Expression of ABCG5 and ABCG8 Is Required for Regulation of Biliary Cholesterol Secretion

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The major pathway for elimination of cholesterol in mammals is via secretion into bile. Biliary cholesterol secretion is mediated by the ATP-binding cassette (ABC) transporters ABCG5 (G5) and ABCG8 (G8) and is stimulated by cholesterol and by the non-cholesterol steroids cholate and diosgenin. To define the relationship between G5G8 expression and biliary cholesterol secretion, we measured G5 and G8 mRNA levels and biliary cholesterol concentrations in genetically manipulated mice expressing 0, 1, 2, 5, 10, or 16 copies of the two genes. Biliary cholesterol levels varied directly with G5G8 copy number and hepatic mRNA levels over a 2- to 3-fold range. Thus neither delivery of cholesterol to the transporter nor levels of cholesterol acceptors in bile were limiting under these conditions. In wild-type mice, cholate and diosgenin both increased biliary cholesterol concentrations 2- to 3-fold. The increase in biliary cholesterol content was dependent on expression of G5 and G8; neither steroid increased biliary cholesterol levels in G5G8−/− mice. Cholate treatment was associated with a farnesoid X receptor (FXR)-dependent increase in hepatic mRNA and protein levels of G5 and G8. In contrast to cholate, diosgenin treatment did not affect G5G8 expression. Diosgenin increased the expression of several pregnane X receptor (PXR) target genes and the cholesterogenic effect of diosgenin was reduced by ~70% in PXR knock-out mice. Thus G5 and G8 are required to modulate biliary cholesterol secretion in response to cholate and diosgenin, but the cholesterogenic effects of these two steroids are mediated by different mechanisms requiring FXR and PXR, respectively.

Cholesterol is an essential constituent of cell membranes that can be acquired by de novo synthesis from acetyl-CoA or obtained from the diet. Humans consuming Western diets synthesize ~1 g of cholesterol/day and ingest ~400 mg of cholesterol, of which ~50% is absorbed (1). An equivalent quantity of cholesterol is lost from the body via biliary secretion, either in the form of free cholesterol or after conversion to bile acids. Biliary cholesterol secretion is mediated by two ATP-binding cassette (ABC) transporters, ABCG5 (G5) and ABCG8 (G8), that function as a heterodimer at the apical membranes of hepatocytes (2). Efficient biliary cholesterol secretion is essential for the maintenance of cholesterol homeostasis; humans and mice lacking G5 and G8 (G5G8−/−) have a marked reduction in biliary cholesterol secretion (3, 4), and their hepatic and plasma levels of cholesterol are exquisitely sensitive to changes in dietary cholesterol content (4, 5).

Whereas biliary cholesterol secretion is markedly reduced in G5G8−/− mice (that is, homozygous ABCG5 and ABCG8 double knock-out mice), transgenic mice overexpressing human G5 and G8 have increased biliary cholesterol concentrations and increased rates of fecal neutral sterol excretion (6). This finding indicated that an increase in G5G8 expression is sufficient to promote biliary cholesterol secretion. However, the relationship between G5G8 expression and biliary cholesterol secretion has not been systematically examined, and it is possible that other factors, such as biliary phospholipid concentrations (7), limit the rate at which cholesterol is secreted into bile.

Biliary cholesterol secretion is increased by cholesterol feeding. The increase in biliary cholesterol secretion induced by cholesterol feeding in mice is effected primarily through changes in the expression of the G5G8 transporter (8). Cholesterol feeding activates the nuclear hormone receptor liver X receptor (9), which up-regulates the transcription of G5 and G8 (9). Treatment of wild-type mice with a liver X receptor agonist increased G5G8-mediated secretion of cholesterol into bile (10). Conversely, liver X receptor knock-out mice fail to increase G5G8 expression in response to cholesterol feeding and, consequently, accumulate cholesterol in their livers (10). Biliary cholesterol secretion is also increased by certain non-cholesterol steroids including cholate, a hydrophobic bile acid, and diosgenin (11), a six-ring steroid found in yams. It is not known whether G5 and G8 mediate the cholesterogenic effects of these non-cholesterol steroids. In mice, cholic acid feeding increases the mRNA levels of G5 and G8 in the liver (9), but whether this increase is required for the cholate-induced increase in biliary cholesterol secretion has not been determined. Diosgenin feeding increased biliary cholesterol secretion in mice without altering the mRNA levels of G5 and G8 in the liver (12), suggesting a G5G8-independent pathway of biliary cholesterol secretion.

