In vitro accumulation of (±)-oxprenolol by rat lung

B.A. HEMSWORTH & J.A. STREET

Pharmacological Research Laboratories, Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET

The lungs possess a marked capacity to concentrate the β-adrenoceptor antagonist propranolol (Hayes & Cooper, 1971; Schneck, Pritchard & Hayes, 1977), and, although the uptake process displays some of the properties of Na^+ dependent carrier mediated transport (Dollery & Junod, 1976), the precise nature of the phenomenon remains obscure. Recent results from these laboratories have shown that several other β-adrenoceptor antagonists are concentrated in lung tissue, both *in vitro* (Street, Gonda, Parkinson & Hemsworth, 1978), and *in vivo* (Street, Hemsworth, Roach & Day, 1979), and it would appear from these latter studies that the lung accumulation of the non-selective drugs propranolol and oxprenolol is significantly greater than the accumulation of the β_1-selective compounds metoprolol, acebutolol, practolol and atenolol. In view of these observations, it was considered worthwhile to study further the lung uptake of oxprenolol, and to investigate the possibility of a common mechanism of uptake for oxprenolol and propranolol in this tissue.

Lung slices from male Wistar rats (250–300 g body wt.) were incubated, with gentle shaking, at 37°C in 3 ml Tyrode's solution (pH 7.4) containing [^{14}C]-oxprenolol at concentrations ranging from 3.3×10^{-7} M to 1.7×10^{-3} M. After incubation, the slices were washed, blotted, weighed and dissolved in 0.5 ml Protosol tissue solubilizer (New England Nuclear). 10 ml 'Dimilume-30' scintillation fluor (Packard Instrument Company) was added, and the total radioactivity in each sample was measured by liquid scintillation spectrometry.

At a concentration of 3.3×10^{-7} M, varying the length of incubation from 5 to 120 min demonstrated saturability of uptake as a function of time, the most rapid uptake occurring up to 60 min, with little increase thereafter. The maximum tissue:medium ratio at this concentration was 35.1 ± 3.5 (mean ± s.e. mean of 6 observations). For a 5 min incubation time, increasing the substrate concentration from 3.3×10^{-7} M to 1.7×10^{-3} M resulted in a progressive increase in oxprenolol uptake. There was some evidence of saturability, but no plateau was seen within this concentration range.

At a substrate concentration of 6.6×10^{-7} M, with a 30 min incubation time, oxprenolol uptake was significantly reduced by low temperature KCN (1 mM) 2,4-dinitrophenol (0.5 mM), N_2 atmosphere, and substitution of LiCl and Tris HCl for NaCl and $NaHCO_3$ respectively in the incubation medium. Ouabain, at a concentration of 1 mM, was without effect. Uptake was significantly reduced by a number of other drugs known to be concentrated in lung tissue, notably propranolol (10 μM), amphetamine (20 μM), chlorpromazine (20 μM) and imipramine (100 μM), whilst concentrations of noradrenaline up to 100 μM had little or no effect.

These results are in agreement with previous findings on the lung uptake of propranolol, and are consistent with the hypothesis for a common mechanism of uptake for propranolol and oxprenolol by the lung.

References

DOLLERY, C.T. & JUNOD, A.F. (1976). Concentration of (±)-propranolol in isolated, perfused lungs of rat. *Br. J. Pharmac.*, **57**, 67–71.

HAYES, A. & COOPER, R.G. (1971). Studies on the absorption, distribution and excretion of propranolol in rat, dog and monkey. *J. Pharmac. exp. Ther.*, **176**, 302–311.

SCHNECK, D.W., PRITCHARD, J.F. & HAYES, A.H. (1977). Studies on the uptake and binding of propranolol by rat tissues. *J. Pharmac. exp. Ther.*, **203**, 621–629.

STREET, J.A., GONDA, I., PARKINSON, H. & HEMSWORTH, B.A. (1978). Lung accumulation of some β-adrenoceptor antagonists. *J. Pharm. Pharmac.*, **30**, 56P.

STREET, J.A., HEMSWORTH, B.A., ROACH, A.G. & DAY, M.D. (1979). Tissue levels of several radiolabelled β-adrenoceptor antagonists after intravenous administration in rats. *Arch. Int. Pharmacodyn. Ther.* (in press).