Br. J. Pharmac. (1981), **73**, 119–125

CHARACTERISTICS OF (±)-[^{14}C]-OXPRENOLOL AND (±)-[^{14}C]-PROPRANOLOL INCORPORATION BY RAT LUNG SLICES

BRIAN A. HEMSWORTH[1] & JAMES A. STREET[2]

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

1 The uptake of (±)-[^{14}C]-oxprenolol and (±)-[^{14}C]-propranolol has been studied in rat lung slices. The loss of these two radiolabelled β-adrenoceptor antagonists from pre-loaded lung slices has also been studied.

2 Over the concentration range studied (3.3×10^{-7} M to 1.7×10^{-3} M) a biphasic uptake of both compounds was observed. At concentrations below 1.5×10^{-4} M approximately, there was some evidence of saturability, but at higher concentrations uptake appeared to be a linear function of drug concentration.

3 At concentrations of 6.6×10^{-7} M and 1.7×10^{-6} M respectively, the uptake of oxprenolol and propranolol was significantly reduced by low temperature, anaerobic conditions, incubation in Na^+-free medium, and by the metabolic inhibitors potassium cyanide and 2,4-dinitrophenol. Ouabain had little or no effect.

4 At the same concentration, oxprenolol uptake was also inhibited in a concentration-dependent manner by propranolol, amphetamine, chlorpromazine and imipramine. Noradrenaline was without effect.

5 The loss of oxprenolol and propranolol from lung slices preloaded with the two compounds was fairly slow, with 60 to 70% of the drug originally taken up still remaining in the tissue after 30 min in fresh medium.

6 Possible mechanisms underlying the pulmonary accumulation of oxprenolol and propranolol are discussed.

Introduction

Distribution studies with the β-adrenoceptor antagonist, propranolol, have shown that this drug appears to be markedly concentrated in the lungs in several species of experimental animals, including mice (Masuoka & Hansson, 1967), rats (Schneck, Pritchard & Hayes, 1977; Street, Hemsworth, Roach & Day, 1979), rabbits (Black, Duncan & Shanks, 1965), dogs and monkeys (Hayes & Cooper, 1971). The quantitative importance of the pulmonary accumulation of propranolol may be illustrated by the finding that concentrations of the drug in this tissue in the rabbit were 100 to 250 times greater than those in the blood (Black *et al.*, 1965). Additionally, recent *in vitro* studies have shown that up to 94% of propranolol may be removed from the pulmonary circulation in a single passage (Blanck & Gillis, 1979).

Dollery & Junod (1976) have investigated the mechanism underlying the accumulation of propranolol in the lung. These workers found evidence for both high and low affinity components of propranolol uptake in isolated perfused lungs of rat. The high affinity component appeared to display some of the properties of Na^+-dependent, carrier-mediated transport, but other experimental findings were not wholly consistent with the involvement of a carrier-assisted mechanism. In contrast, the low affinity component was thought to be dependent upon hydrophobic interactions. However, no definite conclusions could be drawn regarding the precise nature of these two proceses, and they remain largely undefined.

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* (Hemsworth & Street, 1978; Street *et al.*, 1979), and it

[1] Present address: Department of Pharmacology, Life Sciences Bldg, Sunderland Polytechnic, Wharncliffe St, Sunderland, Tyne & Wear.

[2] Present address: Department of Pharmacology, University College, Foster Avenue, Blackrock, County Dublin, Ireland.

0007–1188/81/050119–007 $01.00

would appear from these studies that the lung accumulation of the non-selective drugs propranolol and oxprenolol is significantly greater than the accumulation of the β_1-adrenoceptor selective compounds metoprolol, acebutolol, practolol and atenolol. In view of these observations it was considered worthwhile to study further the characteristics of the lung uptake of oxprenolol, in comparison with propranolol, in order to elucidate further the mechanisms responsible for the accumulation of these two β-adrenoceptor antagonists in the lungs. A preliminary account of this work has been published (Hemsworth & Street, 1979).