To determine the role of G5 and G8 in regulating the amount of cholesterol secreted into bile, we examined the relationship between G5 and G8 expression and biliary cholesterol levels in genetically modified mice expressing 0, 1, 2, 5, 10, or 16 copies of G5G8.

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¶ The abbreviations used are: ABC, ATP-binding cassette; PXR, pregnane X receptor; FXR, farnesoid X receptor; CYP, cytochrome P450.
of the two genes. Next, we examined the role of G5 and G8 in modulating biliary cholesterol levels in response to cholate and diosgenin.

**EXPERIMENTAL PROCEDURES**

**Materials**—Sodium cholate and diosgenin were purchased from Sigma-Aldrich. Sterols were obtained from either Steraloids Inc. (Newport, RI) or Sigma-Aldrich. Rabbit antibodies against the N-terminal regions of mouse ABCG5 (residues 2–375) and ABCG8 (2–400) were generated as described previously (4). Rabbit polyclonal antisera against calnexin and Grp78 (BIP) were from Stressgen Biotechnologies Corporation (Victoria, British Columbia, Canada).

**Animals and Diets**—ABCG5/ABCG8 transgenic mice (G5G8Tg) were generated as described previously (6). Three lines of transgenic mice that expressed 3, 8, and 14 copies of the human G5G8 transgene (as determined by Southern blotting using human genomic DNA as a reference) were used in these experiments. Because each line of mice also has two wild-type G5 and G8 alleles, the mice expressed a total of 5, 10, and 16 copies of G5 and G8, respectively. Mice homozygous for a disrupted Abox5 and Abox8 (G5G8−/−) allele were generated as described previously (4). The G5G8−/− mice used in these studies were offsprings of heterozygous mice of mixed genetic background (C57BL/6J and C72BL6J). Mice lacking Fxr (14) were provided by Ronald Evans (Salk Institute, San Diego, CA). Mice lacking Fxr (14) were provided by Frank Gonzalez (National Institutes of Health, Bethesda, MD). Mice were housed in plastic cages in a temperature-controlled room (22 °C) with a 12-h light cycle. All animal procedures were performed with the approval of the Institutional Animal Care and Research Advisory Committee at the University of Texas Southwestern Medical Center.

**Treatment of Mice with Cholate and Diosgenin**—Diets containing 0.1% cholate, 0.2% cholate, or 1% cholate were made by mixing a powdered chow diet (Diet 7001, Harlan Teklad, Madison, WI) containing 0.02% cholesterol and 4% fat. All animal procedures were performed with the approval of the Institutional Animal Care and Research Advisory Committee at the University of Texas Southwestern Medical Center.

**Biliary Lipid Composition**—Bile was collected from the gallbladder of anesthetized mice using a 30-gauge needle. The concentrations of cholesterol, bile acids, and phospholipids were measured as described above (15). A total of 100–200 mg of liver or jejunum (the middle third of the small intestine) was homogenized by a polytron in 1.2 ml buffer A (250 mM sucrose, 2 mM MgCl2, 20 mM Tris-HCl, pH 7.5) containing protease inhibitors (Complete Protease inhibitor mixture, Roche Diagnostics). The crude preparation was centrifuged at 2000 × g for 10 min at 4 °C. The supernatant was collected and re-centrifuged at 120,000 × g for 45 min at 4 °C. The membrane pellet was resuspended in a solution containing 80 mM NaCl, 2 mM CaCl2, 1% Triton X-100, 50 mM Tris-HCl, pH 8, and protease inhibitors as above.

**Immunoblot Analysis**—The protein concentrations of the tissue membranes were determined using the BCA Kit (Pierce). Membrane proteins (50 μg) were fractionated on 8% SDS-polyacrylamide gels and transferred to Hybond-C Extra Nitrocellulose filters (Amersham Biosciences). The filters were immunoblotted with polyclonal antisera against mouse ABCG5, mouse ABCG8, calnexin and Bip in phosphate-buffered saline, pH 7.4, with Tween 20 (Sigma-Aldrich), 5% powdered milk, and 5% newborn calf serum and then were incubated with horse-radish peroxidase-conjugated donkey anti-rabbit IgG (Jackson ImmunoResearch Laboratories) or donkey anti-mouse IgG (Jackson ImmunoResearch Laboratories) and visualized using SuperSignal substrate system (Pierce).

