Chronic-binge ethanol feeding in mice associates with downregulation of hepatic xanthine oxidase, resulting in reduced uric acid levels in plasma and liver

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Excess alcohol intake mostly results in alcohol-associated liver disease (ALD), a progressive liver condition characterized by steatosis, inflammation and liver injury. Moreover, altered liver metabolism causes the generation of disease-promoting metabolites. As such, uric acid (UA), which is the product of purine metabolism in the liver, has been described to contribute to liver inflammation in alcoholic hepatitis patients by acting as a danger-associated molecular pattern that triggers the inflammasome cascade. Moreover, several studies showed a positive correlation between systemic hyperuricemia and alcohol-associated liver disease. Nevertheless, other studies reported lower serum UA levels in heavy drinkers, leaving a gap in the complete understanding of the role of uric acid in the pathogenesis of ALD. Therefore, we utilized the chronic-binge ethanol feeding model in WT C57Bl6/J mice to assess UA levels and metabolism during murine ethanol-induced liver disease and compare it to pair-fed control mice. We found that serum UA levels were lower in mice receiving an ethanol-containing diet (1.49±0.21 mg/dl) compared to control-fed mice (2.4±0.25 mg/dl). Likewise, liver UA concentrations were reduced in alcohol-fed mice (3.16±0.21mg/g protein) compared to control (4.12±0.36 mg/g protein). In spite of that, urate oxidase activity in the liver wasn't different between the groups (71.73±2.13 and 63.66±2.20 mU/ml in control- and ethanol-fed mice, respectively). Yet, protein levels of xanthine oxidase, an enzyme that uses xanthine/hypoxanthine as a substrate for UA production, was reduced in the livers of mice receiving an ethanol diet, corroborating the decrease in UA levels in ALD mice. Although some differences in UA metabolism between humans and rodents must be taken into consideration, our results open a new discussion about the relationship between uric acid levels and alcohol intake and bring new insights into UA metabolism during alcohol-associated liver disease.