Methods

Uptake studies

Male Wistar rats (250 to 350 g) were killed by decapitation and the lungs were perfused *in situ* with ice-cold 0.9% w/v saline via a cannula introduced into the pulmonary artery. This operation was performed in order to remove residual blood, after which the lungs were removed and washed twice in saline. Slices of whole lung 0.5 mm thick and weighing approximately 30 mg were then prepared at ambient temperature with a Stadie-Riggs tissue microtome.

Only lung slices with two cut surfaces were used, and these were incubated with gentle shaking in 3.0 ml Tyrode solution at pH 7.4 and 37°C. After a 5 min equilibration period, the slices were transferred to fresh incubation medium incorporating (±)-[^{14}C]-oxprenolol or (±)-[^{14}C]-propranolol, diluted with unlabelled drug of comparable purity (>99%) to give final concentrations in the range 3.3×10^{-7} M to 1.7×10^{-3} M. The incubations were then continued for periods of up to 120 min. When incubations were performed in the presence of other drugs or metabolic inhibitors, these were normally present during both equilibration and incubation periods. For experiments involving a Na^+-free medium, the incubation medium was prepared by replacing NaCl with LiCl on a molar basis, and by substituting NaH_2PO_4 and $NaHCO_3$ with 0.05 M Tris-HCl.

At the end of the incubation period the slices were washed twice in fresh, drug-free Tyrode solution, blotted dry, weighed, and digested in 0.5 ml 'Prostosol' tissue solubilizer (New England Nuclear) for 6 to 8 h at 50°C; 10 ml 'Dimilume-30' scintillation fluor (Packard) was then added, and, after dark adaptation for 30 min, the total radioactivity in each sample was measured in a Beckman LS-230 liquid scintillation spectrometer. Radioactivity in samples of the incubation medium was determined by counting 1.0 ml medium in 10 ml NE 260 scintillation fluor (Nuclear Enterprises). In the case of both tissue and medium samples, the counting efficiency was monitored by the use of an internal standard. In calculating the results, the radioactivity taken up into lung slices was expressed as if it were unchanged oxprenolol or propranolol, and the final results were corrected for the presence of labelled drug in the extracellular space (see below).

Metabolism studies

Lung slices were incubated for 30 min in Tyrode solution containing (±)-[^{14}C]-propranolol at a concentration of 3.3×10^{-6} M. Some slices were assayed for total radioactivity, as described above, whilst others were analysed for the presence of the major propranolol metabolites by a modification of the method of Dollery & Junod (1976). Tissue slices were homogenized in 1.0 ml 10% Na_2CO_3 and were shaken for 10 min with 5.0 ml toluene. After shaking, complete phase separation was assisted by centrifugation at 3000 *g* for 5 min, and the organic phase was drawn off and retained. The aqueous residue was re-extracted with a further 5.0 ml toluene and the two toluene extracts were combined. An aliquot of the comined extracts was counted in toluene-based scintillation fluor, whilst the remainder was concentrated in a stream of nitrogen and analysed by thin layer chromatography (t.l.c.) on silica gel F-254 plates (Kodak-Eastman Ltd.) in a solvent system of isopropanol : ammonia: water (20:1:3). Good separation was obtained between propranolol, 4-hydroxypropranolol and desisopropylpropranolol after a 7 h development.

No metabolism studies were carried out with (±)-[^{14}C]-oxprenolol.

Efflux studies

After a 30 min incubation in the presence of (±)-[^{14}C]-oxprenolol or (±)-[^{14}C]-propranolol at a concentration of 3.3×10^{-6} M, some lung slices were assayed for total radioactivity, whilst the remainder were transferred to fresh, drug-free Tyrode solution. These slices were further incubated with gentle shaking for periods of up to 30 min, and the radioactivity remaining in the slices was then measured.

Extracellular space volume

The extracellular space volume was estimated with [^{3}H]-inulin (mol. wt. approx. 5200) as an extracellular marker. Lung slices were incubated for varying periods of time in the presence of [^{3}H]-inulin at a concentration of 10 μg/ml and 2.0 μCi/ml. Radioactivity taken up into the slices was then estimated as before.