**Quantitative Real-time PCR**—Total RNA was extracted from tissues using RNA Stat-60 (Tel-Test), and quantitative real-time PCR was performed to assay the relative amounts of selected mRNAs as determined by linear regression.

**RESULTS**

**Biliary Cholesterol Secretion Is Linearly Related to Copy Number and Expression Levels of G5 and G8**—To determine the relationship between G5G8 expression and biliary cholesterol secretion, we measured biliary cholesterol concentrations in genetically manipulated mice in which G5G8 expression varied over a wide range. Homologous recombination was used to generate mice with either 0 (G5G8−−), 1 (G5G8−/+), 2 (G5G8+/−), 5 (G5G8+/+), 10 (G5G8+−), and 16 (G5G8+++) copies. Data are means ± S.E. The differences between the mean values were tested for statistical significance using two-tailed Student’s t tests. The relationship between transgene copy number and biliary cholesterol secretion rate was determined by linear regression.

![Graph showing relationship between biliary cholesterol concentrations and ABCG5 expression levels.](https://www.jbc.org/)
Biliary lipid secretion in ABCG5/ABCG8 transgenic mice. Cannulas were placed in the common bile ducts of wild-type (WT) mice and of mice expressing 10 (TG1) or 16 (TG2) copies of the G5G8 transgene (5 mice/group), and hepatic bile was collected for 30 min. Biliary cholesterol, bile acid, and phospholipid (PL) concentrations were determined enzymatically, and the secretion rate of each lipid was determined from measurements of bile flow. Bars represent the means ± S.E. for each group.

**Cholate Feeding Does Not Promote Biliary Cholesterol Secretion in G5G8−/− Mice**—Cholate feeding was associated with a 3-fold increase in biliary cholesterol concentrations in wild-type mice (Fig. 3A). The increase in biliary cholesterol concentration observed in the wild-type animals was associated with a corresponding increase in the levels of G5 and G8 mRNA and protein (Fig. 3, A and B). Cholate feeding failed to increase biliary cholesterol secretion in G5G8−/− mice (Fig. 3A). Cholate feeding repressed Cyp8B1 (Fig. 3C), an enzyme in the bile acid biosynthetic pathway known to be down-regulated by bile acids. Therefore the failure of cholate to stimulate biliary cholesterol secretion was not due to a general failure to respond to cholate in these animals. The effect of cholate on the expression of G5 and G8 was liver-specific; cholate feeding did not increase the levels of G5 and G8 mRNA or protein in the intestine, the other major site of expression of these genes in mice (Fig. 4). Thus the increase in G5G8 expression in response to cholate is dependent on factors expressed in the liver that are not present in the gut. Taken together, these findings are consistent with the notion that stimulation of G5 and G8 expression is required for the change in biliary cholesterol levels associated with cholate feeding.

**Cholate Feeding Does Not Increase Hepatic mRNA Levels of G5 or G8 in Fxr−/− Mice**—Cholic acid modulates the expression of several hepatic genes by activating the nuclear receptor FXR. To determine whether the effects of cholate on G5 and G8 are mediated by FXR, Fxr−/− mice and their wild-type littermates were treated with 0.2% cholate for 10 days. Cholate treatment increased hepatic G5 and G8 mRNA levels by 3-fold in wild-type mice but had no effect on G5 and G8 expression in Fxr−/− mice (Fig. 5). Thus FXR is required for the transcriptional activation of G5 and G8 induced by cholate feeding.

