Mechanism of Carbon Tetrachloride-Induced Hepatotoxicity. Hepatocellular Damage by Reactive Carbon Tetrachloride Metabolites

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Z. Naturforsch. **56 c** 649–659 (2001); received February 23/March 28, 2001

Liver Damage, Carbon Tetrachloride, Peroxidation

CCl_4-induced liver damage was modeled in monolayer cultures of rat primary hepatocytes with a focus on involvement of covalent binding of CCl_4 metabolites to cell components and/or peroxidative damage as the cause of injury.

(1) Covalent binding of ^{14}C-labeled metabolites was detected in hepatocytes immediately after exposure to CCl_4. (2) Low oxygen partial pressure increased the reductive metabolism of CCl_4 and thus covalent binding. (3) [^{14}C]-CCl_4 was bound to lipids and to proteins throughout subcellular fractions. Binding occurred preferentially to triacylglycerols and phospholipids, with phosphatidylcholine containing the highest amount of label. (4) The lipid peroxidation potency of CCl_4 revealed subtle differences compared to other peroxidative substances, *viz.,* ADP-Fe^{3+} and cumol hydroperoxide, respectively. (5) CCl_4, but not the other peroxidative substances, decreased the rate of triacylglycerol secretion as very low density lipoproteins. (6) The anti-oxidant vitamin E (α-tocopherol) blocked lipid peroxidation, but not covalent binding, and secretion of lipoproteins remained inhibited. (7) The radical scavenger piperonyl butoxide prevented CCl_4-induced lipid peroxidation as well as covalent binding of CCl_4 metabolites to cell components, and also restored lipoprotein metabolism.

The results confirm that covalent binding of the CCl_3* radical to cell components initiates the inhibition of lipoprotein secretion and thus steatosis, whereas reaction with oxygen, to form CCl_3–OO*, initiates lipid peroxidation. The two processes are independent of each other, and the extent to which either process occurs depends on partial oxygen pressure. The former process may result in adduct formation and, ultimately, cancer initiation, whereas the latter results in loss of calcium homeostasis and, ultimately, apoptosis and cell death.