Thesis Title Characterization of the Effect of Probenecid on Hepatic Drug Metabolism in Rats

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ABSTRACT

The characteristics of hepatic drug-metabolizing enzyme induction by probenecid, a uricosuric drug, were studied in adult male Wistar rats weighing 140 g to 200 g. Repeated administration of probenecid (600 mg/kg, PO, twice daily for 5 days) could significantly shorten the duration of action of two model drugs, zoxazolamine (60 mg/kg, IP, P-450 IA, IIB/ C/ E probe) and hexobarbital (120 mg/kg, IP, P-450 IIB/ C probe). Determination of the activities of hepatic aminopyrine N-demethylase (P-450 IIB & IIIA probe) and aniline hydroxylase (P-450 IIE probe) revealed that the inductive effect of probenecid was both dose- and time-dependent. During the 5-day period of treatment, maximal induction of both enzymes could be achieved when the drug was given at the dose of 600 mg/kg, PO, twice daily, for 5 days. However, significant induction of aminopyrine N-demethylase could be detected even at 1 day after drugs administration.

Aniline hydroxylase was significantly induced only when the drug was given for 5 days in the dose range between 200 and 800 mg/kg. After cessation of probenecid, aniline hydroxylase activity rapidly declined towards normal level while that of aminopyrine N-demethylase was gradually decreased. Induction of both enzymes

seemed to be due to quantitative increase in the enzyme content rather than a qualitative change because Km's of both enzymes were essentially the same as those observed in the control animals. Repeated administration of probenecid did not result in the induction of ethoxyresorufin O-deethylase (P-450 IA1 probe) at any time after drug administration. On the contrary, the activity of ethoxycoumarin O-deethylase (nonspecific substrate of P-450 subfamily II) showed time-course of induction similar to that observed with aminopyrine N-demethylase.

Glucuronidation towards 1-naphthol and 4-methylumbelliferone, the substrates metabolized by isozymes induced by both the phenobarbital (PB)- and 3-methylcholanthrene (3-MC)-type inducers, was also increased after the animals received the same treatment, though with different characteristics and at different degree.

The ultrastructure of hepatocytes from probenecid-treated rats showed a marked proliferation of smooth endoplasmic reticulum, the finding similar to the morphological changes reported after exposure to the PB-type inducers.

Overall results suggested that probenecid possessed not only the induction characteristics of phenobarbital but was also capable of inducing the metabolism of a variety of substrates other than that induced by this group of chemicals.