Equilibration between the medium and the extracellular space of the tissue slice was fairly slow,

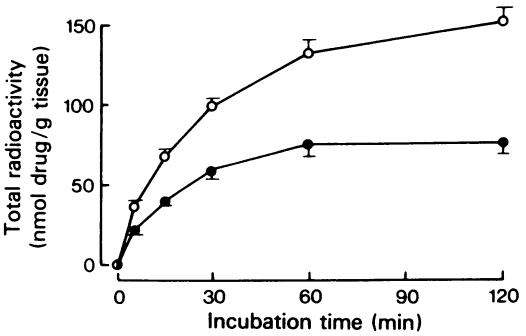

Figure 1 Uptake of radioactivity into rat lung slices as a function of time. Slices were incubated at 37°C for periods of up to 120 min with (±)-[^{14}C]-oxprenolol (●) or (±)-[^{14}C]-propranolol (○) at a concentration of 3.3 × 10^{-6} M. Each point shown here and in the following figures, represents the mean ± s.e. mean of at least 6 slices.

but was essentially complete after 120 min. At this time the 'inulin space' was equivalent to 225 ± 9 μl/g wet lung tissue (mean ± s.e. mean; n = 12).

Drugs and chemicals

The following drugs and chemicals were used in the present study: (±)-[^{14}C]-oxprenolol HCl (sp. act. 9.30 μCi/mg) and unlabelled (±)-oxprenolol HCl (CIBA Laboratories); (±)-[^{14}C]-propranolol HCl (sp. act. 9.15 μCi/mg) and unlabelled (±)-propranolol HCl (ICI Pharmaceuticals Division); [^{3}H]-inulin (The Radiochemical Centre); chlorpromazine HCl (May & Baker); (+)-ampetamine sulphate (SKF); potassium cyanide (Fisons); 2,4-dinitrophenol (BDH).

Results

Uptake studies

During incubation with radiolabelled oxprenolol or propranolol (3.3 × 10^{-6} M) for periods of up to 120 min (Figure 1), the most rapid uptake of radioactivity occurred over the first 30 min. Between 30 and 60 min, uptake was much less rapid and appeared to reach a fairly constant level at 60 min with little increase thereafter.

Figures 2 and 3 show the lung uptake of radioactivity after a 5 min incubation with labelled oxprenolol or propranolol as a function of the drug concentration in the incubation medium. At low concentrations there was some evidence of saturability with both drugs, and this was particularly clear at concentrations below 4.0 × 10^{-5} M (Figure 2). However, at higher concentrations, in the approximate range 1.5 × 10^{-4} M to 1.7 × 10^{-3} M, uptake appeared to be a linear function of drug concentration (Figure 3). The uptake of propranolol exceeded that of oxprenolol over the entire concentration range studied.

With concentrations of labelled propranolol (1.7 × 10^{-6} M) or oxprenolol (6.6 × 10^{-7} M) within the saturable region of the uptake vs substrate concentration curve, the uptake of radioactivity into lung slices over a 30 min incubation period was found to be sensitive to a number of factors (Table 1). Uptake was greatly reduced by low temperature, and was partially inhibited by incubation in Na^{+}-free medium, under anaerobic conditions, or in the presence of the metabolic inhibitors potassium cyanide (KCN) and 2,4-dinitrophenol (2,4-DNP) at concentrations of 1.0 mM and 0.5 mM respectively. Larger concentrations of these two agents failed to produce any additional

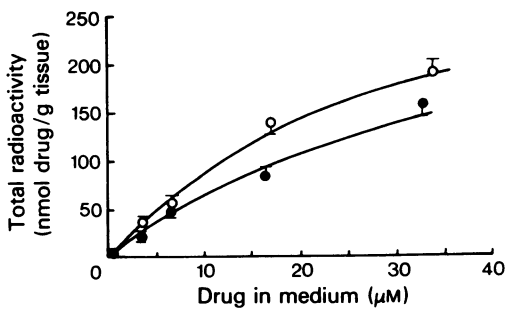

Figure 2 Uptake of radioactivity into rat lung slices after a 5 min incubation at 37°C with (±)-[^{14}C]-oxprenolol (●) or (±)-[^{14}C]-propranolol (○) at concentrations from 3.3 × 10^{-7} M to 3.3 × 10^{-5} M.

