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Influence of dietary sugar on cholesterol and bile acid metabolism in the rat: Marked reduction of hepatic Abcg5/8 expression following sucrose ingestion

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ABSTRACT

Previous studies have indicated that dietary intake of sugar may lower bile acid production, and may promote cholesterol gallstone formation in humans. We studied the influence of dietary sucrose on cholesterol and bile acid metabolism in the rat. In two different experiments, rats received high-sucrose diets. In the first, 60% of the weight of standard rat chow was replaced with sucrose (high-sucrose diet). In the second, rats received a diet either containing 65% sucrose (controlled high-sucrose diet) or 65% complex carbohydrates, in order to keep other dietary components constant. Bile acid synthesis, evaluated by measurements of the serum marker 7-alpha-hydroxy-4-cholesten-3-one (C4) and of the hepatic mRNA expression of Cyp7a1, was markedly reduced by the high-sucrose diet, but not by the controlled high-sucrose diet. Both diets strongly reduced the hepatic – but not the intestinal – mRNA levels of Abcg5 and Abcg8. The differential patterns of regulation of bile acid synthesis induced by the two sucrose-enriched diets indicate that it is not sugar *per se* in the high-sucrose diet that reduces bile acid synthesis, but rather the reduced content of fiber or fat. In contrast, the marked reduction of hepatic Abcg5/8 observed is an effect of the high sugar content of the diets.

1. Introduction

The conversion of cholesterol into bile acids (BAs) and their subsequent secretion into bile is one important route for the elimination of cholesterol from the body [1]. Cholesterol is also secreted directly into bile [2]. Over 95% of BAs are reabsorbed in the intestine, while the fecal loss is compensated for by *de novo* synthesis [1]. However, BAs are potentially toxic, and therefore the metabolism of BAs is carefully regulated [3]. Moreover, disturbances in the composition of the bile may precipitate gallstones [4].

BA synthesis is to a large extent regulated by the levels of circulating BAs, via two negative feedback mechanisms. After their secretion into the intestine, reabsorbed BAs bind to and activate the farnesoid X receptor (FXR) [5] leading to increased intestinal expression of fibroblast growth factor 15 (FGF15; human ortolog FGF19). This protein is transported to the liver where it ultimately inhibits the transcription of the rate-limiting enzyme in BA synthesis, cholesterol 7α-hydroxylase (Cyp7a1) [6]. Another negative feedback mechanism takes place in liver when BAs returning in the portal vein bind and stimulate hepatic FXR, resulting in the inhibition of Cyp7a1 transcription [7]. BA synthesis is also influenced by food components such as water-soluble fibers [8] and fat [9]. The effect of dietary sugar on BA metabolism has not been thoroughly studied. In humans, gallstone formation has been linked to high intake of sugar [10]. Thus, there is substantial reason to better understand the mechanistic interactions between cholesterol and carbohydrate metabolism.

The hepatic protein complex of ATP-binding cassette sub-family G members 5 (ABCG5) and 8 (ABCG8) is responsible for the excretion of hepatic cholesterol into bile [2]. The oxysterol-activated nuclear receptor liver X receptor alpha (LXRα) is known to positively regulate Abcg5/8 [11]. Little is known about the dietary regulation of

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Abcg5/8, however. Cholesterol feeding has been reported to suppress hepatic Abcg5/8 in rats, while cholesterol feeding in mice increases hepatic Abcg5/8 [12]. We recently found that feeding a sucrose-rich diet to mice deficient in the ileal BA transporter (IBAT) normalizes their strongly induced BA synthesis [13]. We here investigated interactions between BA, cholesterol and glucose metabolism by feeding rats sucrose-rich diets and evaluated their effects on liver cholesterol homeostasis.

