INDUCTION OF RAT LIVER BILIRUBIN-CONJUGATING ENZYMES AND GLUTATHIONE S-TRANSFERASE BY RIFAMPICIN*

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Summary

After oral administration of rifampicin and 25-desacetylrifampicin, which is a major metabolite of rifampicin in man but not in rat, to male Wister rats for 7 days, hepatic microsomal cytochrome P450, cytochrome b5, and activities of aniline hydroxylase, aminopyrine demethylase, bilirubin-conjugating enzymes and supernatant glutathione S-transferase were measured. Rifampicin induced bilirubin UDP-glucuronyltransferase, bilirubin UDP-glucosyltransferase, bilirubin UDP-xylosyltransferase and glutathione S-transferase activities, but did not induce mixed function oxidase activities. No inductive effect of desacetylrifampicin on any enzymes was observed. Serum bilirubin increased till the third day, and decreased after 7 days of rifampicin treatment. Plasma clearances of indocyanine green and sulfo-bromophthalein showed a marked delay after 1 day and 7 days of rifampicin treatment. Induction of bilirubin-conjugating enzymes and glutathione S-transferase by rifampicin in rats was different from that in humans, in which selective induction of mixed function oxidase is reported to occur. This species difference does not seem to be derived from the species difference of rifampicin metabolism, because no effect of desacetylrifampicin was observed. These results suggested that in rats rifampicin directly inhibits the hepatic excretion of bilirubin, whereas it enhances bilirubin conjugation due to enzyme induction.

Key Words: Rifampicin, Enzyme induction, Bilirubin, UDP-glucuronyltransferase, Glutathione S-transferase.

Introduction

In man rifampicin (RFP) is reported to induce hepatic mixed function oxidase1) and p-nitrophenol UDP-glucuronyltransferase (PNPGT)2), to increase urinary glucaric acid3) and 6β-hydroxy cortisol4) excretions and to enhance the plasma clearance of hexobarbital5). It is reported, however, not to influence the plasma clearance of antipyrine6) and not to elevate bilirubin UDP-glucuronyltransferase.
(BGT) when compared with untreated controls\(^2\). Thus, the enzyme induction of RFP in man is considered to be selective. On the other hand, RFP is reported not to induce hepatic microsomal mixed function oxidase activities in rats\(^6\).

In this report, we observed the effects of RFP and desacetylrifampicin (DA-RFP) on the changes of activities of hepatic microsomal mixed function oxidase activities, bilirubin-conjugating enzyme activities and liver supernatant glutathione S-transferase activity in rats. In addition, to elucidate the reason for the above difference according to species, the species difference in the effects of RFP and DA-RFP, which is a main metabolite of RFP in man, but which is formed in extremely low quantities in rats\(^7\), was estimated and discussed.

**Methods**

Male Wistar rats weighing about 120 g were used in all experiments. RFP was presented by the Daiichi Pharmaceutical Company (Tokyo, Japan) and DA-RFP by the Japan CIBA-GEIGY Corp (Takarazuka, Japan). Two hundred mg/kg of RFP or DA-RFP, suspended in 0.5% carboxymethylcellulose (20 mg/ml), was administered orally to five rats at 8:00 a.m. every morning for 7 days, and the rats were sacrificed by bleeding on the morning of the 8th day. Rats were fed *ad libitum* during this period. The control group was administered only the same amount of 0.5% carboxymethylcellulose.

The liver was perfused *in situ* with physiological saline, and the microsomal fraction and the 105,000×g supernatant fraction were obtained\(^8\). Hepatic microsomal protein content\(^9\), cytochrome P450\(^10\), cytochrome b\(_5\)\(^11\), aniline hydroxylase\(^12\) aminopyrine demethylase\(^13\), BGT\(^14\), bilirubin UDP-glucosyltransferase (BGLT)\(^15\), bilirubin UDP-xyllosyltrans-