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Research paper

Nicotinamide riboside attenuates alcohol induced liver injuries via activation of SirT1/PGC-1α/mitochondrial biosynthesis pathway

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ABSTRACT

Background: Nicotinamide riboside (NR) is a nicotinamide adenine dinucleotide (NAD^+) precursor which is present in foods such as milk and beer. It was reported that NR can prevent obesity, increase longevity, and promote liver regeneration. However, whether NR can prevent ethanol-induced liver injuries is not known. This study aimed to explore the effect of NR on ethanol induced liver injuries and the underlying mechanisms.

Methods: We fed C57BL/6 J mice with Lieber-DeCarli ethanol liquid diet with or without 400 mg/kg·bw NR for 16 days. Liver injuries and SirT1-PGC-1α-mitochondrial function were analyzed. In in vitro experiments, HepG2 cells (CYP2E1 over-expressing cells) were incubated with ethanol ± 0.5 mmol/L NR. Lipid accumulation and mitochondrial function were compared. SirT1 knockdown in HepG2 cells were further applied to confirm the role of SirT1 in the protection of NR on lipid accumulation.

Results: We found that ethanol significantly decreased the expression and activity of hepatic SirT1 and induced abnormal expression of enzymes of lipid metabolism in mice. Both in vivo and in vitro experiments showed that NR activated SirT1 through increasing NAD^+ levels, decreased oxidative stress, increased deacetylation of PGC-1α and mitochondrial function. In SirT1 knockdown HepG2 cells, NR lost its ability in enhancing mitochondrial function, and its protection against lipid accumulation induced by ethanol.

Conclusions: NR can protect against ethanol induced liver injuries via replenishing NAD^+, reducing oxidative stress, and activating SirT1-PGC-1α-mitochondrial biosynthesis. Our data indicate that SirT1 plays an important role in the protection of NR against lipid accumulation and mitochondrial dysfunctions induced by ethanol.

1. Introduction

Alcoholic liver disease (ALD) is a common clinical complication of long-term alcohol abuse. Its morphological features include alcoholic fatty liver (steatosis), alcoholic hepatitis, and alcoholic cirrhosis. Fatty liver is a uniform and early response of the liver to ethanol consumption. The prevention of the formation of fatty liver is the key to prevent the damages to livers induced by alcohol.

The metabolism of alcohol is mainly catalyzed by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). During long term heavy drinking or binge drinking, cytochrome P450 2E1 (CYP2E1) is activated, playing a critical role in alcohol metabolism [1]. The metabolism of ethanol increases the conversion of nicotinamide adenine dinucleotide (NAD^+) to NADH which decreases the ratio of NAD^+/NADH [2]. NAD^+ is an essential coenzyme of mitochondrial oxidative phosphorylation and energy metabolism and also the

Abbreviations: ADH, alcohol dehydrogenase; ALD, Alcoholic liver disease; ALDH, aldehyde dehydrogenase; CPT-1α, carnitine palmitoyl transterase-1α; CR, calorie restriction; CS, citrate synthase; CYP2E1, cytochrome P450 2E1; FASN, fatty acid synthase; NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyl transferase; NMN, nicotinamide mononucleotide; NMNAT, nicotinamide mononucleotide adenylyl transferase; NR, nicotinamide riboside; NRF-1, nuclear respiratory factor 1; NRF-2, nuclear respiratory factor 2; NRK, nicotinamide riboside kinase; PDHC, pyruvate dehydrogenase complex; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PPAR-α, peroxisome proliferator- activated receptor α; PPAR-γ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SirT1, sirtuin 1; SirT3, sirtuin 3; T2D, type 2 diabetes; TCA cycle, tricarboxylic acid cycle; TFAM, mitochondrial transcriptional factor; UCP2, uncoupling protein-2

