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Original Article

Hepatic fatty acid and cholesterol metabolism in nephrotic syndrome

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Abstract: Heavy proteinuria (nephrotic syndrome) is associated with hypercholesterolemia, hypertriglyceridemia and a high risk of atherosclerosis. Hypertriglyceridemia in nephrotic syndrome (NS) is partly due to increased TG and TG-rich lipoprotein production. However, data on the effect of NS on fatty acid production and catabolic machinery are limited. NS was induced in male Sprague Dawley rats by IP injection of puromycin aminonucleoside. Six weeks after the second injection the animals were euthanized, liver was harvested and processed. The NS group exhibited heavy proteinuria, hypercholesterolemia, hypertriglyceridemia, activation of SREBP-1 and LXR α/β, up-regulation of FAS, ACC and HMG CoA reductase. In contrast hepatic tissue ChREBP activity was reduced in NS excluding its role in upregulation of FA synthetic pathway. Despite increased expression and nuclear translocation of PPARα, expression of ACO and abundance of CPT and L-FABP, were decreased in the liver of nephrotic animals. Therefore, NS results in upregulation of FA production machinery. Increased hepatic fatty acid production capacity in NS is compounded by reduced FA catabolism, events that contribute to the associated hypertiglyceridemia.

Keywords: Atherosclerosis, dyslipidemia, proteinuria, cardiovascular disease, fatty acids

Introduction

Heavy glomerular proteinuria, a hallmark of nephrotic syndrome (NS), is associated with profound dysregulation of lipid/lipoprotein metabolism, severe hyperlipidemia, and lipiduria. Hypercholesterolemia, increased plasma low-density lipoprotein (LDL), impaired LDL and high-density lipoprotein (HDL) clearance, and depressed maturation of HDL are common features of dyslipidemia in NS [1-4]. These abnormalities are due to acquired hepatic LDL receptor and HDL docking receptor (SRB1) deficiencies as well as urinary excretion and reduced plasma concentration and enzymatic activity of lecithin cholesterol acyltransferase (LCAT) [5-9]. In addition plasma concentrations of triglycerides, very low-density lipoprotein (VLDL), and intermediate-density lipoprotein (IDL) are increased, and triglyceride content of various lipoproteins is elevated in humans and animals with nephrotic syndrome [10-13].

Liver plays a critical role in fatty acid and triglyceride (TG) homeostasis. Fatty acid metabolism in hepatocytes is mediated through 1) uptake of free fatty acids derived from hydrolysis of phospholipids and triglycerides contained in IDL and HDL by hepatic lipase, and endocytosis of the chylomicron remnants via and LDL receptor related protein (LRP), and of immature HDL via β chain ATP synthase 2) de novo fatty acid synthesis, 3) fatty acid catabolism by oxidation in the mitochondria, peroxisomes, and endoplasmic reticulum; 4) fatty acid utilization in synthesis of triglyceride and its incorporation in VLDL for release in the plasma. Previous studies have shown that NS results in impaired clearance of TG-rich lipoproteins, VLDL, chylomicrons, and their remnants [3, 13-18]. The latter is caused by down-regulations of the primary pathways of TG-rich lipoprotein clearance including lipoprotein lipase [19, 20] and VLDL receptor [21] in the muscle and adipose tissues and of hepatic triglyceride lipase [22] in the

liver. In addition, increased hepatic production of fatty acids and triglycerides has been demonstrated in various models of nephrotic syndrome [23-26].

Hypertiglyceridemia in animals with nephrotic syndrome is associated with increased hepatic tissue expression and activity of hepatic Acyl CoA: diacylglycerol acyltransferase (DGAT-), the enzyme which catalyzes the final step in triglyceride biosynthesis [27]. In addition, hepatic production of fatty acids and enzymatic activities of acyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), the key enzymes in fatty acid biosynthesis are increased in rats with nephrotic syndrome [28]. However, data on the molecular mechanisms involved in dysregulation of hepatic fatty acid production and catabolism in nephrotic syndrome are limited. We, therefore, sought to investigate the expressions and activities of molecules involved in regulation of fatty acid and cholesterol synthesis and catabolism in the liver of rats with experimental nephrotic syndrome.

