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FXR agonists and FGF15 reduce fecal bile acid excretion in a mouse model of bile acid malabsorption

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Abstract Bile acid malabsorption, which in patients leads to excessive fecal bile acid excretion and diarrhea, is characterized by a vicious cycle in which the feedback regulation of bile acid synthesis is interrupted, resulting in additional bile acid production. Feedback regulation of bile acid synthesis is under the control of an endocrine pathway wherein activation of the nuclear bile acid receptor, farnesoid X receptor (FXR), induces enteric expression of the hormone, fibroblast growth factor 15 (FGF15). In liver, FGF15 acts together with FXR-mediated expression of small heterodimer partner to repress bile acid synthesis. Here, we show that the FXR-FGF15 pathway is disrupted in mice lacking apical ileal bile acid transporter, a model of bile acid malabsorption. Treatment of *Asbt*$^{-/-}$ mice with either a synthetic FXR agonist or FGF15 downregulates hepatic cholesterol 7α-hydroxylase mRNA levels, decreases bile acid pool size, and reduces fecal bile acid excretion. These findings suggest that FXR agonists or FGF15 could be used therapeutically to interrupt the cycle of excessive bile acid production in patients with bile acid malabsorption.—Jung, D., T. Inagaki, R. D. Gerard, P. A. Dawson, S. A. Kliewer, D. J. Mangelsdorf, and A. Moschetta. **FXR agonists and FGF15 reduce fecal bile acid excretion in a mouse model of bile acid malabsorption.** ***J. Lipid Res.*** **2007.** 48: **2693–2700.**

Supplementary key words bile acid metabolism • nuclear receptors • transporters • farnesoid X receptor • fibroblast growth factor 15

Bile acids are anionic detergents synthesized from cholesterol in the liver that are released postprandially into the small intestine, where they facilitate the solubilization of fatty acids, cholesterol, and lipophilic vitamins. In the ileum, >95% of bile acids are reabsorbed by the apical ileal sodium-dependent bile acid transporter (ASBT; SLC10A2) (1) and returned to the liver as part of the cycle referred to as enterohepatic circulation (2). In humans, a reduction in intestinal bile acid reabsorption and subsequent increase in fecal bile acid excretion contributes to the chronic diarrhea and steatorrhea that occur in a number of different clinical contexts, including congenital diarrhea, idiopathic secretory diarrhea, Crohn's disease, postinfectious diarrhea, postvagotomy diarrhea, postgastrectomy syndrome, and short bowel syndrome. Although mutation of the *ASBT* gene is one cause for bile acid malabsorption in humans (3), in most cases the molecular mechanisms underlying the disruption of enterohepatic circulation are unknown. *Asbt*$^{-/-}$ mice were described recently and shown to recapitulate key aspects of bile acid malabsorption in humans (4). *Asbt* deletion eliminates the reabsorption of intestinal bile acids. As a consequence, *Asbt*$^{-/-}$ mice have increased fecal bile acid excretion, reduced bile acid pool size, increased bile acid synthesis, and alterations in bile acid pool composition (4).

Bile acids are intracellular ligands for the nuclear farnesoid X receptor (FXR; NR1H4) (5, 6), a transcriptional regulator of numerous genes involved in maintaining cholesterol and bile acid homeostasis (5–7). Among its many actions, FXR represses transcription of the gene encoding cholesterol 7α-hydroxylase (*CYP7A1*), the first and rate-limiting enzyme in the classic pathway of bile acid synthesis (8, 9). FXR represses *CYP7A1* transcription through a bipartite mechanism involving coordinated actions in intestine and liver. In ileum, FXR induces the expression of fibroblast growth factor 15 (FGF15), a hormone that plays an overarching role in regulating bile

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Abbreviations: ASBT, apical sodium-dependent bile acid transporter; CYP7A1, cholesterol 7α-hydroxylase; CYP8B1, sterol 12α-hydroxylase; FGF15, fibroblast growth factor 15; FXR, farnesoid X receptor; IBABP, ileal bile acid binding protein; SHP, small heterodimer partner; TCA, taurocholate; TβMCA, tauro-β-muricholate.

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acid homeostasis. In liver, FXR induces the expression of small heterodimer partner (SHP; NR0B2), an orphan nuclear receptor that binds to the *CYP7A1* promoter through interactions with another orphan nuclear receptor, liver receptor homolog 1 (NR5A2) (10, 11). Induction of both FGF15 and SHP is required for the FXR-mediated repression of *CYP7A1* and bile acid synthesis (12). FXR also represses the hepatic expression of sterol 12α-hydroxylase (CYP8B1), an enzyme controlling the ratio of the primary bile acids cholate and β-muricholate in mice (13), and induces the expression of the bile acid export pump (ABCB11) (14, 15) and the ileal bile acid binding protein (IBABP) (5, 16, 17).