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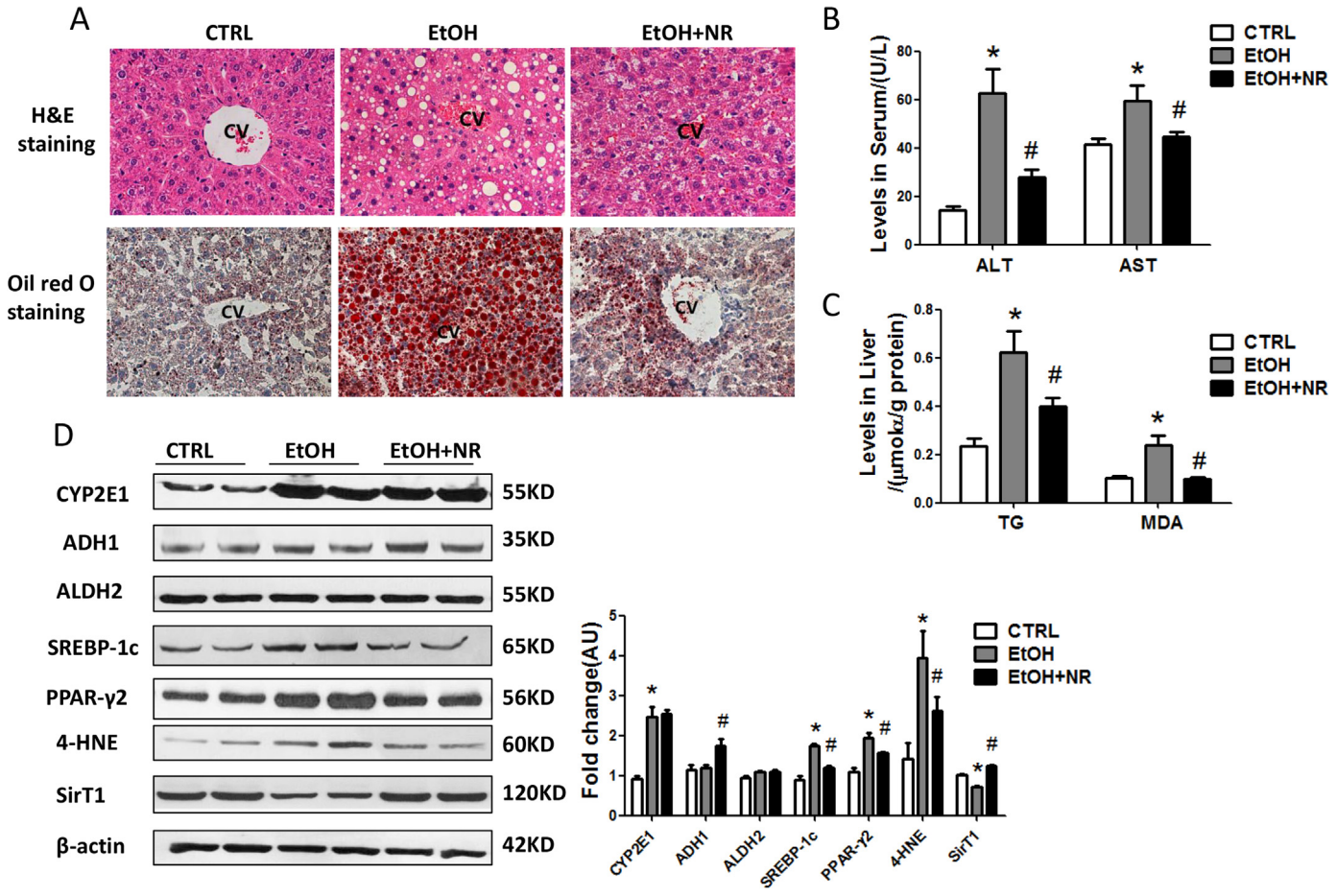