Materials and methods

Animals

Male Sprague-Dawley rats weighing 180 to 200 g were housed in temperature- and light-controlled space with 12-hour light (500 lux) and 12-hour dark (≤5 lux) cycles. The rats were allowed free access to food (Purina Rat Chow, Purina Mills, Inc., Brentwood, MO, USA) and water. Animals were randomized into the nephrotic and control groups. The rats assigned to the nephrotic group received sequential intraperitoneal injections of puromycin aminonucleoside on day 1 (130 mg/kg) and day 14 (60 mg/kg). The rats assigned to the control group received placebo injections of 5% dextrose in water. Six weeks after the initial puromycin or placebo injections, animals (N =6 per group) were placed in individual metabolic cages for a 24-hour urine collection. The next day, under general anesthesia (Nembutal 50 mg/kg, IP), the animals were sacrificed between the hours of 9 and 11 a.m., and the liver was immediately removed, frozen in liquid nitrogen, and stored at −70°C for subsequent processing. In addition, blood was collected using cardiac puncture. All experiments were approved by the University of California, Irvine Institutional Committee for the Use and Care of Experimental Animals.

Preparation of liver homogenates and nuclear extracts

Frozen tissue was homogenized in 1 ml of 20 mM Tris · HCl (pH 7.5) buffer containing 2 mM $MgCl_2$, 0.2 M sucrose and protease inhibitor cocktail (Sigma, St. Louis). The crude extract was centrifuged at 2,000 *g* at 4°C for 15 min to remove tissue debris. The supernatant which contained hepatic cytosolic proteins was used for Western blot analyses.

Extraction of hepatic nuclear proteins was performed using CelLytic NuCLEAR Extraction Kit following the manufacturer's protocol (Sigma, St. Louis, USA). Protein concentration was measured using a BCA Protein Assay Kit purchased from Pierce Biotechnology (Rockford, IL) following the manufacturers' protocol.

Western blot analyses

Target proteins in the cytoplasmic and/or nuclear fractions of the liver tissue were quantified by Western blot analysis using the following antibodies. Rabbit antibodies against rat ACC, sterol regulatory element binding protein (SREBP)-1, SREBP-2, SCAP, Insig-1, Insig-2, Peroxisome proliferator-activated receptor (PPAR)α, liver-type fatty acid binding protein (L-FABP), and liver x receptor (LXR) α/β antibodies were purchased from Santa Cruz Biotechnology. Antibody against carbohydrate responsive element-binding protein (ChREBP) was obtained from Novus Biologicals (Littleton, CO) and against FAS was obtained from Cell Signaling Technology (Danvers, MA). Histone (Santa Cruz Biotechnology) and β-actin (Sigma) served as control for nuclear and cytosolic target proteins respectively. Aliquots containing 20-100 µg of protein were fractionated on 4-20% Bis-Tris gels (Invitrogen, CA) at 120 V for 2 h. Western blott ananlysis was performed as previously described [6].

RT-PCR

RNA from liver was isolated using TRIzol (Invitrogen, Carlsbad, CA) per the manufacturer's protocol. First strand cDNA was made from 5 mg of the isolated total RNA primed with oligo (dT) using an Invitrogen Superscript synthesis

Table 1. Plasma concentrations of cholesterols, creatinine, triglycerides, HDL cholesterol, free fatty acid, hepatic free fatty acid, liver weight and urinary protein excretion in the nephrotic (NS) and control (CTL) groups

	Control	NS
Plasma Creatinine (mg/dL)	0.22 ± 0.04	0.56 ± 0.10*
Urine Protein/creat ratio	0.08 ± 0.01	1.25 ± 0.35**
Plasma total Cholesterol (mg/dL)	90.1 ± 6.5	496.6± 28.6***
Plasma Triglyceride (mg/dL)	65.9 ± 6.8	416 ± 416.1***
Total/HDL Cholesterol Ratio	2.69 ± 0.52	3.22 ± 0.22
Plasma LDL (mg/dL)	42.6 ± 4.99	243.6 ± 7.99***
Plasma Free Fatty acid (mM)	0.5 ± 0.05	1.2 ± 0.3*
Liver Weight g/100 g BW	4.25 ± 0.17	7.14 ± 0.43**
Liver Free Fatty acid (mM/100 mg)	1.2 ± 0.06	1.6 ± 0.09*

*p<0.05, **p<0.01, ***p<0.005, n=6 in each group.

