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Diet and alcohol induced fatty liver, oxidative stress and DNA damage

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It has been shown that oxidative stress and the generation of reactive oxygen species (ROS) also initiates DNA lesions and thus is involved in the pathogenesis of hepatic cancer.

In liver, ROS can be induced by Cytochrome P450 2E1 (CYP2E1). Once induced by CYP2E1, ROS can react with polyunsaturated fatty acids resulting in the generation of reactive aldehydes (MDA and 4-HNE) as lipid peroxidation (LPO)-products in the body. The LPO-products can react with DNA bases such as deoxyadenosine and deoxycytidine to form the exocyclic DNA-adducts. The formation of DNA adducts is one of the earliest damaging events to occur in the cellular genome and highly mutagenic. If not repaired, the adduct formation in surviving cells can lead to mutations upon cell division. Once these mutations accumulate they may disrupt genomic integrity leading to malignancy.

In this study, we investigate the contribution of fatty liver induced through a variety of different mechanism to certain DNA lesions which are important in the development of cancer. In addition, mechanisms by which oxidative stress occurs are studied.

In human liver biopsies, the scores of CYP2E1 show that there is an increased induction of Cytochrome P450 2E1 in patients with ASH compared to patients with NASH and that this induction of CYP2E1 also results in an increased level of 4-hydroxy-nonenal in ASH patients as compared to NASH and finally in an increase in carcinogenic DNA lesions (εdA) in ASH significantly more than in NASH. There was no difference in 8-OHdG between ASH and NASH patients so that mechanisms which lead to 8-hydroxy-deoxyguanosine generation may not be of relevance in this disease.

In an animal model using MCDD for ten weeks with and without ethanol in doses of 0.5 and 2 grams per kg bodyweight per day, an induction of CYP2E1 was observed by MCDD, which was not further increased by the addition of alcohol. This increase of CYP2E1 was accompanied by a similar increase in the generation of carcinogenic εdA-DNA adducts. A second experiment using higher alcohol concentrations with a high fat diet showed that indeed ethanol increased CYP2E1 but this was further increased when high fat diet was applied. A similar in εdA was observed after alcohol administration. In the experiment with high fat diet in which only 16 % of total calories was given as alcohol, there was an increase in εdA and CYP2E1 but only little in 4-hydroxy-nonenal and not in 8-hydroxy-deoxyguanosine and alcohol did not

further increase εdA, which shows the relatively low edition of alcohol with 16 % of total calories which was not in the position to further increase CYP2E1 and εdA.

Our data clearly show that the correlation between CYP2E1 induction and occurrence of these DNA lesions exists which is not surprising since CYP2E1 produces reactive oxygen species as a side reaction product involvements and the metabolism of ethanol, acetone or free fatty acids. Thus, CYP2E1 induction by itself is a risk factor for the production of carcinogenic DNA lesions. Lipid peroxidation products such as 4-hydroxy-nonenal and DNA lesions are more pronounced in alcoholic liver disease as compared to non-alcoholic fatty liver disease. Therefore, we can conclude fatty liver by itself is the risk factor for the production of oxidative stress and the carcinogenic DNA lesions. This is mediated by Cytochrome P450 2E1. In humans alcoholic fatty liver seems to have a greater input on CYP2E1 induction and DNA lesions as compared to non-alcoholic fatty livers. Measurements of exocyclic etheno-DNA lesions in liver biopsies from patients with fatty liver may give an estimate of the risk that exposed in the future with respect to hepatocellular carcinoma.