LUNG ACCUMULATION OF SOME β-ADRENOCEPTOR ANTAGONISTS

J.A. Street, I. Gonda, H. Parkinson and B.A. Hemsworth,
Department of Pharmacy, University of Aston, Birmingham B4 7ET, England

It is now well established that, in addition to its respiratory function, the lung plays an important metabolic role in removing a number of endogenous substances from the circulation, including peptides, lipids, nucleotides and biogenic amines. In addition, the lung has been found to be a major site of sequestration for a number of drugs including imipramine, chlorpromazine, amphetamine and the β-adrenoceptor antagonist propranolol (Junod, 1976). The present report describes preliminary work to investigate the lung accumulation of a number of radiolabelled β-adrenoceptor antagonists with a range of physical and pharmacological properties.

Lung slices from male Wistar rats were incubated for 30 min at 37°C in 3 ml Tyrode's solution (pH 7.4) containing one of the β-blocking drugs propranolol, oxprenolol, metoprolol, acebutolol, practolol or atenolol at a concentration of 1 μg/ml. After incubation, the slices were washed, blotted, weighed and dissolved in 0.5 ml Protosol tissue solubilizer (New England Nuclear) and the total radioactivity was measured by liquid scintillation spectrometry. Table 1 shows the lung uptake *in vitro*, expressed as the tissue: medium concentration ratio; together with the apparent partition coefficients between octanol and 0.1 M phosphate buffer (pH 7.4, 37°C) for several β-adrenoceptor antagonists. The results show a significant correlation ($r = 0.84$; $P<0.05$) between the degree of lung uptake and the log partition coefficient, suggesting that lipophilicity plays an important role in the accumulation of β-adrenoceptor antagonists by the lung *in vitro*.

Table 1.

Compound	Tissue: Medium Ratio	Apparent Octanol: Buffer Partition Coefficient
Propranolol	27.23 ± 0.34	26.35 ± 0.28
Oxprenolol	23.32 ± 1.99	4.10 ± 0.02
Metoprolol	7.00 ± 2.47	1.48 ± 0.03
Acebutolol	3.14 ± 0.19	1.27 ± 0.01
Practolol	2.37 ± 0.28	0.12 ± 0.002
Atenolol	2.02 ± 0.12	0.04 ± 0.001

The results are the Mean ± s.e.m. of 4 - 6 experiments.

The *in vivo* lung uptake of these β-blocking drugs was also studied in the rat after i.v. administration of the compounds at a dose of 1 mg/kg. Comparison of the *in vivo* and *in vitro* data revealed a significant correlation ($r = 0.94$, $P<0.01$), showing that the tissue slice method gives a reasonably good indication of the lung uptake of these compounds *in vivo*.

The tissue: medium concentration ratios for propranolol and oxprenolol were significantly higher than the corresponding ratios for metoprolol, acebutolol, practolol and atenolol. The latter four compounds have been reported to have a selective action on cardiac β_1 receptors rather than on bronchial β_2 receptors, and it may be that selective tissue distribution influences the 'cardioselectivity' of these drugs.

Junod, A. (1976). Pharmac. Ther. B., 2, 511 - 521.