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THE ROLE OF N-SULFATION IN THE PROMOTION PHASE OF CARCINOGENESIS BY N-HYDROXY-2-ACETYLAMINOFLUORENE IN MALE RAT LIVER.


The liver is one of the organs in the male rat that is highly susceptible to the carcinogenic action of N-hydroxy-2-acetylaminofluorene (N-OH-AAF). A major route for the formation of reactive intermediates and macromolecular adducts from the carcinogen is N-oxidation through sulfontransferases. The role of this N-oxidation in the promotion phase of carcinogenesis by N-OH-AAF was the objective of this study. We used an initiation-promotion (selection) model for tumor-induction as originally developed by Roberts and colleagues (1). This model consists of treatment with diethylstilbestrol (single dose; initiation) followed by N-OH-AAF (several doses) coupled with partial hepatectomy (promotion/selection). The focal liver cell populations (foci), which are the first aberrant cells that appear with this treatment are considered to be preneoplastic lesions and can be detected by g-glutamyl-transpeptidase staining (GGT). The effects of inhibition of sulfotransferase activity towards N-OH-AAF with pentachlorophenol (PCP (2)) during N-OH-AAF treatment on the number and volume of GGT foci was investigated. PCP treatment during promotion with N-OH-AAF reduced the volume occupied by GGT -cells by 65%, without significantly affecting the number of GGT foci found per cubic cm. It is therefore concluded that this promotion (selection) by N-OH-AAF of initiated cells depends for a large part on the sulfotransferase pathway.

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CYTOTOXICITY AND BIOTRANSFORMATION STUDIES WITH BROMOBENZENE IN RAT HEPATOCYTE CULTURES

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Bromobenzene (BrB) is toxic to hepatocytes in vivo as well as in vitro. This toxicity is related to biotransformation and GSH depletion. BrB hepatotoxicity is elicited by metabolites that are generated by phenobarbital (PB)-inducible forms of cytochrome P-450, i.e. isoenzymes belonging to family II. In hepatocyte primary cultures a loss in cytochrome P-450 level is observed. In rat hepatocytes this loss is greater than in other mammalian species (1). Little is known about the behaviour of the different cytochrome P-450 isoenzymes and their residual activities in primary hepatocyte cultures. In order to validate the use of hepatocyte cultures as an in vitro model system for studying biotransformation, we investigated BrB cytotoxicity and biotransformation in rat hepatocytes immediately after cell isolation and after 24 h in primary culture. Toxicity (at conc up to 2 mM) was only observed in the freshly isolated cells. In these cells the levels of GSH were considerably lower than in cells after 24 h in culture. A BrB-dependent decrease in GSH was found in cells after exposure for 24 h. GSH/GSSG ratios changed from about 3 in control cells to about 1.5 in cells exposed to 2 mM BrB. BrB was metabolised to 2-, 3-, and 4-bromophenol, which were conjugated with glucuronic acid and sulphate. No changes in the ratio of 4-bromophenol/2-bromophenol were observed.

These results indicate that cytochrome P-450 isoenzymes involved in BrB metabolism belonging to family I and II are approximately equally stable in rat hepatocyte primary culture. Similar studies with liver cells derived from other mammalian species are in progress.


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