2. Materials and methods

2.1. Animal experiment 1

Male Sprague Dawley rats (200g, B&K/Scanbur, Sollentuna, Sweden) were divided into 4 groups of 6 animals each. Our aim was to study the effect of a sucrose-enriched diet on BA and cholesterol metabolism. We have previously shown that dietary sucrose suppresses BA synthesis more strongly in mice where BA production was induced by IBAT deficiency [13]. Therefore we included a group of mice treated with cholestyramine as a mean of stimulating BA synthesis. In detail, the study groups were as follow: 1) animals fed a normal control diet (R36, Labfor, Lidköping, Sweden), 2) animals fed a high-sucrose diet; i.e. the control diet enriched with 60% sucrose, and the addition of 10% fructose (Sigma–Aldrich, St Louis, MO) to the drinking water, 3) animals fed the control diet supplemented with 2.5% cholestyramine (Questran Loc, Bristol-Myers Squibb, New York, NY), and 4) animals given both cholestyramine and sucrose added to the control diet together with the fructose-supplemented drinking water. Since the high-sucrose diet was made by replacing 60 weight% of the control diet with sucrose, this consequently reduced other components of the high-sucrose diet, for details see Table 1. At day 10, all animals were sacrificed by decapitation under Isoflurane (Baxter, Deerfield, IL) anesthesia. Liver and intestine were collected, frozen in liquid nitrogen and stored at −80 °C. Blood was centrifuged and serum was stored at −80 °C.

2.2. Animal experiment 2

Male Sprague Dawley rats (200g, B&K/Scanbur) were divided into 4 groups with 6 animals per group. This second experiment was a modified repetition of experiment 1, but it was conducted with a more controlled high-sucrose diet. The only difference between the control diet and the controlled high-sucrose diet in this study was the replacement of polysaccharides in the control diet with sucrose in the controlled high-sucrose diet. These diets were used to be able to distinguish which results in study 1 that were due to increased dietary sucrose and which that could be due to changes in the other dietary components. The cholestyramine treatment was not used in this study, instead two groups were treated with the peroxisome proliferator-activated receptor alpha (PPARα) antagonist GW 6471 (Tocris Bioscience, Bristol, UK). This was done to evaluate the role of PPARα in the sugar-mediated suppression of BA synthesis. More specifically, rats were fed either 1) a control diet (D11724, Research Diets Inc., New Brunswick, NJ) and were intraperitoneally (IP) injected with vehicle, 2) the same control diet and were IP injected with GW 6471 (4 mg/kg body weight), 3) a controlled high-sucrose diet (65% sucrose; D11725, Research Diets Inc.) with the addition of 10% fructose to the drinking water and were IP injected with vehicle, or 4) the same controlled high-sucrose diet and fructose water together with IP injections of GW 6471. The injections of vehicle (NaCl with 3.8% DMSO) and GW 6471 were made in the mornings of the four final days of the experiment. At day 10, all animals were sacrificed by decapitation under Isoflurane anesthesia. Liver tissue and intestine were collected, frozen in liquid nitrogen and stored at −80 °C for later analyzes. Blood was centrifuged and serum was stored at −80 °C for future analyzes.

Animals in both experiments were kept under standardized conditions with free access to water and chow. Light cycle hours were from 6 a.m. to 6 p.m. The study was approved by the Stockholm South Ethical Committee on Animal Research in Huddinge, Sweden.

Table 1
Composition of the diets used.

	Experiment 1		Experiment 2	
	Control diet (R36)	High-sucrose diet (R36 + 60% sucrose)	Control diet (D11724)	Controlled high-sucrose diet (D11725)
Fat (g/kg)	40	16	50	50
Carbohydrates (g/kg)	557	823	660	660
Polysaccharide (g/kg)	537	215	650	0
Sucrose (g/kg)	20	608	0	650
Vitamin mix incl. sucrose (g/kg)			10	10
Protein (g/kg)	185	74	203	203
Fiber (g/kg)	35	14	50	50
Kcal/g	3.3	3.7	3.9	3.9

Bold represents main constituents of the diets, the categories in plain text are subcategories of the carbohydrate portion.

