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Alcohol Dehydrogenase 3 Polymorphism and Induction of Cytochrome P450 2E1: Relevance for Ethanol Carcinogensis and Liver Disease

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Since it was reported that individuals possessing the alcohol dehydrogenase (ADH) 3*1 allele have an increased risk for the upper aerodigestive tract cancer, in this study we investigated the effect of ADH3 polymorphism on the metabolism of ethanol. Twenty-two healthy volunteers with ADH_3^{1-1}, ADH_3^{1-2}, ADH_3^{2-2} genotype received an oral dose of alcohol of 0.3g/kg, and their salivary acetaldehyde (AA) concentrations were determined over a period of 240min. AA levels were measured using HPLC with fluorescence detection of its 2-diphenylacetyl-1,3-indandione-1-azine derivative. The result showed that individuals with ADH_3^{1-1} had higher salivary AA concentrations compared to individuals with ADH_3^{1-2} or ADH_3^{2-2}. The higher salivary concentrations of AA in individuals with ADH_3^{1-1} give further evidence for a genetic predisposition to the upper aerodigestive tract cancer in heavy alcoholics due to the presence of ADH_3^{1-1}.

Chronic alcohol consumption results in an induction of CYP2E1 in the liver but also in extrahepatic tissues, which is associated with an increased metabolism of alcohol and an enhanced production of harmful free radicals. However, the amount and duration of ethanol consumption leading to an induction of CYP2E1 is not known. To investigate this, five male volunteers consumed 40g alcohol daily as red wine for four weeks. The alcohol was always consumed during the evening over a period of 1 to 3 hours. CYP2E1 induction was measured at time points 0, 1, 2, 3 and 4 week using the chlorzoxazone test. The data demonstrated that even one week of moderate alcohol consumption leads to a significant CYP2E1 induction, which may be of importance in the pathogenesis of alcoholic liver disease and in alcohol associated carcinogenesis. According to this rapid CYP2E1 induction by ethanol, an increased production of potentially harmful free oxygen radicals and alcohol-drug interactions can already be assumed in moderately alcohol consuming people after one week drinking.

The CYP2E1 induction in ASH and NASH and its role in the pathogenesis of liver diseases have also been evaluated in this study. Immunohistochemistry was performed in liver biopsies from eighteen patients with ASH and fifteen patients with NASH. A

diffuse pattern of CYP2E1 induction was observed in ASH, which is more pronounced as in NASH. This induction could disappear rapidly following alcohol withdrawal. In NASH only five of fifteen patients had a moderate induction of CYP2E1 while the remaining had a slight or no induction at all. The degree of hepatic CYP2E1 expression decreases with the severity of the histomorphologic injury. The hepatic CYP2E1 expression does not reflect the severity nor does it reflect the prognosis of the liver disease. This may suggest that CYP2E1 induction may operate only in the first stage of the disease or takes only a partial role in the pathogenesis of NASH.