alpd2012-0063

# Acetaldehyde-derived Advanced Glycation End-products Promote Alcoholic Liver Disease

Joseph George*, Nobuhiko Hayashi, Masayoshi Takeuchi and Mikihiro Tsutsumi

Department of Gastroenterology & Hepatology and Department of Advanced Medicine, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan

Chronic ingestion of ethanol increases acetaldehyde and leads to the production of acetaldehyde-derived advanced glycation end-products (AA-AGE). We evaluated the cytotoxicity of AA-AGE on hepatocytes and examined the role of AA-AGE in the pathogenesis of alcoholic liver disease (ALD). Rat hepatocyte cultures were treated with N-ethyllysine (NEL) or AA-AGE and the cell viability was evaluated using MTT assay. Male Wistar rats were fed with liquid diet containing 5% ethanol for 8 weeks followed with normal diet for 12 weeks. A group of animals were sacrificed at 4, 6, and 8th week and the remaining animals at 12, 14, 16, 18 and 20th week. The liver sections were stained for AA-AGE and 4-hydroxy-nonenal (4-HNE). Liver biopsy obtained from ALD patients was also stained for AA-AGE and 4-HNE. The hepatocyte viability was significantly reduced in cultures treated with AA-AGE compared to control cultures or with NEL. Severe fatty degeneration was observed during the chronic administration of ethanol increasing from 4-8 weeks. The staining of AA-AGE and 4-HNE was strongly correlated with the degree of ALD in both rat and human. In rats, hepatic fatty degeneration was completely disappeared and the staining for both AA-AGE and 4-HNE returned to normal at 12th week of abstinence. Staining for AA-AGE and 4-HNE was completely absent in normal human liver. Our data demonstrated that AA-AGE is toxic to hepatocytes, but not NEL. Chronic ethanol ingestion produces AA-AGE and reactive oxygen species (ROS) contributing to the pathogenesis of ALD. Abstinence of alcohol results in complete disappearance of both AA-AGE and 4-HNE suggesting that AA-AGE may play a significant role in the pathogenesis of ALD.