2.3. Quantitative real-time reverse transcriptase polymerase chain reaction (rt-qPCR) assay of mRNA

Total RNA was isolated from individual liver and proximal and distal intestinal samples using Trizol reagent (Invitrogen, Carlsbad, CA). One μg of total RNA was transcribed to cDNA by random hexamer priming and Omniscript (Qiagen, Valencia, CA). Rt-qPCR was run on cDNA by SYBR Green using an ABI prism 7700 Sequence Detection System (Applied Biosystems, Foster City, CA) following guidelines for SYBR Green assay. Data was normalized to actinβ (liver and distal intestine) or Cyclophilin A (Ppia; proximal intestine) expression in the same preparations. The comparative Ct Method was used to quantify the results. Primer sequences are available upon request.

2.4. Liver cholesterol analysis

Liver cholesterol content was analyzed using gas chromatography–mass spectrometry (GC–MS). D7-cholesterol, water, NaCl and Folch solution were added to a 10% liver homogenate in Tris buffer. After centrifugation at 2500 rpm for 5 min, the lower phase was dried under nitrogen gas. Folch was added and again dried under nitrogen. 0.5 M KOH in EtOH was added and the samples heated to 70 °C in a water bath for 1.5 h, whereafter water and hexane were added before centrifugation at 2500 rpm for 5 min. The upper phase was dried under nitrogen. Samples were silylated with 0.4 mL pyridine/hexametyldisilizane/chlorotrimetylsilane (3:2:1, v/v/v) at room temperature overnight and thereafter dried under nitrogen at 60 °C. Samples were then dissolved in 100 μL hexane and analyzed using GC–MS. Liver cholesterol content is expressed per mg liver protein. Liver protein was analyzed by the DC protein assay from Bio-Rad Laboratories (Hercules, CA).

2.5. Serum cholesterol analysis

Total serum cholesterol was determined spectrophotometrically using commercially available reagents (Instrumentation laboratory

company, Lexington, MA (experiment 1) or Roche Diagnostics (experiment 2)).

2.6. 7α-Hydroxy-4-cholesten-3-one (C4) assay

The concentration of C4 was assayed as described [14]. Briefly, serum (200 μL in experiment 1 and 100 μL in experiment 2) was diluted in isotonic NaCl and internal standard (7β-hydroxy-4-cholesten-3-one) was added. The samples were extracted on C8 Isolute SPE columns (500 mg, 3 mL; International Sorbent Technology LTD, Hengoed, UK). The eluted product was dried under nitrogen and dissolved in 100 μL acetonitrile, and 50 μL was separated by high-pressure liquid chromatography (HP 1100 series; Hewlett–Packard GmbH, Waldbronn, Germany) at 20 °C (mobile phase: acetonitrile/water 95:5; 1 mL/min) by using a Nova-Pak C_{18} steel column, 3.9 × 300-mm ID, 4-μm particle size (Waters Corp, Milford, MA) at the wavelength 241 nm. C4 was corrected for total cholesterol and expressed as mg/mole.

2.7. Statistics

Data are presented as means ± SEM. Significance of differences between groups were tested by two-way ANOVA followed by Tukey's multiple comparison test, after log transformations, using GraphPad Prism version 6.01 for Windows, (GraphPad Software, La Jolla, CA).

3. Results

We evaluated how dietary sucrose affects BA and cholesterol homeostasis, by feeding rats two different diets enriched with sucrose. We found that a sucrose-rich diet low in fat, protein and fiber reduced BA synthesis, shown by reduced levels of the serum marker of BA synthesis, C4 (Fig 1A), as well as by lowered mRNA levels of Cyp7a1 (Fig 1B). Further, this diet also strongly reduced the mRNA levels of the hepatic cholesterol transporters Abcg5/8 (Fig. 2A–B). The intestinal expression of Abcg8 was reduced by less than 50%, and that of Abcg5 was not altered at all (Fig. 2C–D). Following the apparent reduction in BA synthesis and hepatic cholesterol secretion, liver cholesterol was increased (Fig. 1C), whereas serum cholesterol levels did not change (Fig. 1D). The gene expressions of the LDL receptor and 3-hydroxy-3-methyl-glutaryl-CoA reductase (Hmg-CoA reductase) were reduced in rats on the high-sucrose diet (Fig. 3E–F), indicating that the reduced BA synthesis and Abcg5/8 expression were likely causes for the increased hepatic cholesterol level.