**Diosgenin Does Not Stimulate Biliary Cholesterol Secretion in G5G8−/− Mice**—To determine whether G5 and G8 mediate the increased biliary cholesterol secretion associated with diosgenin feeding, both G5G8−/− mice and their wild-type littermates were fed diets containing 1% diosgenin for 1 week. As has been previously reported (22), diosgenin treatment was associated with a 2–3-fold increase in biliary cholesterol levels in wild-type mice (Fig. 6A). No increase in G5 or G8 mRNA or protein levels was seen in either the livers (Fig. 6, B and C) or the intestine (not shown) of diosgenin-treated wild-type animals, which is consistent with the findings of Kosters et al. (12). ABCG5 and ABCG8 are synthesized as glycoproteins in the endoplasmic reticulum. During transit through the Golgi, maturation of the N-linked glycans on both proteins results in a significant increase in their apparent molecular masses. Immunoblot analysis revealed that the relative amounts of mature and precursor forms of the proteins were not changed by diosgenin treatment (Fig. 6B). In contrast to the wild-type mice, biliary cholesterol levels of the G5G8−/− mice did not change with diosgenin treatment. Thus, G5 and G8 are required for the diosgenin-stimulated increase in biliary cholesterol concentration, but the effect is not due to increased expression of G5 and G8 nor to a change in the proportion of G5 and G8 that reaches the Golgi complex.
Biotics such as pregnenolone/H9251

The effect of diosgenin on this gene was ameliorated in the liver and small intestine of the wild-type mice (Fig. 7).

Diosgenin in PXR-deficient mice. Diosgenin treatment in-nuclear receptor PXR (23) Therefore we examined the effect of lipid secretion and hepatic gene expression by activating the

real-time PCR was repeated once, and similar results were

level observed in chow-fed wild-type mice, which was arbitrarily set to 1. The real-time PCR was repeated once, and similar results were obtained. WT, wild type; KO, knock-out.

Diosgenin Activates Expression of PXR Target Genes—Xenobiotics such as pregnenolone α-carbonitrile stimulate biliary lipid secretion and hepatic gene expression by activating the nuclear receptor PXR (23) Therefore we examined the effect of diosgenin in PXR-deficient mice. Diosgenin treatment increased the expression of Cyp3a11, a known PXR target gene, in the liver and small intestine of the wild-type mice (Fig. 7).

The effect of diosgenin on this gene was ameliorated in Pxr−/− mice (that is, homozygous PXR knock-out mice) (Fig. 7). Expression of Abcc2, a target gene of nuclear receptor constitutive androstane receptor, was not affected by diosgenin (Fig. 7). These data indicated that diosgenin treatment leads to activation of PXR.

Promotion of Biliary Cholesterol Excretion by Diosgenin Is Largely Mediated by PXR—To determine whether the increase in biliary cholesterol secretion associated with diosgenin treatment is mediated by PXR, biliary cholesterol levels were measured in Pxr−/− mice after treatment with diosgenin for 1 week. The diosgenin-stimulated increase in biliary cholesterol levels was reduced by 70% in the Pxr−/− mice (Fig. 8A). No changes were observed in biliary levels of phospholipids or bile acids, the two other major biliary lipids, in wild-type or Pxr−/− mice (Fig. 8A). The mRNA levels of major biliary lipid transporting genes Abcb4, Abcb11, Abcg5, and Abcg8 were not altered sig-

ificantly by diosgenin treatment in wild-type mice (Fig. 8B).

These data are consistent with a major role for the PXR signaling pathway in the choleretic effect of diosgenin.

DISCUSSION

The major findings of this study were that the rate of biliary cholesterol secretion is directly proportional to hepatic expression of G5 and G8 and that G5 and G8 are required for the choleretic effects of cholate and diosgenin. The level of expression of G5 and G8 was the major determinant of biliary cholesterol secretion rates over a 16-fold range of expression. Neither the delivery of cholesterol to the transporter nor the levels of cholesterol acceptors in bile were rate-limiting. Expression of G5 and G8 was required for the stimulation of biliary cholesterol secretion by either cholate or diosgenin, but the two choleretic agents activated G5G8-mediated cholesterol secretion by different mechanisms. Cholate treatment was associated with a coordinate increase in hepatic G5 and G8 mRNA and
protein, which is consistent with its major effect at the transcriptional level. In contrast, diosgenin did not increase expression levels of G5 and G8. A major component for the choleretic effect of diosgenin was mediated through PXR.