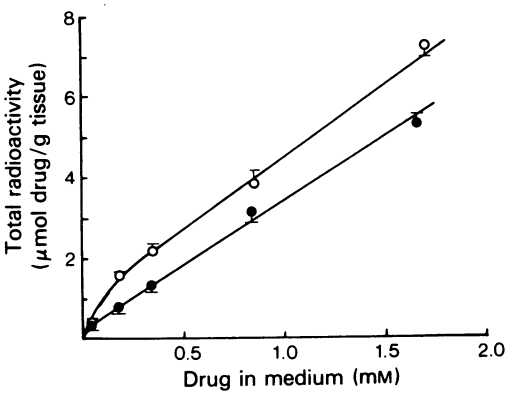

Figure 3 Uptake of radioactivity into lung slices after a 5 min incubation at 37°C with (±)-[^{14}C]-oxprenolol (●) or (±)-[^{14}C]-propranolol (○) at concentrations up to 1.7 × 10^{-3} M. Some points below 3.3 × 10^{-5} M have been omitted for the sake of clarity.

Table 1 Effect of various experimental conditions on the incorporation of radiolabelled oxprenolol and propranolol into rat lung slices

Experimental condition	*Incorporation of Radioactivity (% control)* *Oxprenolol*	*Propranolol*
Control	100	100
Temp. 0–4°C	22.2 ± 1.4*	29.9 ± 5.4*
Na^+-free medium	59.5 ± 3.2*	61.6 ± 3.4*
N_2 atmosphere	64.8 ± 3.6*	71.3 ± 7.3*
KCN 1.0 mM	60.3 ± 4.4*	67.8 ± 6.1*
2,4-DNP 0.5 mM	56.8 ± 1.8*	69.6 ± 6.3*
Ouabain 1.0 mM	97.8 ± 8.3	98.6±8.7
Glucose omission	101.9 ± 6.5	100.1 ± 7.2

The incorporation of radioactivity into lung slices was measured after a 30 min incubation with (±)-[^{14}C]-oxprenolol (6.6×10^{-7} M) or (±)-[^{14}C]-propranolol (1.7×10^{-6} M). Incorporation was measured under various experimental conditions and expressed as a percentage of the uptake into slices incubated under control conditions. Results shown are the mean ± s.e. mean of groups of at least 6 slices. Separate groups of control slices were used for each experimental parameter varied, and differences between test groups and their respective controls were assessed by means of the Student's *t*-test.

*Statistically different from control value ($P<0.05$).

inhibition of uptake. Incubation in a glucose-free medium or in the presence of ouabain (1.0 mM) had little or no effect.

At the same concentration of labelled oxprenolol (6.6×10^{-7} M), the uptake of radioactivity was reduced in a concentration-dependent manner by a number of other basic amines which are known to be concentrated in lung tissue: namely propranolol, amphetamine, imipramine and chlorpromazine (Figure 4). The inhibitory potencies of these drugs expressed as the IC_{50} values were as follows: propranolol 6.0×10^{-5} M; (+)-amphetamine 8.5×10^{-5} M; imipramine 1.0×10^{-4} M; chlorpromazine 2.0×10^{-4} M. In contrast, noradrenaline had no effect at concentrations up to 1×10^{-4} M.

Metabolism studies

Of the total radioactivity taken up into lung slices after a 30 min incubation with (±)-[^{14}C]-propranolol 89.6 ± 4.6% (mean ± s.e. mean; n = 8) was extractable into toluene at alkaline pH. Analysis of the toluene extracts by t.l.c. revealed that all the