To study the mechanism for how this diet reduced BA synthesis, we analyzed the mRNA expression of Fxr in liver and intestine and its downstream targets Fgf15 in intestine and Shp-1 in liver, and found no effects on these (Fig. 3A–D). The FXR protein level in liver was also not affected (not shown). This indicates that this diet modulates BA synthesis independent of the FXR pathways.

Cholestyramine treatment markedly stimulated BA synthesis, as evident from the increases in C4 levels and Cyp7a1 mRNA (Fig. 1A–B). When giving cholestyramine together with the high-sucrose diet, BA synthesis was reduced compared to cholestyramine treatment alone, shown by a reduced C4 level (Fig 1A). Cholestyramine did not affect hepatic or intestinal Abcg5/8 expression (Fig. 2). However, in combination with the high-sucrose diet, the hepatic levels were reduced to the same extent as when animals were given the high-sucrose diet alone (Fig. 2A–B). The combination of cholestyramine and the high-sucrose diet increased liver cholesterol similar to giving the high-sucrose diet alone, while cholestyramine treatment alone had no effect on liver cholesterol (Fig. 1C).

Cholestyramine as well as the combination of cholestyramine and the high-sucrose diet reduced Fgf15 mRNA levels, compared to untreated rats and rats given only the high-sucrose diet respectively (Fig. 3D). Neither cholestyramine treatment alone nor the combination of cholestyramine with the high-sucrose diet did affect LDL receptor mRNA expression, in contrast to the high-sucrose diet when given exclusively (Fig. 3E). Cholestyramine treatment increased cholesterol synthesis as shown by increased Hmg-CoA reductase mRNA levels, but there was no significant reduction when combining with the high-sucrose diet (Fig. 3F).