Bile acid malabsorption interrupts the normal feedback repression of bile acid synthesis, resulting in a vicious cycle of increased bile acid production. In the present study, we examined FXR signaling in $Asbt^{-/-}$ mice and tested whether FXR agonists and FGF15 can be used to restore feedback regulation in this genetic model of bile acid malabsorption.

MATERIALS AND METHODS

Animals

$Asbt^{-/-}$ mice were generated previously (4) and maintained on a pure 129S6/SvEv strain background with matching wild-type mice in a temperature-controlled room (22–23°C) under a 12 h light/12 h dark cycle. Mice were maintained on a normal chow diet (Purina 5001; Harlan Teklad, Madison, WI). Twenty 12 week old male mice were treated by oral gavage with 100 mg/kg mouse body weight of a selective, synthetic FXR agonist, GW4064 (18) (a gift from Dr. Timothy Willson, GlaxoSmithKline) or vehicle [PEG 400/Tween 80 (4:1, v/v)] daily for 6 days. On the last day of treatment, mice were fasted for 2 h, then gavaged and euthanized after an additional 2 h. Bile was stored at −20°C, and liver, gallbladder, and small and large intestine were frozen in liquid nitrogen and stored at −80°C until further analysis. All experiments were approved by the Institutional Animal Care and Research Advisory Committee at the University of Texas Southwestern Medical Center.

FGF15 adenovirus infections

FGF15 adenovirus was generated as described (12). Six 4–6 week old male mice were infected with adenovirus by injection into the jugular vein using a 3/10 ml syringe (Becton Dickinson Co., Franklin Lakes, NJ). Each mouse received 7.5×10^9 particles/g body weight in 0.1 ml of saline. Mice were euthanized at 5 days after injection, total RNA was prepared from the liver and ileum, and fecal bile acid measurements were performed.

Bile acid measurements

For fecal bile acid excretion, stools from individually housed wild-type and $Asbt^{-/-}$ mice were collected during the final 3 days of the study and then dried, weighed, and ground. Bile acids were extracted as described by Turley, Daggy, and Dietschy (19), and bile acid concentration was determined by an enzymatic assay. The bile acid pool size was determined as the total bile acid content of gallbladder, bile, and intestine. These tissues were removed and bile was extracted as described (19). The total bile acid content and the individual bile acid compositions were determined by high-performance liquid chromatography (20) using the following bile salts as standards: tauro-β-muricholate (TβMCA), tauroursodeoxycholate, taurohyodeoxycholate, taurocholate (TCA), glycocholate, taurochenodeoxycholate, taurodeoxycholate, glycochenodeoxycholate, glycodeoxycholate, and taurolithocholate.

Lipid measurements

Hepatic (0.2 g of liver) lipids were extracted according to Folch, Lees, and Sloane Stanley (21). Bile acids were quantified enzymatically using the 3α-hydroxysteroid dehydrogenase (Sigma Chemical Co., St. Louis, MO) method (22), and the bile acid hydrophobicity index was calculated according to Heuman (23). Serum and liver triglycerides were measured using a reagent from Thermo Trace, Ltd. (Melbourne, Australia), and glycerol standards from Sigma Chemical Co. Serum and liver cholesterol levels were measured using reagent from Roche and cholesterol standards from Sigma Chemical Co.

mRNA measurements

RNA extraction from liver was performed using the RNA STAT-60 reagent (Tel-Test B, Inc., Friendswood, TX). RNA was treated with RNase-free DNase (Roche) and reverse-transcribed (Superscript II; Invitrogen) using random hexamers (Roche) to a final concentration of 20 ng/μl. Gene-specific primers were designed using Primer Express Software (PE Biosystem). Primer sequences have been reported (12, 24) and are available upon request. Real-time quantitative PCR was performed as described previously (25) using SYBR Green I chemistry (SYBR Green PCR Master Mix; ABI) on the ABI Prism 7900HT Sequence Detection System. Each sample was run in triplicate with 25 ng of template and 150 nM of each primer. Relative fold changes were calculated using the comparative cycle times method with cyclophilin as the reference gene and the wild-type mice from each strain as the calibrators. All real-time quantitative PCR data were generated using RNA isolated from tissues of individual animals.

Statistics

Values are expressed as means ± SEM. Comparison between two groups was assessed by Student's *t*-test. Comparison between multiple groups was assessed using ANOVA, followed by a post hoc Newman-Keuls test (Primer of Biostatistic Software).