The rate of cholesterol secretion into bile is frequently inferred from the concentration of cholesterol in gallbladder bile (4, 6, 10, 24). Because G5 and G8 are expressed in gallbladder epithelial cells (25), it is possible that the cholesterol concentration in gallbladder bile of genetically manipulated mice reflects the translocation of cholesterol across the gallbladder epithelium rather than the biliary cholesterol secretion rate. Several observations make this possibility unlikely. First, direct measurement of biliary cholesterol secretion rates in the G5G8 transgenic mice revealed a direct relationship between the level of G5G8 expression and the rate of biliary cholesterol secretion (Fig. 2). Analogous experiments by Klett et al. (26) demonstrated that the rate of biliary cholesterol secretion is markedly reduced in mice lacking G8 and that infusion of taurocholate fails to increase biliary cholesterol secretion in these animals. Second, cholate feeding, which coordinately increases G5G8 expression and biliary cholesterol concentrations, increases biliary cholesterol secretion rates (27). Third, intravenous injection of recombinant adenovirus-expressing human G5 and G8 markedly increases cholesterol concentrations in gallbladder bile in G5G8−/− mice (2). In these animals, G5 and G8 are expressed in the liver but not in the gallbladder.2 Taken together, these findings indicate that the increased cholesterol levels in gallbladder bile of G5G8−/− mice reflect an increase in biliary cholesterol secretion.

We showed previously that cholesterol feeding increases the expression of G5 and G8 (8), resulting in increased biliary cholesterol excretion. The results of the present study indicate that cholate also stimulates biliary cholesterol secretion by increasing the expression of G5 and G8. Cholate feeding increases cholesterol absorption in mice (28), and the increased influx of dietary cholesterol may promote biliary cholesterol secretion, but expression of G5 and G8 is required for this process. Therefore cholesterol and cholic acid, the major naturally occurring steroids in mammals, promote biliary cholesterol secretion by activating transcription of G5 and G8 in the liver. Whereas cholesterol feeding increases the expression of G5 and G8 both in the liver and in the intestine (8), cholic acid has its effect only in the liver (Fig. 4). Cholate did not increase G5G8 expression in Pxr−/− mice, indicating that the effect of cholate on biliary cholesterol secretion is mediated by FXR.

The only agent known to increase biliary cholesterol secretion without increasing G5G8 expression is diosgenin (12). The present data confirm that diosgenin increases biliary cholesterol concentrations without increasing the hepatic mRNA or protein levels of G5 or G8 (12, 29). However, G5 and G8 are required for the choleretic effect of diosgenin; no increase in biliary cholesterol was seen in diosgenin-treated G5G8−/− mice. To elucidate the mechanism by which diosgenin stimulated G5G8-dependent biliary cholesterol secretion, we measured hepatic mRNA levels of several genes encoding biliary lipid transporters and nuclear receptor targets in diosgenin-treated mice. Diosgenin treatment was associated with increased hepatic mRNA levels of CYP3A11, a well characterized

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2 H. H. Hobbs and J. C. Cohen, unpublished observations.
target of the nuclear receptor PXR (Fig. 6). The finding that
diosgenin increased expression of a PXR target gene, together
with the previous observation that the PXR ligand pregneno-
lone α-carbonitrile increased biliary cholesterol secretion in
rats (30), suggested that the diosgenin-stimulated increase in
biliary cholesterol secretion may be mediated by PXR. The
increase in biliary cholesterol concentrations in diosgenin-
treated mice was markedly attenuated in Pxr−/− mice. Thus, a
major component of the effect of diosgenin on biliary cholesterol
secretion was mediated by PXR.

Our data indicate that diosgenin increases biliary cholesterol
secretion by activating PXR, which in turn alters the expression
of proteins that promote cholesterol secretion in a G5G8-
dependent manner, perhaps by increasing the proportion of
G5G8 that is on the canalicular membrane or by increasing the
V_{max} of the transporter. Some ABC transporters reside in sub-
apical compartments and are delivered to the canalicular mem-
brane when the demand to secrete bile increases (31), but we
have not been able to document any subapical accumulation of
G5 or G8 (32). However, it remains possible that PXR increases
expression of proteins that increase the efficiency of cho-
lesterol transport across the canalicular membrane by activat-
ing the G5G8 heterodimer, by altering the micro-environment
of the transporter, or by promoting the release of cholesterol
into the bile. Additional studies will be required to pinpoint the
mechanisms by which PXR activation promotes G5G8-depend-
ent secretion of cholesterol into bile.

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