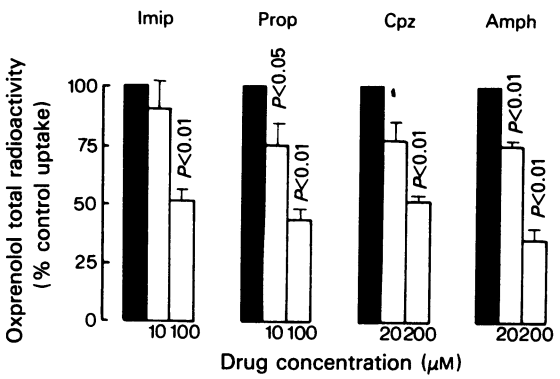

Figure 4 The effects of imipramine (Imip), propranolol (Prop), chlorpromazine (Cpz) and (+)-amphetamine (Amph) on the uptake of radioactivity into rat lung slices after a 30 min incubation at 37°C with (±)-[^{14}C]-oxprenolol (6.6×10^{-7} M). Uptake in the presence of drugs is expressed relative to the uptake into slices incubated under control conditions (solid column).

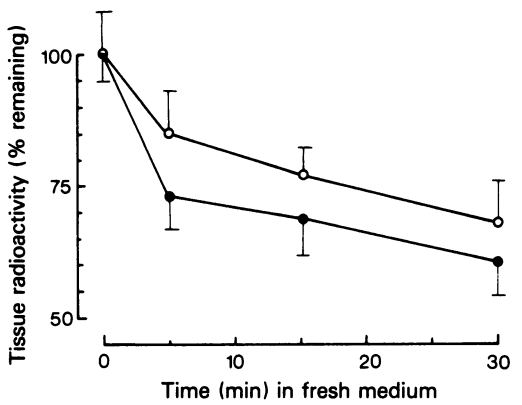

Figure 5 The loss of radioactivity from rat lung slices pre-loaded with labelled oxprenolol (●) or propranolol (○). Slices were incubated at 37°C for 30 min in medium containing (±)-[^{14}C]-oxprenolol or (±)-[^{14}C]-propranolol at a concentration of 3.3×10^{-6} M. Slices were then transferred to fresh drug-free medium, where they were gently shaken for periods of up to 30 min.

toluene-soluble radioactivity was attributable to labelled propranlol.

Efflux studies

The loss of radioactivity from lung slices preloaded with labelled oxprenolol or propranolol appeared to follow a biphasic pattern (Figure 5). Initial efflux was fairly rapid, but this was followed by a slower subsequent loss of radioactivity. At all times the percentage of propranolol remaining in the tissue was greater than that for oxprenolol. After incubation in fresh medium for 30 min, approximately 60% of oxprenolol and 70% of propranolol orginally taken up was still present in the slices.

Discussion

The propranolol metabolism studies indicated that at least 90% of the radioactivity taken up into lung slices during a 30 min incubation with labelled propranolol was accounted for by the parent compound itself. It appears, therefore, that little or no metabolism of propranolol occurred during this period. Similar findings were reported by Dollery & Junod (1976) for the perfused rat lung using perfusion times of up to 10 min. Oxprenolol is metabolized *in vivo* to a lesser extent than propranolol (Reiss, Brechbuhler, Brunner, Imhof & Jack, 1974; Johnsson & Regardh, 1976), and it was therefore assumed that the metabolism of oxprenolol by lung slices, like that of propranolol, would be of minor or negligible proportions. For this reason a separate metabolism study with oxprenolol was considered unnecessary. For both β-blocking drugs the total radioactivity taken up into lung slices under the present experimental conditions was therefore taken as an adequate measure of the incorporation of the parent compound.

The observed relationship between the lung uptake of propranolol or oxprenolol and the concentration of each drug in the incubation medium suggests the existence of at least two components of uptake for these drugs. At low drug concentrations a saturable component was evident but at higher concentrations a linear component of uptake became predominant. Similar biphasic relationships between uptake and substrate concentration have been reported for the uptake of propranolol by isolated perfused lung of the rat (Dollery & Junod, 1976), and for the lung uptake of a number of other basic amines, including imipramine, amphetamine, chlorcyclizine and methadone (Anderson, Orton, Pickett & Eling, 1974).

