Metadoxine prevents diet-induced non-alcoholic steatohepatitis in mice

Jinghua Du, Wen Zhao, Yu Lu, Dongdong Li, Xiwei Yuan, Yuguo Zhang, Rongqi Wang, Yuemin Nan*

Department of Traditional and Western Medical Hepatology, Third Hospital of Hebei Medical University, Shijiazhuang, China

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver disorders worldwide. Metadoxine appears to be an effective strategy to manage alcoholic steatohepatitis. However, its role during non-alcoholic steatohepatitis (NASH) remains poorly defined.

AIM

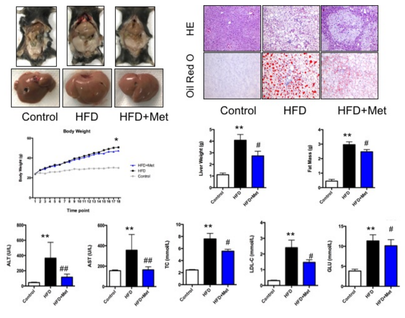
The study aimed to assess the therapeutic efficacy and mechanisms of metadoxine in NASH.

METHOD

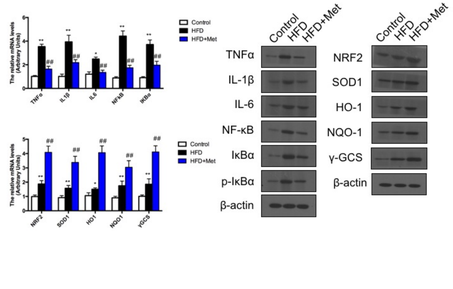
Male C57BL/6J mice were randomly divided into three groups of six animals. The treatments were as follows: 1): Control group: standard diet. 2) NASH group: 42% fat “high fat” diet (HFD) ad libitum for 16 weeks. 3) Metadoxine group: HFD and a single oral dose of metadoxine (200 mg/kg). Mice body weight, liver weight, fat mass was measured. Sera were collected for the analysis of biochemical markers and livers were obtained for further histological staining and gene expression analysis. Transmission electron microscope (TEM) was used to observe the cell ultrastructure. The expression of inflammation genes, lipogenesis genes, and oxidative stress genes were assessed by real-time PCR and western blot.

RESULTS

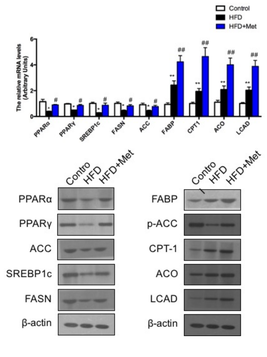
After 16-week dietary intervention, metadoxine decreased the body weight and liver weight compared to the HFD group. Liver sections showed that HFD mice developed marked macro- and microvesicular steatosis, as well as multifocal necrosis compared to the controls. However, metadoxine treatment abolished steatosis. Less lipid droplets were observed in the metadoxine treated animals in Oil Red O-stained sections. Metadoxine treated mice showed lower serum concentrations of ALT, AST and TC, LDL-C, and GLU than HFD mice. Moreover, we found mRNA levels of TNF-α, IL-1β, NF-κB, IκBα were higher in HFD-fed mice than control group. However, metadoxine treatment could decrease these genes and protein expression. In addition, metadoxine significantly increase the expression of lipogenesis genes (PPAR-α/γ, SREBP1c, FASN and ACO). Hepatic mRNA levels of oxidative stress gens were increased in HFD group, and metadoxine treatment further enhanced the expression of oxidative stress factors, such as NRF2, SOD1, HO-1, NQO1.



Metadoxine protects against dietary-induced steatohepatitis and liver injury. Histopathological changes of the liver sections from mice fed with control or HFD. Haematoxylin and eosin stained (up, original magnification ×200) and oil red O stained (down, original magnification ×200) liver sections showed decreased intrahepatic lipid in metadoxine treated mice. Body weight curve in each groups. Levels of ALT, AST, TC and TG in the plasma in the control, HFD and metadoxine treated mice. Values are mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared with HFD.



Metadoxine decrease inflammatory and oxidative stress related cytokines. Expression of TNF-α, IL-1β, IL-6, NF-κB, IκBα, p-IκBα was higher in HFD-fed mice than control group. However, metadoxine treatment could decrease these genes expression. We also analyzed the effects of metadoxine on key antioxdative gens Nrf2, SOD1, HO-1, SOD, γGCS. Hepatic mRNA and protein levels of these genes were dramatically increased in HFD-induced steatohepatitis. Values are mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared with HFD.



Effects of metadoxine on hepatic lipid metabolism in HFD-fed mice. The expression of enzymes involved in fatty acid and triglyceride synthesis, including PPAR α/γ, SREBP1c, as well as those of its responsive ACC, FASN, was decreased in HFD diet fed mice and increased by metadoxine administration. The hepatic levels of the mRNAs for FABP, CPT-1, ACO, LCAD were significantly increased in mice fed with HFD, and were further increased in metadoxine treated mice. Values are mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared with HFD.

CONCLUSIONS

Our data established a therapeutic role of metadoxine in NASH development. Metadoxine has a protective effect on NASH and its mechanims may be related to decrease the lipid accumulation, inhibit the oxidative stress and ultimately deduce inflammation.

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CONTACT INFORMATION

Yuemin Nan, MD, PhD, Department of Traditional and Western Medical Hepatology, Third Hospital of Hebei Medical University, Shijiazhuang, China
Tel: +86 311 66781227; Fax: +86 311 87023626; E-mail address: nanyuemin@163.com