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HISTAMINE: AN INHIBITOR OF CYTOCHROME P-450-CATALYSED DRUG METABOLISM

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INTRODUCTION

Many xenobiotic substances have been shown to inhibit the hepatic cytochrome P-450 mixed function oxidase system (1). An imidazole ring is a common structural feature of several of these compounds, which include the drugs cimetidine and ketoconazole as well as some pesticides (2). The inhibitory properties of cimetidine have been particularly well characterised. Thus, *in vivo* and *in vitro* studies have shown that it alters the metabolism of a wide range of xenobiotics (3); we have recently examined its inhibitory effect on the oxidation of the beta-adrenoceptor antagonist, metoprolol (4). Cimetidine was developed as a specific antagonist of histamine at H_2-receptors and is a close structural analogue of histamine (5). Accordingly, it was thought that histamine may also be capable of inhibiting cytochrome P-450-catalysed oxidation. This hypothesis was tested in rat liver microsomes using metoprolol as a substrate.

MATERIALS AND METHODS

Liver microsomes from male Wistar rats (200-250g), starved for 18h, were prepared as described previously (4) and incubated with metoprolol and histamine for 5 minutes at 37°C, pH 7.25 in the presence of a NADPH generating system. A freshly prepared solution of histamine in water was used for each experiment. Under these conditions the rate of appearance of α-hydroxymetoprolol and O-desmethylmetoprolol, both assayed by HPLC (4), were linear with respect to time and protein concentration (1-1.5 mg/ml chosen for kinetic experiments). Apparent inhibition constants were obtained by fitting the data using a non-linear least squares algorithm (ELSFIT). Inhibition of metoprolol by all routes was assessed by determining the concentration at which histamine impaired the disappearance of metoprolol by 50% (IC_{50}).

RESULTS

Histamine inhibited the α-hydroxylation and O-desmethylation of metoprolol when the 2 compounds were co-incubated with rat liver microsomes (Figure 1). K_i values were 159 μM for α-hydroxylation and 324 μM for O-desmethylation (mean of 2 determinations). Histamine also inhibited metoprolol oxidation by all routes giving an IC_{50} value of 333 μM. When microsomes were incubated for various time periods with histamine before addition of metoprolol, no increase of inhibition was observed.

DISCUSSION

Structure-activity studies have indicated that imidazoles substituted at the 1- and 4(5)-positions on the ring are potent inhibitors of cytochrome P-450-mediated oxidation, whereas this property is lost on substitution at the 2-position (2). Binding to cytochrome P-450 and inhibition of metabolism are dependent on a sterically unhindered nitrogen atom at the 3-position (6). Histamine is a 4(5)-substituted imidazole and our findings that this biogenic amine is an inhibitor of the cytochrome P-450-catalysed oxidation of metoprolol would, therefore, support predictions based on structure-activity considerations.

Histamine was about an order of magnitude less potent an inhibitor than cimetidine (K_i = 9 μM for α-hydroxylation, 38 μM for O-desmethylation,

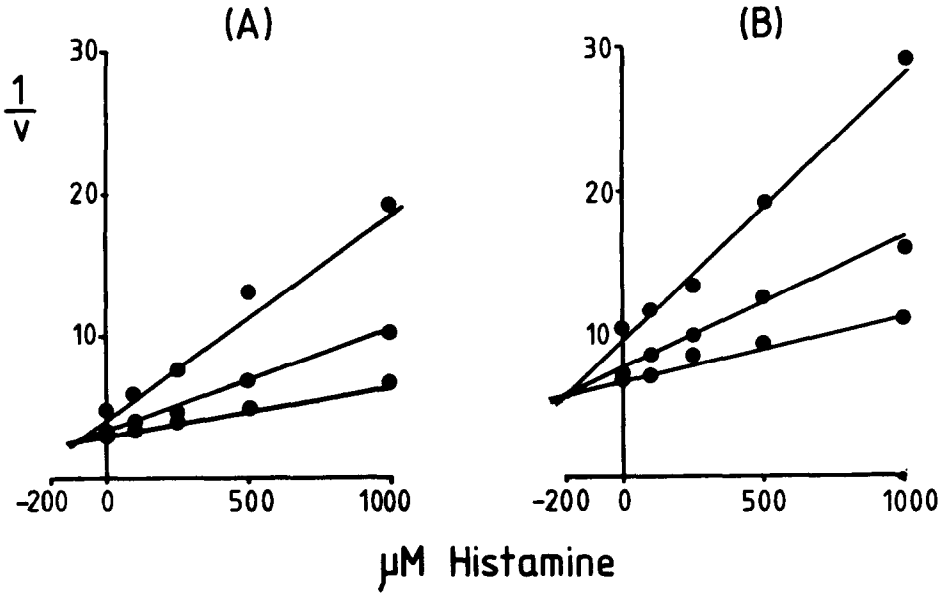

Figure 1: Dixon plots of 1/rate (v, nmoles min^{-1} mg $protein^{-1}$) of (A) ∝-hydroxymetoprolol and (B) O-desmethylmetoprolol appearance against histamine concentration.

reference 4). The stronger basicity of histamine (pKa 9.8) (7) compared to cimetidine (pKa 6.8) (3) and differences in lipophilicity as well as steric factors may explain this observation.

It is not known whether histamine or its precursors/metabolites are present in high enough concentration to inhibit hepatic mixed function oxidation in vivo. Total homogenates of rat and human liver contain histamine in concentrations of 0.5-5 μg/g wet tissue weight (7). Some of it is present in mast cells (7) but other evidence suggests that it is metabolised by enzymes in the cytoplasm of hepatocytes (8).

The inhibition of metoprolol ∝-hydroxylation and O-desmethylation by histamine appeared to be competitive in nature since plots of substrate concentration/rate against inhibitor concentration gave lines which were essentially parallel. This suggests a direct interaction of the inhibitor with the catalytic site(s) of oxidation. The possibility exists that histamine is itself a substrate for cytochrome P-450. Metabolic activation does not appear to be a requirement for its inhibitory action since pre-incubation with microsomes and a NADPH-generating system did not lead to an increase in the extent of inhibition.

A number of endogenous compounds are known to be substrates for the mixed function oxidase system but their ability to compete with xenobiotics for drug metabolising enzymes has not been defined. Our findings have demonstrated a direct inhibitory action of histamine on the cytochrome P-450-catalysed oxidation of metoprolol. The occurrence of such inhibition in vivo would suggest a role for histamine in the regulation of drug metabolising enzymes.

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