VC Rev

1979

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TOXICOLOGY AND APPLIED PHARMACOLOGY 49, 505–515 (1979)

Formation and Inactivation of a Chemically Reactive Metabolite of Vinyl Chloride[1]

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Received December 18, 1978; accepted March 17, 1979

Formation and Inactivation of a Chemically Reactive Metabolite of Vinyl Chloride. PESSAYRE, D., WANDSCHEER, J. C., DESCATOIRE, V., ARTIGOU, J. Y., AND BENHAMOU, J. P. (1979). *Toxicol. Appl. Pharmacol.* 49, 505–515. The mechanisms responsible for, and protecting against, metabolic activation of vinyl chloride were investigated in the rat. When [^{14}C]vinyl chloride was incubated with hepatic microsomes, a ^{14}C-labeled material became irreversibly bound to microsomal proteins; binding required NADPH, was decreased by CO, SKF 525-A, or glutathione, and was increased by 1,1,1-trichloropropene-2,3-oxide (TCPO). Inhalation of a 5% vinyl chloride atmosphere decreased hepatic cytochrome *P*-450 and glutathione. Pretreatment of the animals with DDT or phenobarbital (1) increased *in vitro* irreversible binding to microsomal proteins measured in the presence, but not in the absence, of TCPO and increased the *in vivo* loss of cytochrome *P*-450 during inhalation of vinyl chloride, but (2) decreased the *in vitro* irreversible binding to 10,000*g* supernatant proteins and the *in vivo* loss of glutathione during inhalation of vinyl chloride. These results are consistent with the views that (1) vinyl chloride is activated by cytochrome *P*-450 into its chemically reactive epoxide, (2) the epoxide may be inactivated by epoxide hydrase or by binding to glutathione, (3) pretreatment with DDT or phenobarbital increases both the formation rate of the epoxide and its inactivation rate by epoxide hydrase, and (4) cytochrome *P*-450 destruction is related to the formation rate of the epoxide, whereas glutathione depletion seems related to only that fraction of the formed epoxide which has escaped inactivation by microsomal epoxide hydrase and has diffused in the cytosol.

Vinyl chloride (chloroethylene) is massively used in the manufacture of plastics: Polymerization of this monomer leads to polyvinyl chloride, the most widely used synthetic plastic (Berk *et al.*, 1976). In workers exposed to vinyl chloride, angiosarcomas of the liver and/or hepatic fibrosis have been observed (Berk *et al.*, 1976). Hepatic angiosarcomas and liver lesions have been reproduced in experimental animals chronically exposed to vinyl chloride (Torkelson *et al.*, 1961; Lester *et al.*, 1963; Viola *et al.*, 1971; Maltoni and Lefemine, 1975; Prodan *et al.*, 1975).

Several carcinogenic and/or hepatotoxic compounds are transformed by the hepatic microsomal mixed-function oxidase system (MFOS) into chemically reactive metabolites that (1) covalently bind *in vitro* to microsomal proteins, (2) covalently bind *in vivo*

[1] This work was supported by Grant 021 R 07 from Faculté de Médecine Xavier-Bichat (Université de Paris VII), and ATP 58-78-90 from Institut National de la Santé et de la Recherche Médicale (INSERM).

[2] Recipient of a fellowship from the Fonds d'Etudes du Corps Médical Hospitalier.

0041-008X/79/090505-11$02.00/0