THE CENTRAL UPTAKE OF β-ADRENOCEPTOR ANTAGONISTS

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Since the original observation by Pritchard & Gillam (1964) that the β-adrenoceptor antagonist propranolol was effective in the management of hypertension, a number of other compounds in this class have been reported to possess antihypertensive properties (Kelly, 1976). Although the precise mechanism whereby β-adrenoceptor antagonists lower arterial blood pressure has not yet been fully elucidated, recent evidence suggests the central nervous system as a possible site of action (Day & Roach 1974). The present report describes preliminary work to investigate the central uptake and distribution of a number of clinically used β-adrenoceptor antagonists after systemic administration in experimental animals.

The radioactively labelled compounds propranolol, oxprenolol, practolol, atenolol acebutolol and metoprolol were injected into a femoral vein in halothane anaesthetized male wistar rats at a dose of 1 mg/Kg, or alternatively were injected into conscious animals via a catheter previously implanted in the jugular vein. After sacrifice of the animals blood and tissue samples were taken, freeze-dried, and stored in sealed vials at room temperature until assayed for total radioactivity by catalytic oxidation and liquid scintillation spectrometry. The total radioactivity in each sample was equated to the concentration of the labelled compound and its metabolites.

All six β-adrenoceptor antagonists were detected in the central nervous system 5 mins after administration, but there were differences in the ability of each compound to traverse the blood-brain barrier and achieve appreciable concentrations in the CNS. The hydrophilic compound atenolol was detected in brain tissue after 5 mins at a concentration of $0.08^{\pm}$ 0.02 µg/g wet weight and the concentration of atenolol in the blood was found to be $1.49^{\pm}$ 0.02 µg/ml; this gives a ratio of atenolol in brain/blood of 0.054. A similar calculation of the concentration in brain/concentration in blood for another hydrophilic β-blocking drug, practolol, showed a ratio of 0.18 whereas with the lipid soluble compounds, oxprenolol and propranolol, the respective ratios were 3.26 and 8.37. Quantitively similar results were obtained in both conscious and anaesthetized animals. The partially lipid soluble compounds acebutolol and metoprolol were also incorporated into the CNS and the penetration into the CNS of each of the six compounds studied showed a significant correlation ($r = 0.85$, $p < 0.05$) with the antihypertensive potency in man estimated from current data (Myers and others, 1976).

Since in man there is normally a delay in the onset of the antihypertensive effect with β-adrenoceptor antagonist therapy, it was considered worthwhile to examine the effect of pretreatment on the subsequent central uptake of labelled drugs. Pretreatment of groups of rats for 7,14 and 21 days with unlabelled atenolol appeared to cause an increase in the amount of labelled atenolol subsequently taken up into the brain, whilst the concentration of radioactive atenolol in the blood, liver and lung was reduced. These results are consistent with the hypothesis that a central action may contribute to the antihypertensive effect observed after chronic administration of β-adrenoceptor antagonists.

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