system. Gene transcript levels of ACO, PPARα, and SREBP-1c were quantified by Taqman gene expression assays (Applied Biosystems, Foster City, CA) using RT-PCR. Gene-specific intron-spanning primers and TaqMan probes were factory designed and optimized by the manufacturer. The reference assay ID for each gene is as follows: ACO (Rn00677251-m1), SREBP-1c (Rn01495769-m1), PPARα (Rn00566193-m1). GAPDH was used as the internal control (Rn99999916-s1). TaqMan PCR was performed using an ABI 7900 HT Sequence Detection System, using the standard cycling conditions recommended by the manufacturer (50°C for2 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15 s, 60°Cfor 1 min).

Plasma and tissue free fatty acid content

Plasma and hepatic free-fatty acid content was measured using a fatty acid assay kit (BioVision Inc. CA, USA) per manufacturer's protocol.

Miscellaneous

A colorimetric assay was used to measure serum and urine creatinine and blood urea nitrogen concentration using a kit obtained from Bioassay systems (Hayward, CA) following the manufacturers protocol. Urine protein was measured using a rat urinary protein assay kit (Chondrex Inc. Redmond, WA) following the manufacturer's protocol. Plasma total cholesterol (Stanbio Laboratory, Boerne, TX), triglyceride (Stanbio Laboratory), HDL cholesterol (Wako Chemicals, Richmond, VA) were measured using protocols provided by the manufacturer. Plasma LDL cholesterol concentration was determined by calculation using the following equation: LDL = total cholesterol – HDL cholesterol – (TG/5).

Data analysis

Student's *t*-test was used in statistical evaluation of the data, which are shown as means ± SEM. *P* values <0.05 were considered significant.

Results

General data

Data are summarized in **Table 1**. As expected, the nephrotic group exhibited heavy proteinuria and hypoalbuminemia. In addition, the NS animals had increased plasma creatinine concentration when compared to the control group pointing to the presence of glomerulosclerosis. This was accompanied by significant hypercholesterolemia, hypertriglyceridemia, and elevated LDL concentrations. Plasma and hepatic tissue free-fatty acid levels were significantly increased in the nephrotic animals when compared to normal controls.

Fatty acid synthesis pathway: Hepatic tissue expression of SREBP-1c was markedly elevated and nuclear abundance of LXRα/β and SREBP-1 were significantly increased in the nephrotic group (**Figure 1A-C**). This was accompanied by increased protein abundance of Insig-1 and SCAP (**Figure 1D**, **1E**), a significant increase in protein abundance of FAS and ACC (**Figure 1F**, **1G**) and a significant decrease in nuclear ChREBP abundance (**Figure 1H**). Taken together these findings point to activation of sterol-responsive as opposed to carbohydrate-