RESULTS

A synthetic FXR agonist restores FXR activity in $Asbt^{-/-}$ mice

Interruption of enterohepatic circulation in $Asbt^{-/-}$ mice results in increased fecal bile acid excretion and reduced bile acid pool size (4). Because bile acids are endogenous ligands for FXR, we analyzed whether $Asbt^{-/-}$ mice have reduced FXR activity in intestine and liver. In ileum, mRNA levels of the FXR target genes *Fgf15* and *Shp* were reduced to below detection in $Asbt^{-/-}$ mice (**Fig. 1**). A decrease also was seen in *Ibabp* expression. In liver, *Shp* and *Bsep* mRNA levels were reduced significantly (**Fig. 2**). Consistent with decreased expression of *Fgf15* in the intestine and *Shp* in the liver, hepatic *Cyp7a1* and *Cyp8b1* mRNA levels increased by 12-fold and 6-fold, respectively (Fig. 2). Thus, $Asbt^{-/-}$ mice have decreased FXR activation

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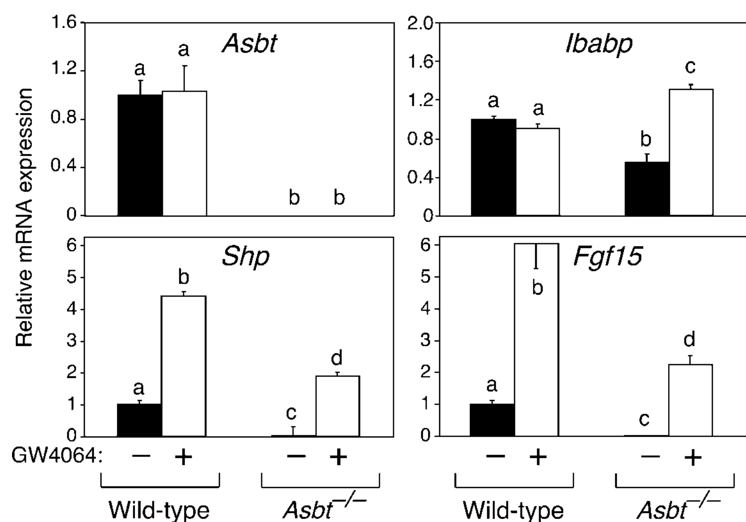

Fig. 1. Effects of the synthetic farnesoid X receptor (FXR) agonist GW4064 on FXR target gene expression in ileum of wild-type and *Asbt*$^{-/-}$ mice. Quantitative PCR analysis was performed on mRNA from ileum of male mice (n = 10) treated for 6 days with vehicle (black bars) or GW4064 (white bars). Values were normalized to an internal standard using vehicle-treated wild-type mice as calibrators. Data represent means ± SEM and are plotted as fold change relative to vehicle-treated wild-type mice. Different lowercase letters indicate statistical significance ($P < 0.05$) between groups. ASBT, apical sodium-dependent bile acid transporter; FGF15, fibroblast growth factor 15; IBABP, ileal bile acid binding protein; SHP, small heterodimer partner.

in both liver and intestine accompanied by loss of feedback regulation of *Cyp7a1* and *Cyp8b1*.

To examine whether FXR activity can be restored by an FXR agonist that does not require ASBT for intestinal absorption, *Asbt*$^{-/-}$ mice were administered the selective, synthetic FXR agonist, GW4064. In ileum, GW4064 administration caused marked increases in *Fgf15*, *Shp*, and *Ibabp* expression (Fig. 1). In liver, GW4064 induced *Shp* and *Bsep* and suppressed *Cyp7a1* and *Cyp8b1* expression (Fig. 2). In experiments performed in parallel in wild-type mice, GW4064 had the expected effects, including induction of *Fgf15* and *Shp* in ileum, induction of *Shp* and *Bsep* in liver, and repression of *Cyp7a1* and *Cyp8b1* in liver (Figs. 1, 2). These results demonstrate that GW4064 can restore the loss of FXR signaling in *Asbt*$^{-/-}$ mice.