Fig. 1. NR alleviates hepatic steatosis and oxidative stress in mice fed with Chronic-plus-binge ethanol. Mice were treated with chronic-plus-binge ethanol feeding and NR supplementation for 16 days. (A) Representative images of mouse liver, H&E staining and oil red O staining with 200 × magnification. (B) Serum ALT and AST levels. (C) Liver TG and MDA levels. (D) Western blot analysis of alcohol metabolic enzymes (CYP2E1, ADH1 and ALDH2), lipid metabolic regulators (SREBP-1c and PPAR-γ2), 4-HNE and SirT1 in mouse liver. Results were expressed as fold changes of control. Data are expressed as mean ± SEM. n = 6–8/group, $^{*}P < 0.05$ compared with the CTRL group; $^{\#}P < 0.05$ compared with the EtOH group. Abbreviations: NR, nicotinamide riboside; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; MDA, malondialdehyde CYP2E1, cytochrome P450 2E1; ADH1, alcohol dehydrogenase 1; ALDH2, aldehyde dehydrogenase 2; SREBP-1c, sterol regulatory element binding protein-lc; PPAR-γ2, peroxisome proliferator-activated receptor γ2; 4-HNE, 4-hydroxynonenal; SirT1, sirtuin 1; PGC-1α, peroxisome proliferator- activated receptor γ coactivator-1α.

substrate of NAD^+ consuming enzymes [3]. Steatosis induced by high-fat diet triggers the reduction in nicotinamide phosphoribosyl transferase (NAMPT)-mediated NAD^+ biosynthesis and contribute to the pathogenesis of type 2 diabetes (T2D) [4]. Decline in nuclear NAD^+ during aging, perhaps due to defects in nicotinamide mononucleotide adenylyl transferase (NMNAT) which regulates NAD^+ synthesis from nicotinamide mononucleotide (NMN), causes impairment in mitochondrial homeostasis [5]. The function of NAD^+ was further tested by inactivation of poly (ADP-ribose) polymerase 1, a major cellular NAD^+ consumer. Increasing tissue NAD^+ levels and activates mitochondrial metabolism in brown adipose tissue and muscle, culminates in a solid protection against metabolic disease [6]. Hence, an understanding of how alcohol affects NAD homeostasis and NAD^+ consuming enzymes may provide an important insight into the mechanisms of ALD.

Sirtuin 1 (SirT1), is an NAD^+-dependent class III protein deacetylase and/or ADP-ribosyltransferase, whose activation is regulated by the intracellular level of NAD^+, inhibited by the reaction product nicotinamide (NAM) [7]. So far, the relationship between SirT1 and liver damage is not conclusive, even though most studies favor the protective effect of SirT1. Either protein or mRNA expression of SirT1 has been found to be suppressed with alcohol consumption in human livers with alcoholic hepatitis or animal alcoholic models [8,9]. Activation of SirT1 by resveratrol prevents alcoholic liver steatosis [10]. In contrast, increased SirT1 expression has been found in nuclei of hepatocytes in mice with significant liver tumor burden compared to control mice on a B6C3 background [11]. SirT1 acts as a metabolic and redox sensor of changes in nutrient and energy status, such as calorie restriction and fasting [12], during which processes SirT1 is induced and mitochondrial biogenesis increases in mice [13,14]. One target of SirT1 is peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), which plays a central role in glucose/fatty acid metabolism in fasting [14,15]. Resveratrol increased SirT1 activity and then induced mitochondrial activity through modulating PGC-1α functions, renders the animals resistant to diet-induced obesity [16]. Taken together, it's supposed that regulating SirT1 activity and improving mitochondrial biogenesis might be important mechanisms for the protection against ALD.

Nicotinamide riboside (NR), a form of vitamin B3 and NAD^+ precursor, is converted to bioavailable NAD^+, via nicotinamide riboside kinase (NRK) and NMNAT, or by the action of nucleoside phosphorylase and NAM salvage [17,18]. The level of NAD^+ in human blood rose 2.7-folds with a single oral dose of NR in a pilot study [19]. Numerous studies have shown that NR supplementation increases NAD^+ level, enhances mitochondrial biogenesis and oxidative metabolism, protects against metabolic disease, neurodegenerative disorders and age-related physiological decline in mammals [20–22]. In this study, we will

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