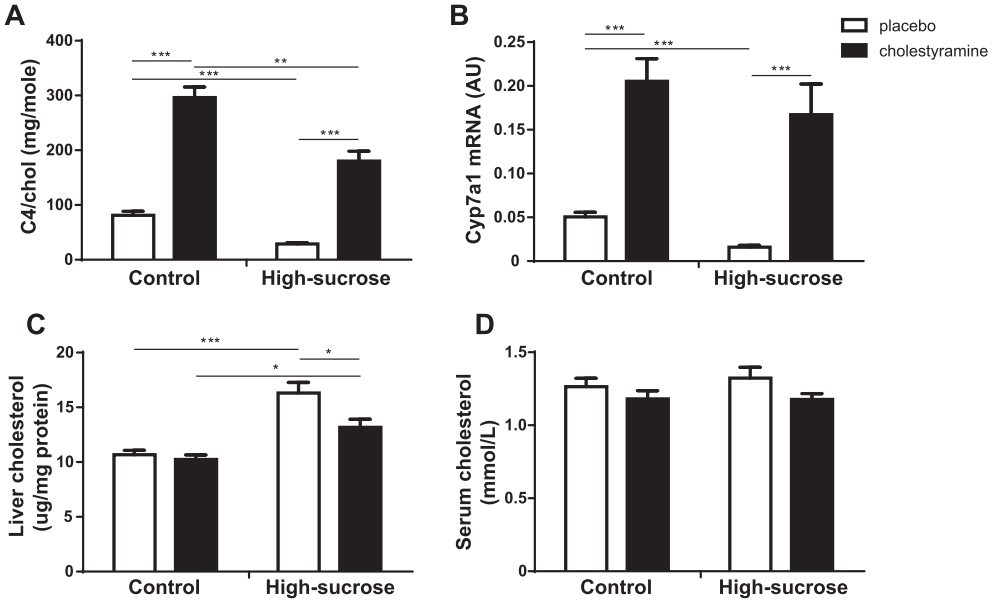

Fig. 1. Effects on bile acid synthesis and cholesterol levels by feeding rats a high-sucrose diet. Bile acid synthesis was analyzed by serum C4/cholesterol (A) and liver Cyp7a1/β actin mRNA (B). Cholesterol levels were analyzed in liver (C) and serum (D). Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (Two-way ANOVA followed by Tukey's multiple comparisons test).

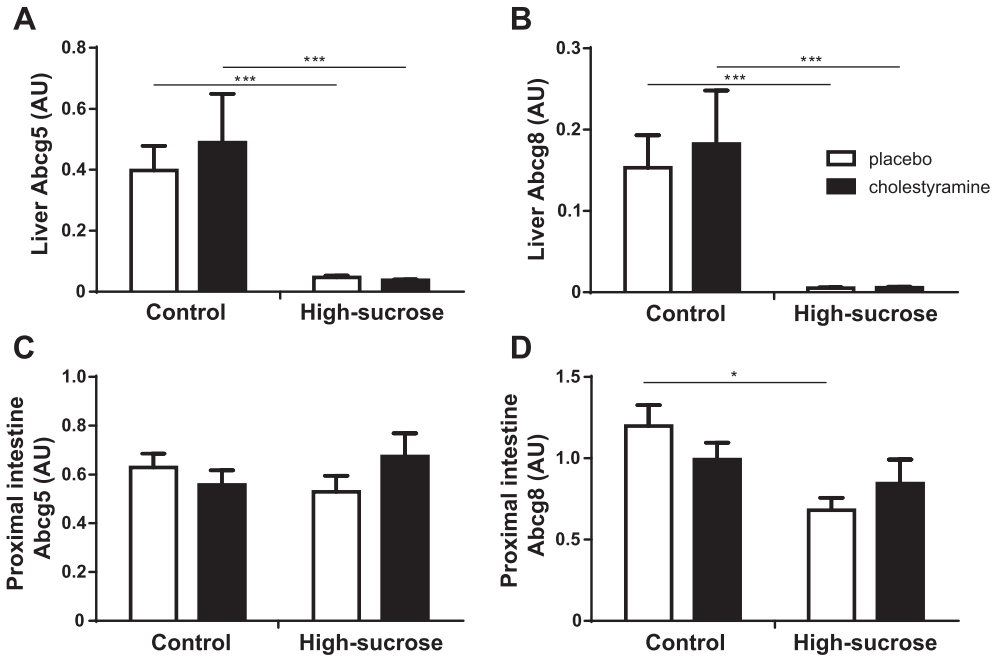

Fig. 2. Effects on Abcg5 and Abcg8 mRNA expression in liver and proximal intestine by feeding rats a high-sucrose diet. Liver Abcg5 (A) and Abcg8 (B) mRNA expressions were related to β actin mRNA, whereas proximal intestine Abcg5 (C) and Abcg8 (D) mRNA expressions were related to Cyclophilin A mRNA. Data are presented as means ± SEM. *, $P < 0.05$; ***, $P < 0.001$ (Two-way ANOVA followed by Tukey's multiple comparisons test).

