

## The effect of labetalol on the release of [<sup>3</sup>H]-labelled noradrenaline and its metabolites from dog isolated saphenous vein

G.M. DREW, G.P. LEVY &  
A.T. SULLIVAN

*Department of Pharmacology, Glaxo-Allenburys Research (Ware) Ltd., Ware, Hertfordshire, SG12 0DJ*

Recently it has been suggested that labetalol, a competitive antagonist at  $\alpha$ - and  $\beta$ -adrenoceptors, can cause the release of noradrenaline from sympathetic nerve endings in the anococcygeus muscle of the rat (Doggrell & Paton, 1978). The possibility of such a releasing action has been investigated further in strips of dog saphenous vein preloaded with [<sup>3</sup>H]-labelled noradrenaline.

Saphenous veins were removed from anaesthetized beagle dogs, cut into helical strips and incubated in Krebs solution containing ascorbic acid (0.11 mM), EDTA (0.004 mM) and 1-[<sup>3</sup>H] noradrenaline hydrochloride (10  $\mu$ Ci/ml) for 2 h at 37°C. At the end of the incubation the strips were rinsed with fresh Krebs and placed in a 2 ml organ bath under an initial tension of 1 g. The Krebs solution in the organ bath was renewed every 10 min for 90 min to wash out the [<sup>3</sup>H]-noradrenaline from the extracellular space. At the end of this time the tissue was exposed to various concentrations of labetalol for 10 min and then washed with fresh Krebs (5  $\times$  10 min); this procedure was repeated up to three times. Throughout the experiment the Krebs solution was maintained at 37°C and gassed with 5% CO<sub>2</sub> in O<sub>2</sub>. The radioactivity in each 2 ml portion of Krebs solution was determined by scintillation counting.

The repeated administration of labetalol (10<sup>-5</sup> M) on four successive occasions caused a reproducible 2–4 fold increase in the overflow of radioactivity from the saphenous vein strips. The effect was dose related over the range 10<sup>-7</sup>–10<sup>-5</sup> M labetalol. This effect of labetalol was unaffected by omission of Ca<sup>2+</sup> from, or by the addition of cocaine (3  $\times$  10<sup>-5</sup> M) to, the Krebs solution; cocaine itself had no effect on the total release of radioactivity. Exposure of the tissue to phen-

tolamine (10<sup>-8</sup>–10<sup>-6</sup> M) or propranolol (10<sup>-7</sup>–10<sup>-5</sup> M) (concentrations causing a similar degree of  $\alpha$ - or  $\beta$ -adrenoceptor blockade to labetalol) caused only a small increase in release of radioactivity and then only at the highest concentrations used.

In separate experiments the radioactivity released from the saphenous vein strips was analysed by paper chromatography (Muldoon, Vanhoutte & Tyce, 1978). The results indicated that the increase in the release of radioactivity caused by labetalol (10<sup>-5</sup> M) was due mainly to an increase in 3,4-dihydroxyphenylglycol formation. This suggests that labetalol releases noradrenaline from an intraneuronal storage site and that the noradrenaline is subsequently metabolized, primarily by cytoplasmic monoamine oxidase; the resultant metabolites then diffuse into the extracellular space. This effect of labetalol is not related to its  $\alpha$ - or  $\beta$ -adrenoceptor antagonist properties, or to its ability to block uptake, (Drew, Hilditch & Levy, 1978). Similar findings have been reported for piperoxan (Borowski, Starke, Ehrl & Endo, 1977), phenoxybenzamine (Graefe, Stefano & Langer, 1973) and prazosin (Cambridge, Davey & Massingham, 1977).

### References

- BOROWSKI, E., STARKE, K., EHRL, H. & ENDO, T. (1977). A comparison of pre- and postsynaptic effects of  $\alpha$ -adrenolytic drugs in the pulmonary artery of the rabbit. *Neuroscience*, **2**, 285–296.
- CAMBRIDGE, D., DAVEY, M.J. & MASSINGHAM, R. (1977). The pharmacology of antihypertensive drugs with special reference to vasodilators,  $\alpha$ -adrenergic blocking agents and prazosin. *Med. J. Aust. Special Suppl.*, **2**, 62–68.
- DOGGRELL, S.A. & PATON, D.M. (1978). Effect of labetalol on adrenergic transmission in the rat anococcygeus muscle. *Br. J. Pharmac.*, **62**, 380P.
- DREW, G.M., HILDITCH, A. & LEVY, G.P. (1978). Effect of labetalol on the uptake of [<sup>3</sup>H]-(-)-noradrenaline into the isolated vas deferens of the rat. *Br. J. Pharmac.*, **63**, 471–474.
- GRAEFE, K.H., STEFANO, F.J.E. & LANGER, S.Z. (1973). Preferential metabolism of (-)-<sup>3</sup>H-norepinephrine through the deaminated glycol in the rat vas deferens. *Biochem. Pharmac.*, **22**, 1147–1160.
- MULDOON, S.M., VANHOUTTE, P.M. & TYCE, G.P. (1978). Norepinephrine metabolism in canine saphenous vein: prevalence of glycol metabolites. *Am. J. Physiol.*, **3**, H235–243.

## The effect of a high dose of prazosin, and transmural stimulation, on the disposition of transmitter noradrenaline in the rabbit pulmonary artery and the dog saphenous vein

M.J. ANDERSON, D. CAMBRIDGE,  
M.J. DAVEY & R. MASSINGHAM

*Department of Medicinal Biology, Pfizer Central Research, Pfizer Ltd., Sandwich, Kent*

P.M. VANHOUTTE & T. VERBEUREN

*Department of Internal Medicine, Universitaire Instelling Antwerpen, Wilrijk, Belgium*

We have previously reported that high doses of prazosin (>10<sup>-6</sup> M) cause an increase in [<sup>3</sup>H]-efflux from quiescent, [<sup>3</sup>H]-noradrenaline labelled strips of