animals were killed by decapitation. The brain was quickly removed from the skull and placed in ice-cold 0·32 M sucrose. Bilateral striata were dissected out and homogenized in ice-cold 0·4 M perchloric acid containing ethylhomocholine iodide as internal standard. ACh was extracted by the method of Hanin et al (1972) and estimated by HPLC (Potter et al 1983; Eva et al 1984). The results are expressed as percent of control. Statistical analysis was done using a paired *t*-test.

Results and discussion

Oxotremorine, oxotremorine-1, and U-77053 significantly increased striatal ACh concentration. α-Methyl oxotremorine, BM-5, and α-methyl U-77053 significantly decreased ACh concentration in the striatum (Fig. 1). Muscarinic agonists such as oxotremorine, pilocarpine, and arecoline have been reported to increase ACh concentration in the brain (Haubrich & Reid 1972; Sethy & Francis 1988). Antimuscarinic agents like atropine, benztropine and trihexyphenidyl have been shown to decrease ACh content in the brain (Sethy & Van Woert 1973; Consolo et al 1974; Cheney et al 1976). The results of the present study indicate that substitution of an α-methyl group in the acetylenic amine converts a muscarinic agonist to an antagonist with respect to alterations in striatal ACh concentration.

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Letter to the Editor

J. Pharm. Pharmacol. 1991, 43: 671–672
Communicated December 21, 1990

The enantiomeric distribution of propranolol is not influenced by its β-blocking activity

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Propranolol is a lipophilic β-blocker (Hinderling et al 1984). When studying the distribution of propranolol in obese men, Poirier et al (1990) found a decreased volume of distribution as compared with normal subjects. In the rat, propranolol distributes only to a minor extent in adipose tissue (Bianchetti et al 1980). Poirier et al (1990) suggested that the β-blocking activity of propranolol could induce vasoconstriction, and so inhibit the distribution of propranolol to adipose tissues. We have studied this possibility by comparing the tissue distribution of *R*- and *S*-propranolol in rat fat and muscle after intravenous administration of the racemate, with that after administration of the enantiomers separately.

Male Wistar rats (SPF) 12 months old, 553 ± 9·84 g, were purchased from the breeding laboratories of the University of Leuven, Belgium. The rats were fasted for 16 h before drug administration, with free access to water. Silicone catheters were implanted in both jugular veins under ether anaesthesia without administration of anticoagulant (Chindavijak et al 1988). The drugs were administered to conscious animals 2 h after insertion of the catheters and interruption of ether anaesthesia; each rat was used only once. Propranolol racemate (1 mg kg^{-1}), *S*-(−)-propranolol (0·5 mg kg^{-1}) or *R*-(+)-propranolol (0·5 mg kg^{-1}) in 0·9% NaCl (saline) was administered via one of the jugular catheters at volumes of 0·2 mL per 100 g body weight. Sixty min after drug administration, the rats were decapitated and exsanguinated. Blood was collected in heparinized plastic tubes and the haematocrit was measured. For assay of the propranolol enantiomers, 2 blood samples and 2 plasma samples (100 μL) were stored at −20°C in stoppered glass tubes. Suprarenal fat and muscle from the hind limb and the lumbar region were excised, washed in ice-cold phosphate buffer 0·05 M pH 7·4 and homogenized by a Potter Elvehjem homogenizer. Fat was homogenized in three vol of water, muscle in three vol of buffer. The homogenates were stored in plastic tubes at −20°C until analysis.

The propranolol enantiomers were analysed using an indirect HPLC system with fluorescence detection, and (*R,R*)-*O,O*-

