

Activation of natural killer T cells during alcohol consumption induces liver injury and death, a role for Fas and TNF- α

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ABSTRACT

Background & Aims: Chronic alcohol abuse induces liver injury and increases severity of viral hepatitis, but the precise mechanisms responsible are not well understood. In particular, little is known about the role of natural killer T (NKT) cells in alcohol induced liver injury. NKT cells have emerged as mediators of important regulator and effector functions, in autoimmune diseases and liver injury. This study analyzes the role of NKT cells in a model of chronic alcohol consumption. **Methods:** Mice were fed alcohol by an intragastric tube and assayed for serum ALT values, liver histology and liver mononuclear cells, before and after activation of NKT cells by their ligand α -galactosylceramide (α -GalCer). **Results:** In alcohol consuming animals, liver NKT cells increase and activation of these cells by α -GalCer causes lethal liver injury. This is due to alcohol-induced sensitization of hepatocytes to cell-mediated lysis, developing concomitant to increased cytolytic activity of NKT cells. NKT cell-mediated cell lysis proceeds by the Fas pathway and Fas is essential for alcohol associated liver injury. However, tumor necrosis factor (TNF)- α plays an additional role as a defect in TNF receptor 1 (TNFR1) inhibits alcohol associated liver injury. **Conclusion:** Alcohol consumption induces an increase of NKT cells in the liver and high sensitivity of hepatocytes to cell mediated lysis. Stimulation of NKT cells during alcohol consumption induces serious liver injury by a mechanism, involving concomitant signals by Fas and TNFR1 on alcohol stressed hepatocytes.