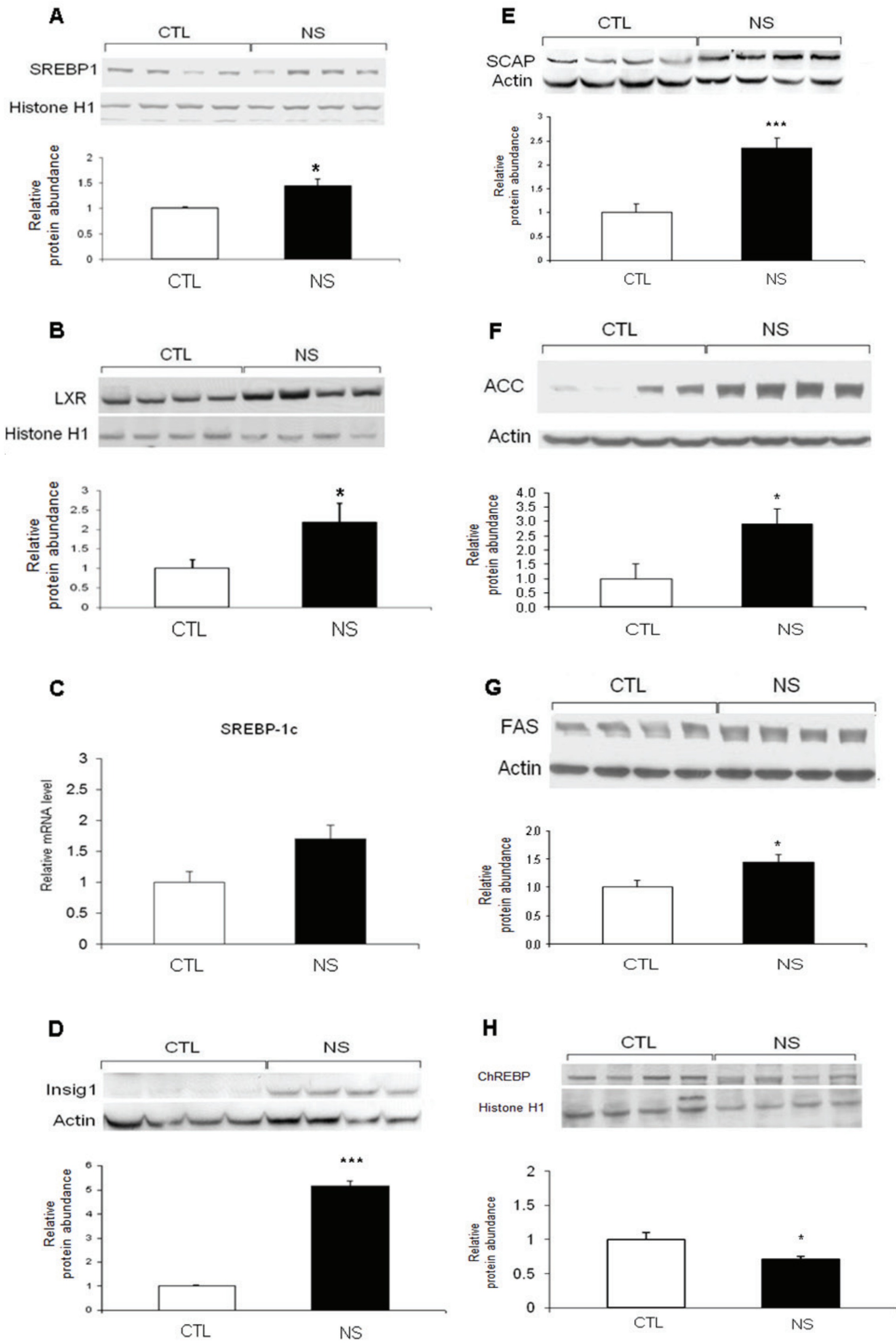
A
CTL
NS
SREBP1
Histone H1
Relative protein abundance
CTL
NS
B
LXR
Histone H1
C
SREBP-1c
Relative mRNA level
D
Insig1
Actin
E
SCAP
Actin
F
ACC
G
FAS
H
ChREBP

Figure 1. A, B. Representative western blots and group data depicting nuclear abundance of hepatic tissue LXR and SREBP1 in the nephrotic (NS) and control (CTL) groups. C. Bar graphs depicting SREBP-1c mRNA abundance in hepatic tissues of nephrotic and control animals. D, E. Representative western blots and group data depicting protein abundance of hepatic tissue Insig1 and SCAP in the nephrotic (NS) and control (CTL) groups. F, G. Representative western blots and group data depicting protein abundance of hepatic tissue ACC and FAS in the nephrotic (NS) and control (CTL) groups. H. Representative western blots and group data depicting nuclear abundance of hepatic tissue ChREBP in the nephrotic (NS) and control (CTL) groups. n=6 in each group. *$p<0.05$, ***$p<0.005$.

responsive pathways as the cause of the observed upregulation of fatty acid synthesis machinery in nephrotic syndrome contrasting that seen in chronic renal failure [29].

Fatty acid catabolism

Hepatic mRNA expression and nuclear abundance of PPAR-α were significantly increased in animals with nephrotic syndrome (**Figure 2A**, **2B**). However, upregulation and activation of PPAR-α was paradoxically associated with a significant reduction in the CPT and L-FABP protein abundance and ACO mRNA expression, the key enzymes that are regulated by PPAR-α and play a central role in fatty acid catabolism (**Figure 2C**, **2D**).

Cholesterol synthesis

Hepatic nuclear protein abundance of SREBP-2 was unchanged in the nephrotic animals when compared with controls (**Figure 2E**). However, protein abundance of HMG-CoA reductase and ACAT-2 were both significantly elevated in the nephrotic animals (**Figure 2F**).