The results of the inhibition experiments with propranolol and oxprenolol (Table 1) were also compatible with the existence of more than one component of uptake, and revealed the existence of a component sensitive to temperature, extracellular Na^+, metabolic inhibitors and anoxia. It may be that this component and the saturable component are the same, and the results suggest that an energy-requiring, Na^+-dependent, carrier-mediated transport system may possibly be involved. However, in this respect, the lack of effect with oubain is somewhat paradoxical. Such a carrier-mediated mechanism has been proposed to account for the high concentrations of amphetamine found in the lungs (Drew & Nicholls, 1978). It is probable also that, since propranolol and oxprenolol are small lipophilic molecules, a proportion of these compounds taken up by the lung may be due to diffusion and non-specific hydrophobic binding, and this may account for the linear component of uptake. Binding of propranolol to the external membranes of blood platelets and erythrocytes has been reported (Lemmer, Wiethold, Hellenbrecht, Bak & Grobecker, 1972), and, additionally, propranolol binding to cell organelles, such as mitochondria, has been observed (Huunan-Seppala, 1972). It seems possible, therefore, that both extracellular and intracellular components may contribute to the pulmonary binding of propranolol and oxprenolol. Binding of these lipophilic β-adrenoceptor antagonists to extra- and intracellular membrane systems may be a reflection of hydrophobic interaction with phospolipid constituents of the membrane, as reported by Huunan-Seppala (1972) and Harris & Stahl (1978).

In view of the large inhibition of uptake induced by temperature reduction (~70 to 80%) compared with the inhibitions produced by Na^+-free medium, anaerobic conditions and maximally-inhibiting concentrations of metabolic inhibitors (~30 to 40%), it seems that temperature reduction may be affecting not only the saturable but also the linear component of uptake. This may be explained by considering the fact that the ionization of β-adrenoceptor antagonists is sensitive to changes in temperature. It would appear that, with compounds of this type, the relative proportion of the unionized species and hence the 'apparent' lipophilicity, is lowered by temperature reduction (Street, 1979). It is possible, therefore, that at low temperatures the contribution from diffusion and non-specific hydrophobic binding may be reduced, since the magnitude of these two processes should be a function of the concentration of unionized species.

For ionizable drugs, the rate and extent of diffusion across biological membranes may be modified by the existence of pH gradients between extracellular and intracellular compartments. Drew & Nicholls (1978) have recently found that the apparent intracellular pH of guinea-pig lung was 6.30, as compared to the plasma pH of 7.25. Such a pH gradient would be expected to enhance, to some extent, the passive transport of basic drugs such as propranolol (pKa =

9.45) and oxprenolol (pKa = 9.20), and this phenomenon may account in some part for the large number of basic lipophilic amines which are found to be concentrated in lung tissue. However, it must be stated, that at the present time it is not known whether a transmembrane pH gradient exists in the lungs of species other than the guinea-pig.

The present findings on the concentration of propranolol and oxprenolol in the lungs have a number of implications. The lungs represent an important site of sequestration for these two drugs, and for several other β-adrenoceptor antagonists (Hemsworth & Street, 1978; Street *et al.*, 1978; 1979) Pulmonary binding of propranolol and oxprenolol is reversible to some extent and although uptake is fairly rapid, subsequent efflux appears to be much less rapid. Thus, the lung is able to act as a capacitor, rapidly storing large amounts of these compounds and releasing them slowly. The consequence of this phenomenon is the damping of any abrupt variation in the blood levels of these drugs after their administration. It follows that any factor which affects the uptake or release of propranolol or oxprenolol may produce an unwarranted change in the circulating blood level of drug. It is clear from the experiments of Dollery & Junod (1976) and from the present experiments, that a number of other basic amines may inhibit the pulmonary uptake of propranolol and oxprenolol. Additionally, such compounds may also accelerate drug efflux (Dollery & Junod, 1976). Thus, drugs such as imipramine and chlorpromazine, if co-administered with propranolol or oxprenolol, may increase the circulating blood levels, and hence the pharmacological effects, of the β-adrenoceptor antagonists. A further factor which may reduce the storage capacity of the lungs for propranolol and oxprenolol may be the presence of necrotic or fibrotic lung disease, where the functional integrity of cells may be compromised. Under these circumstances the drug distribution volume may be reduced, with a corresponding increase in blood levels of drug.