In rats fed the controlled high-sucrose diet, BA synthesis was not affected (Fig. 4A–B), while hepatic Abcg5/8 mRNA levels were markedly suppressed just as seen in the first experiment (Fig. 4E–F). Interestingly, intestinal Abcg5/8 transcript levels were not affected by the controlled high-sucrose diet (Fig. 4G–H). Liver cholesterol was not altered by the controlled high-sucrose diet (Fig. 4C), in contrast to the high-sucrose diet in the first experiment, indicating that the stable BA synthesis during the controlled high-

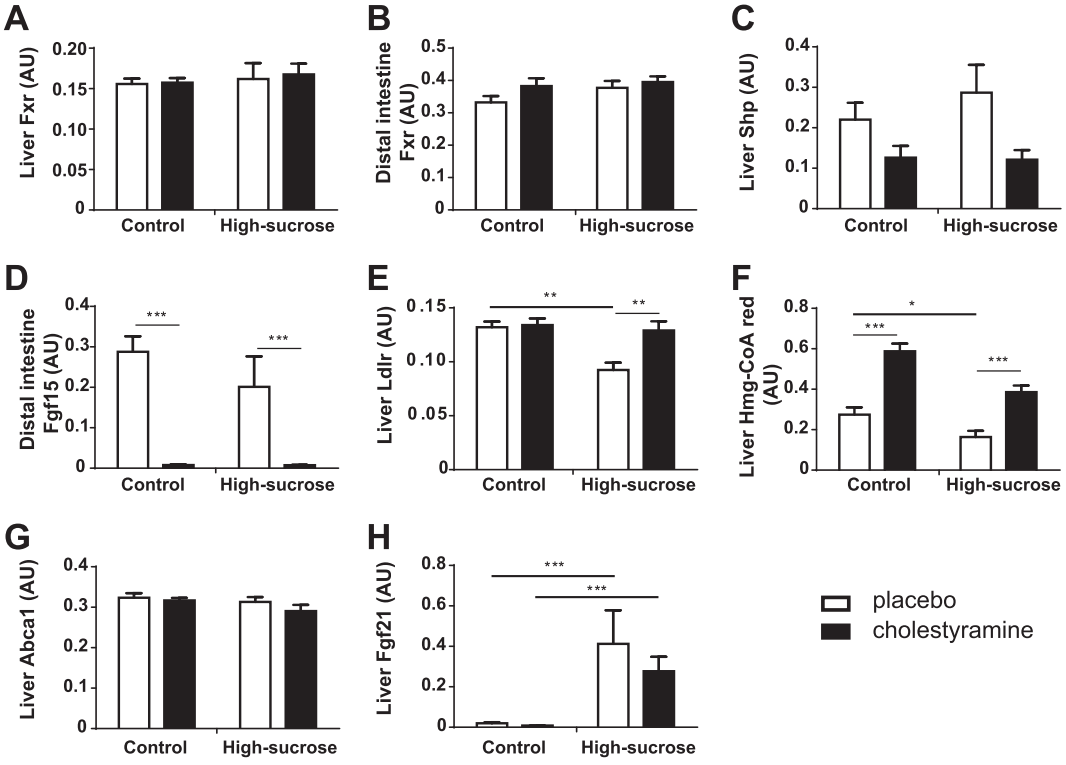

Fig. 3. Effects on gene expression in liver and distal intestine by feeding rats a high-sucrose diet. Liver and distal intestine Fxr (A) and (B), liver Shp (C), distal intestine Fgf15 (D), liver LDL receptor (Ldlr) (E), liver Hmg-CoA reductase (F), liver Abca1 (G) and liver Fgf21 (H) mRNA expression. Gene expression in liver and distal intestine was related to β actin. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ (Two-way ANOVA followed by Tukey's multiple comparisons test).

