Decompensated MASH-Cirrhosis Model by Acute and Toxic Effects of Phenobarbital

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Abstract

Metabolic dysfunction-associated Steatohepatitis (MASH), is a prominent cause for liver cirrhosis. MASH-cirrhosis is responsible for liver complications and there is no specific treatment. To develop new therapeutic approaches, animal models are needed. The aim of this study was to develop a fast animal model of MASH-cirrhosis in rats reflecting the human disease. Carbon tetrachloride (CCl4) injections in combination with a high-fat Western diet (WD) were used to induce MASH-cirrhosis. To accelerate liver injury, animals received phenobarbital (PB) in their drinking water using two different regimens. Rats developed advanced MASH-cirrhosis characterized by portal hypertension, blood biochemistry, hepatic ballooning, steatosis, inflammation and fibrosis. Importantly, rats receiving low-dose PB for the long term (LT) showed ascites after 6 weeks, whereas rats with high-dose short-term (ST) PB developed ascites after 8 weeks. ST- and LT-treated rats showed increased portal pressure (PP) and decreased mean arterial pressure (MAP). Of note, hepatocyte ballooning was only observed in the LT group. The LT administration of low-dose PB with CCl4 intoxication and WD represents a fast and reproducible rat model mimicking decompensated MASH-cirrhosis in humans. Thus, CCl4 + WD with LT low-dose phenobarbital treatment might be the preferred rat animal model for drug development in MASH-cirrhosis.