Discussion

Nephrotic syndrome results in profound alteration of lipid metabolism and plasma lipid profile. Genes encoding enzymes involved in fatty acid synthesis are independently regulated by SREBP-1c, LXRα/β and ChREBP [30, 31]. The present study revealed significant upregulation of FAS and ACC, the key enzymes in fatty acid synthesis, in the liver of nephrotic animals. This was associated with increased expression of SREBP-1c mRNA, significantly increased nuclear translocation (activation) of SREBP-1 and LXRα/β and reduction of nuclear translocation of ChREBP. These observations indicate that the observed upregulation of enzymes involved in fatty acid synthesis is driven by activation of the sterol responsive but not carbohydrate responsive pathways.

Despite increased mRNA expression and nuclear translocation of PPARα, which is the master regulator of genes encoding the key enzymes and proteins involved in fatty acid catabolism, the nephrotic animals exhibited significant down-regulation of hepatic tissue L-FABP, CPT and ACO. PPARα is predominantly expressed in tissues with high fatty acid catabolic rates, such as the liver. It promotes fatty acid catabolism by raising L-FABP, CPT and ACO expression, leading to stimulation of mitochondrial and peroxisomal β-oxidation. FABP serves as the vehicle for delivery of fatty acids to intracellular sites of utilization and as such plays an important role in cellular fatty acid metabolism [32]. Thus up-regulation/activation of PPARα should increase fatty acid metabolism by increasing the expression of its target genes. However, we found a conspicuous discordance between PPARα activity and expression of its target genes in the liver tissue of nephrotic animals. The underlying mechanism for the observed discordance may be due to increased nuclear LXRα/β which by its competitive binding to RXR can prevent dimerization of RXR with PPARα a step which is essential for expression of its target genes.

Activation and eventual translocation of SREBPs to the nucleus in response to cellular sterol depletion is mediated by detachment and ubiquitination of Insigs from the SCAP-SREBP complex. In contrast, inhibition of SREBP activation by excess cellular sterol is mediated by binding of the SCAP-SREBP complex to Insigs and the consequent retention of the complex in the ER [33, 34]. In addition to their role in the regulation of SREBP activity, Insigs participate in posttranslational regulation of HMG-CoA reductase. Accumulation of sterols leads to conformational modification of HMG-CoA reductase, its binding to Insig 1 and Insig-2 and ubiquitination of HMG-CoA reductase, thereby the reduction of cholesterol biosynthesis [35]. In view of their critical role in the regulation of SREBP activity, we examined the expression of SCAP and Insigs in the liver of the animals studied. The study revealed a significant increase in protein abundance of SCAP

