I-Serine Supplementation Attenuates Alcoholic Fatty Liver by Enhancing Homocysteine Metabolism in Mice and Rats.

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BACKGROUND: Hyperhomocysteinemia plays an important role in the development of hepatic steatosis, and studies indicate that homocysteine-lowering treatment inhibits the development of fatty liver.

OBJECTIVE: We evaluated the effects of l-serine on alcoholic fatty liver and homocysteine metabolism.

METHODS: In a binge ethanol study, male C57BL/6 mice were divided into 4 groups: control, ethanol + vehicle, and ethanol + 20 or 200 mg/kg l-serine. Mice were gavaged with ethanol (5 g/kg body weight) 3 times every 12 h with or without l-serine which was given twice 30 min before the last 2 ethanol doses. Control mice were fed isocaloric dextran-maltose. In a chronic ethanol study, male Wistar rats were divided into 3 groups: control, ethanol, and ethanol + l-serine. Rats were fed a standard Lieber-DeCarli ethanol diet (36% ethanol-derived calories) for 4 wk with or without dietary l-serine supplementation (1%; wt:vol) for the last 2 wk. In control rats, the ethanol-derived calories were replaced with dextran-maltose. The effects of l-serine were also tested in AML12 cells manipulated to have high homocysteine concentrations by silencing the genes involved in homocysteine metabolism.

RESULTS: Binge ethanol treatment increased serum homocysteine and hepatic triglyceride (TG) concentrations by >5-fold vs. controls, which were attenuated in the 200-mg/kg l-serine treatment group by 60.0% and 47.5%, respectively, compared with the ethanol group. In the chronic ethanol study, l-serine also decreased hepatic neutral lipid accumulation by 63.3% compared with the ethanol group. l-Serine increased glutathione and S-adenosylmethionine by 94.0% and 30.6%, respectively, compared with the ethanol group. Silencing betaine homocysteine methyltransferase, cystathionine β-synthase, or methionine increased intracellular homocysteine and TG concentrations by >2-fold, which was reversed by l-serine when l-serine-independent betaine homocysteine methyltransferase was knocked down.

CONCLUSION: These results demonstrate that l-serine ameliorates alcoholic fatty liver by accelerating l-serine-dependent homocysteine metabolism.