted to certain areas, and this may be relevant to both the antihypertensive response and the lack of behavioural effects. Reductions of noradrenaline in the periphery could contribute to the antihypertensive response or on the other hand be totally responsible. Obviously BRL 13776 warrants further investigation and it is intended to proceed to clinical studies.

References

POYSER, R.H., SHORTER, J.H. & WHITING, R.L. (1974). The production of hypertension and the effects of some antihypertensive agents in the conscious cat. *Br. J. Pharmac.*, **51**, 149P.

SHELLENBERGER, M.K. & GORDON, J.H. (1971). A rapid, simplified procedure for simultaneous assay of norepinephrine, dopamine and 5-hydroxytryptamine from discrete brain areas. *Anal. Biochem.*, **39**, 356-372.