Wilson Disease: abnormal methionine metabolism and the role of inflammation and steatosis in early stages of liver disease

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INTRODUCTION

Wilson disease (WD) is a rare autosomal recessive disorder of copper transport featuring hepatic copper accumulation and development of hepatic steatosis. The mechanisms linking copper accumulation to hepatic steatosis remain unclear. Copper has been shown to inhibit the enzyme S-adenosylhomocysteine hydrolase (SAHH), central in methionine metabolism and in regulating S-adenosylhomocysteine (SAH) and S-adenosylmethionine (SAM) levels. The SAM/SAH ratio is an indicator of methylation capacity and plays an important role in regulating gene expression, and SAM regulates the production of antioxidant glutathione (GSH). This study aims to examine the effects of copper induced SAHH inhibition and treatment with copper chelator penicillamine (PCA) in the pathogenesis of inflammation and steatosis in an animal model of WD in order to establish a link between methionine metabolism and gene expression regulation.

ANIMALS AND METHODS

Livers and blood were collected from 7 toxic milk (tx-j) and 7 C3H control mice at 12 weeks of age, 7 PCA treated tx-j mice, 7 untreated tx-j mice, and 7 control mice at 24 weeks of age. All mice were fed the same diet except the tx-j mice receiving oral PCA. We measured methionine metabolism metabolites SAM, SAH, and GSH (HPLC) and SAHH activity. Lipid metabolism genes glucose related protein (GRP78), sterol regulatory element binding protein 1c (SREBP1c), carnitine palmitoyltransferase 1 (CPT1a), and peroxisome proliferator activated receptor α (PPARα), and proinflammatory tumor necrosis factor α (TNFα) were measured via RT-PCR.

RESULTS

- Hepatic copper levels in tx-j mice were 35-40 times greater than controls (p<0.0001) while PCA treated tx-j mice accumulated half the copper levels of untreated tx-j mice (p<0.0001).
- At 24 weeks, SAHH activity was reduced in tx-j mice (p<0.01) but similar to controls in PCA treated tx-j mice.
- Hepatic SAHH levels increased in PCA treated and untreated tx-j groups (p<0.05), lowering the SAM/SAH ratio (p<0.05).
- Liver GSH was increased in untreated tx-j mice but was re-established similar to controls in PCA treated tx-j mice (p<0.0001).
- GRP78, SREBP1c, CPT1a, and PPARα expressions were reduced in untreated tx-j mice at both 12 and 24 weeks and further reduced in PCA treated tx-j mice.
- TNFα expression was higher in untreated tx-j mice than in controls but was reduced in PCA treated tx-j mice (p<0.05).

CONCLUSIONS

Copper accumulation is associated with SAHH enzyme activity inhibition in tx-j mice, which was restored in PCA treated tx-j mice. The SAM/SAH ratio was reduced in PCA treated and untreated tx-j mice leading to changes in inflammation and steatosis gene expression. These findings support the hypothesis that copper induced abnormal methionine metabolism and subsequent inflammation and steatosis play a role in the pathogenesis of early liver disease in WD.

REFERENCES