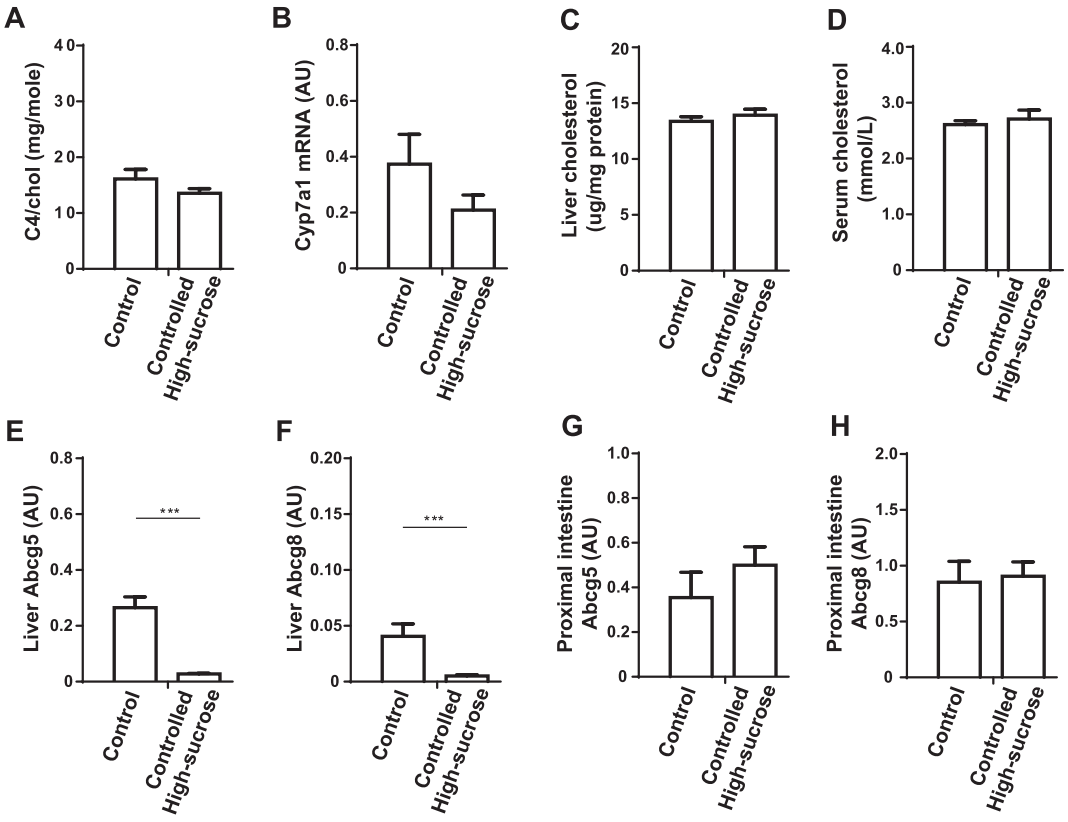

Fig. 4. Effects on bile acid synthesis, cholesterol levels and Abcg5/8 expression by feeding rats a controlled high-sucrose diet. Bile acid synthesis was analyzed by serum C4/cholesterol (A) and liver Cyp7a1/β actin mRNA (B). Cholesterol levels were analyzed in liver (C) and serum (D). Liver Abcg5 (E) and Abcg8 (F) mRNA expressions were related to β actin mRNA and proximal intestine Abcg5 (G) and Abcg8 (H) mRNA expressions were related to Cyclophilin A mRNA. Data are presented as means ± SEM. ***, $P < 0.001$ (Two-way ANOVA followed by Tukey's multiple comparisons test).

sucrose diet (Fig. 4A–B) is paralleled by stable liver cholesterol levels. Serum cholesterol levels were not affected by the controlled high-sucrose diet (Fig. 4D), as also seen during the high-sucrose diet in the first experiment. LDL receptor and Hmg-CoA reductase were not affected by the controlled high-sucrose diet (Supplementary Figure 2), in contrast to when the high-sucrose diet was given in the first experiment.

As the controlled high-sucrose diet did not affect BA synthesis, we were not able to test the hypothesis of PPARα-involvement in the regulation. Therefore we do not show the PPARα inhibition data. The only effect by treatment with GW 6471 was reduced serum cholesterol levels. This level was normalized when giving the controlled high-sucrose diet.