In conclusion, it is unlikely that this role of the lungs is important for the long-term disposal of propranolol and oxprenolol, since hepatic metabolism and urinary excretion are the major determinants of the ultimate fate of these drugs. However, it is possible that the lungs may acutely modulate the pharmacokinetic behaviour and hence the pharmacological activity of these lipophilic β-adrenoceptor antagonists, and may, additionally, provide a potential site for drug interaction.

The authors would like to thank Dr D.E. Case of ICI Pharmaceuticals Division and Dr V.B. Whitmarsh of CIBA Laboratories for the generous gifts of radiolabelled and unlabelled propranolol and oxprenolol. This work was financially supported by the Science Research Council and CIBA-GEIGY.

References

ANDERSON, M.W., ORTON, T.C., PICKETT, R.D. & ELING, T.E. (1974). Accumulation of amines in the isolated perfused rabbit lung. *J. Pharmac. exp. Ther.*, 189, 456–466.

BLACK, J.W., DUNCAN, W.A.M. & SHANKS, R.G. (1965). Comparison of some properties of pronethalol and propranolol. *Br. J. Pharmac.*, **25**, 577–591.

BLANCK, T.J.J. & GILLIS, (1979). β-adrenergic receptor ligand binding by rabbit lung. *Biochem. Pharmac.*, **28**, 1903–1909.

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

DREW, G. & NICHOLLS, P.J. (1978). Uptake of amphetamine by guinea-pig lung in vitro. *J. Pharm. Pharmac.*, **30** (Suppl.), 55P.

HARRIS, W.E. & STAHL, W.L. (1978). Interactions of adrenergic compounds with brain membrane constituents. *Biochem. Pharmac.*, **27**, 2015–2019.

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.

HEMSWORTH, B.A. & STREET, J.A. (1978). Accumulation of β-adrenoceptor antagonists in the lung. *Proceedings of the VIIth International Congress of Pharmacology*, Abstract No. 2916, Oxford: Pergamon Press.

HEMSWORTH, B.A. & STREET, J.A. (1979). *In vitro* accumulation of (±)-oxprenolol by rat lung. *Br. J. Pharmac.*, **66**, 438P.

HUUNAN-SEPPALA, A. (1972). Binding of propranolol and chlorpromazine by mitochondrial membrances, *Acta chem. scand.*, **26**, 2713–2733.

JOHNSSON, G. & REGARDH, C.G. (1976). Clinical Pharmacokinetics of β-adrenoceptor blocking drugs. *Clin. Pharmacokin.*, **1**, 233–263.

LEMMER, B., WIETHOLD, G., HELLENBRECHT, D., BAK, I.J. & GROBECKER, H. (1972). Human blood platelets as cellular models for investigations of membrane active drugs: beta-adrenergic blocking agents. *Naunyn-Schmiedebergs Arch. Pharmac.*, **275**, 299–313.

MASUOKA, D. & HANSSON, E. (1967). Autoradiographic distribution studies of adrenergic blocking agents. II. ^{14}C-propranolol, a β-receptor type blocker. *Acta pharmac. tox.*, **25**, 447–455.

REISS, W., BRECHBUHLER, S., BRUNNER, L., IMHOF, P.R. & JACK, D.B. (1974). The metabolism of β-blockers in relation to their pharmacokinetic and pharmacodynamic behaviour. In *β-Blockers—Present Status and Future Prospects.* ed. Schweizer, W. pp. 276–289. Berne, Switzerland: Hans-Huber Publishers.

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. (1979). Studies on the properties of some β-adrenoceptor antagonists. *Ph.D Thesis, Department of Pharmacy, The University of Aston in Birmingham.*

STREET, J.A., GONDA, I., PARKINSON, H. & HEMSWORTH, B.A. (1978). Lung accumulation of some β-adrenoceptor antagonists. *J. Pharm. Pharmac.*, **30** (Suppl.), 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. *Archs. int. Pharmacodyn. Ther.*, **237**, 180–190.

(*Received August 4, 1980.*)