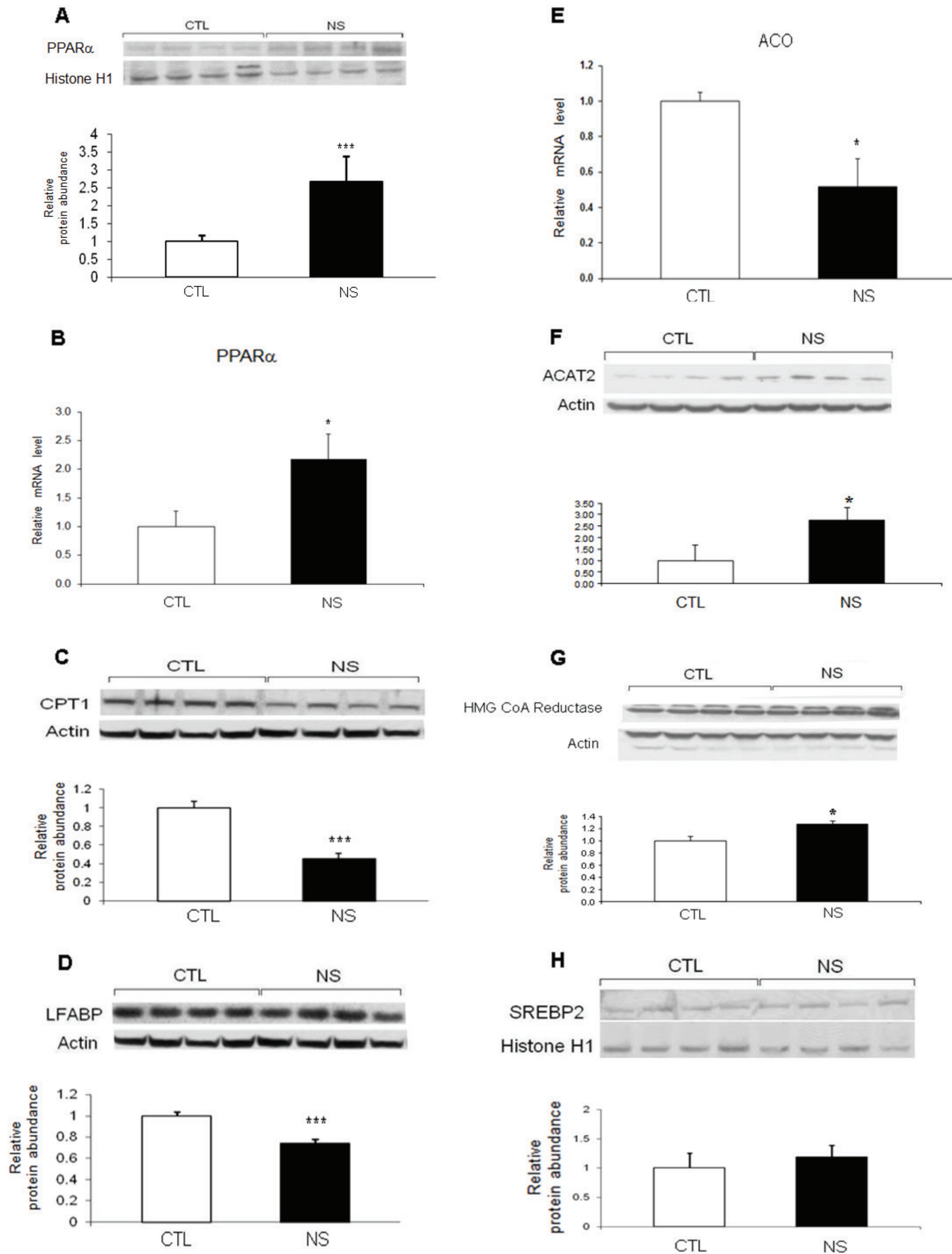

Figure 2. A. Representative western blot and group data depicting nuclear abundance of hepatic tissue PPARα in the nephrotic (NS) and control (CTL) groups. B. Bar graphs depicting PPARα mRNA abundance in hepatic tissues of nephrotic and control animals. C, D. Representative western blots and group data depicting protein abundance of hepatic tissue CPT1 and LFABP in the nephrotic (NS) and control (CTL) groups. E. Bar graphs depicting ACO mRNA abundance in hepatic tissues of nephrotic and control rats. F, G. Representative western blots and group data depicting protein abundance of hepatic tissue ACAT2 and HMG CoA Reductase in the nephrotic (NS) and control (CTL) groups. H. Representative western blots and group data depicting nuclear abundance of hepatic tissue SREBP2 in the nephrotic (NS) and control (CTL) groups. n=6 in each group. *p<0.05, ***p<0.005.

and Insig1 in the liver of nephrotic animals. Earlier studies conducted in our laboratories have revealed severe post-transcriptional down-regulations of hepatic tissue LDL receptor and HDL docking receptor (SRB1) as well as marked upregulation of ACAT-2 in nephrotic syndrome [5-7, 9]. By restricting hepatic uptake of LDL and HDL, acquired LDL receptor and SRB1 deficiencies lead to elevated plasma cholesterol concentration and diminished liver tissue cholesterol content. This is compounded by marked upregulation of hepatic tissue ACAT which by accelerating esterification of cholesterol, lowers free cholesterol concentration of hepatocytes. The reduction in free cholesterol, in turn triggers, activation of SREBP-1 and SREBP-2. This can account for the activation of SREBP-1and upregulation of its target genes encoding enzyme involved in fatty acid synthesis. Simultaneously activation of SREBP-2 leads to increased expression of HMG-CoA reductase expression and hence cholesterol biosynthesis as seen here and our previous studies [36]. Thus acquired hepatic LDL receptor and SRB1 deficiencies as well as upregulation of ACAT play a central role in activation of sterol-mediated upregulation of fatty acid and cholesterol biosynthesis in nephrotic syndrome.

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Disclosures

The authors have no conflicts of interest to disclose.

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