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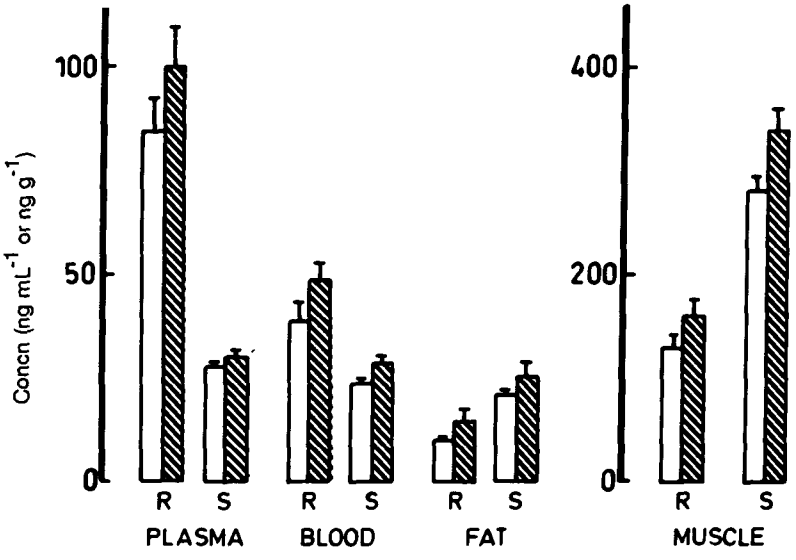

FIG. 1. Concentrations of *R*- and *S*-propranolol 60 min after intravenous administration of *RS*-propranolol (1 mg kg^{-1}), *R*-propranolol 0·5 mg kg^{-1}) or *S*-propranolol (0·5 mg kg^{-1}). Means ± s.e. are given. □, Administration of either *R*- or *S*-propranolol. ▨, Administration of *RS*-propranolol.

diacetyl tartaric acid anhydride as the derivatizing agent (Lindner et al 1989). All measurements were in duplicate.

The ratio of total tissue concentration to blood concentration was calculated for both fat and muscle. As the concentrations of the propranolol enantiomers in muscle of the lumbar region and the hind limb were comparable, the results were pooled. All results are given as means ± s.e. and pertain to propranolol free base. The two-tailed Mann-Whitney test for non-paired data was used to assess significance at the level of $P < 0.05$.

Concentrations of *R*- and *S*-propranolol in fat, muscle, blood and plasma and K_p values in fat and muscle are shown in Figs 1 and 2. For both enantiomers, the concentrations after administration of racemic propranolol are higher than after administration of the single enantiomers. However, when the ratios of total tissue concentration to total blood concentration are calculated, no differences can be observed as shown in Fig. 2. This means that the tissue distribution of neither enantiomer is influenced by the presence of the other. Therefore, the suggestion of Poirier et al (1990) that the vasoconstriction induced by *S*-(−)-propranolol diminishes the distribution of propranolol itself in adipose tissue, is unlikely to be the case. This is in accordance with Bickel (1984) who stresses that relative blood flow through adipose tissue is not a major determining factor. Moreover, for storage of basic lipophilic drugs in adipose tissue, lipophilicity comes into play only if lean tissue binding is of minor importance in the distribution process (Steiner et al 1991; Xie et al 1991).

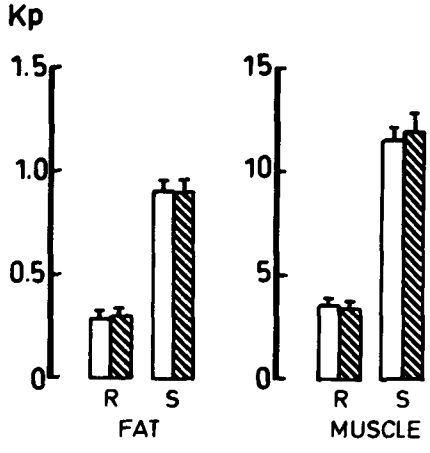

FIG. 2. Ratio of total tissue concentrations to total blood concentrations of *R*- and *S*-propranolol 60 min after intravenous administration of *RS*-propranolol (1 mg kg^{-1}), *R*-propranolol (0·5 mg kg^{-1}) or *S*-propranolol (0·5 mg kg^{-1}). Means ± s.e. are given. □, Administration of either *R*- or *S*-propranolol. ▨, Administration of *RS*-propranolol.

In conclusion, the minimal distribution of propranolol to fat despite its lipophilicity, is not due to the vasoconstrictor effect of the active *S*-enantiomer.

This work was supported by a grant of the National Fund for Scientific Research (grant number 3.9006.87). A. M. Vermeulen was a grantee from the I.W.O.N.L. from October 1, 1989, to September 30, 1990, and a Research Assistant of the National Fund for Scientific Research from October 1, 1990.

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