4. Discussion

The present studies have shown marked effects on hepatic cholesterol metabolism in rats treated with sugar-enriched diets. The discordant data on how BA synthesis is influenced by two different types of sucrose-enriched diets, i.e. a reduction by the high-sucrose diet but not by the controlled high-sucrose diet, indicate that the increased sugar content *per se* did not cause the reduction of BA synthesis observed in the first experiment. Since pronounced reductions in hepatic Abcg5/8 gene expression were seen during both diets high in sucrose, that effect is more likely a consequence of the increased sugar content in the diets.

Previous studies investigating the possible regulation of Cyp7a1 by sugar have shown inconsistent results. Glucose treatment of human hepatocytes stimulates Cyp7a1 expression [15]. Insulin treatment of human hepatocytes have also affected Cyp7a1 expressions variably, with reports of reduced [16] as well as increased [17] mRNA levels. In a recent study, feeding mice a high-fructose diet resulted in approximately 50% reduced Cyp7a1 mRNA and protein levels [18]. We have also reported that feeding mice a sucrose-enriched diet reduced BA synthesis [13]. When we studied mice that were fed the controlled high-sucrose diet, this was not seen, however (Supplementary Figure 1).

Liver cholesterol increased in response to the high-sucrose diet in the first experiment, which would increase oxysterol levels that could activate the nuclear receptor LXR [19] and its target genes Abcg5/8 [11] and Cyp7a1 [20]. Therefore, the suppressed expression of these genes suggests that the LXR pathway was not involved. Further support for this was that the LXR target gene ATP-binding cassette transporter A1 (Abca1) was not affected.

Microarray analyses of gene transcripts from livers obtained at the first experiment indicated that sucrose feeding increased PPARα targets such as fibroblast growth factor 21 (Fgf21), sulfotransferase 2A1 (Sult2a1), rat tribbles homolog 3 (Trib3) and fatty acid-binding protein 5 (Fabp5) (not shown; the increase in Fgf21 was confirmed using rt-qPCR). Since PPARα agonists, such as fibrates, reduce BA synthesis, we hypothesized that dietary sugar could work through this pathway [21] and tested this in the second experiment. However, since the more controlled high-sucrose diet did not reduce Cyp7a1, we were unable to evaluate this possibility. The reason for the reduced BA synthesis by the high-sucrose diet in the first experiment could be the reduced fiber and fat content of that diet. Another potential explanation for the different effects of the two types of high-sucrose diets on BA synthesis is of course that they may have different effects on the intestinal microflora; this was not explored either.

The strong reduction in hepatic mRNAs for Abcg5/8 in rats fed a diet high in sugar remained when fiber and fat contents were controlled. This phenomenon is obviously species-specific, since we did not observe such an effect in wild-type mice treated with this diet (Supplementary Figure 1). Also when a high-fructose diet was given, there was no effect on hepatic Abcg5/8 in mice [18]. Previous examples of such a species difference in the regulation of hepatic Abcg5/8 include the response to cholesterol feeding, where mice exhibit increased and rats decreased mRNA levels [12].

A possible explanation for the pronounced reductions of hepatic Abcg5/8 by both high-sucrose diets is that increased insulin may mediate the inhibitory effect, since insulin has been shown to reduce Abcg5/8 expression in rat hepatocytes [22]. However, this potential mechanism needs to be studied further. It is also of interest that the expression of intestinal Abcg5 was not affected by either diet, even though the Abcg5 mRNA levels in liver were essentially eliminated. Intestinal Abcg8 was only reduced by the high-sucrose diet used in the first experiment, and not to the same extent as in liver. This indicates a tissue specific regulation of Abcg5/8, which may have physiological relevance.

In conclusion, we found a strongly suppressed expression of the hepatic cholesterol transporter complex Abcg5/8 when feeding rats diets high in sugar. BA synthesis was reduced when feeding a high-sucrose diet to rats when the dietary fiber and fat contents were simultaneously reduced, whereas a controlled high-sucrose diet in which dietary fiber and fat were kept constant did not affect BA synthesis.

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Disclosures

None relevant to this study.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.04.070.

Transparency document

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