GW4064 reduces bile acid pool size and alters bile composition in *Asbt*$^{-/-}$ mice

In agreement with previous work (4), basal fecal bile acid excretion was ∼10-fold higher in *Asbt*$^{-/-}$ mice compared with wild-type mice (**Fig. 3A**). GW4064 administration caused a substantial decrease (70%) in fecal bile acids in *Asbt*$^{-/-}$ mice but had no effect in wild-type mice. Although not addressed in this study, the discrepancy between decreased *Cyp7a1* expression and unaltered fecal bile acid output in wild-type mice might be explained by an increased activity of the alternative, acidic pathway

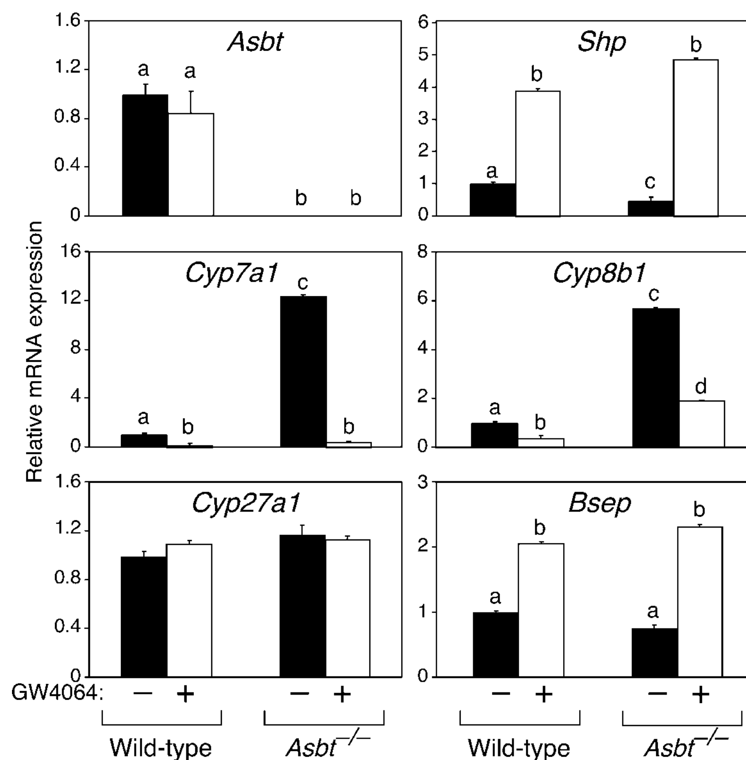

Fig. 2. Effects of GW4064 on FXR target gene expression in liver of wild-type and *Asbt*$^{-/-}$ mice. Quantitative PCR analysis was performed on mRNA from liver of male mice (n = 10) treated for 6 days with vehicle (black bars) or GW4064 (white bars). Values were normalized to an internal standard using vehicle-treated wild-type mice as calibrators. Data represent means ± SEM and are plotted as fold change relative to vehicle-treated wild-type mice. Different lowercase letters indicate statistical significance ($P < 0.05$) between groups. CYP7A1, cholesterol 7α-hydroxylase; CYP27AI, sterol 27-hydroxylase; CYP8B1, sterol 12α-hydroxylase.

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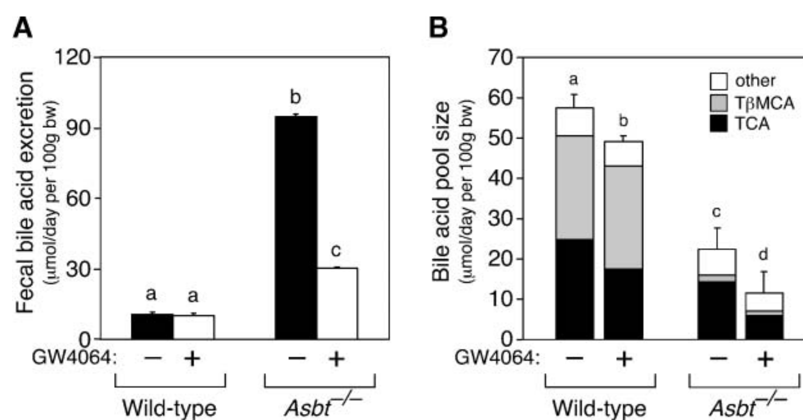

Fig. 3. GW4064 decreases fecal bile salt excretion and bile acid pool size in *Asbt*$^{-/-}$ mice. Fecal bile acid excretion (A) and bile acid composition and pool size (B) were measured in male wild-type and *Asbt*$^{-/-}$ mice (n = 10) treated with vehicle (black bars) or GW4064 (white bars). The same mice used for Figs. 1, 2 were analyzed. Data represent means ± SEM. Different lowercase letters indicate statistical significance ($P < 0.05$) between groups. bw, body weight; TCA, taurocholate; TβMCA, tauro-β-muricholate.

of bile acid synthesis. On the other hand, because intestinal bile acid absorption is compromised in *Asbt*$^{-/-}$ mice, the robust decrease in bile acid excretion caused by GW4064 should depend entirely on the downregulation of de novo bile acid synthesis in the liver. Indeed, treatment of *Asbt*$^{-/-}$ mice with GW4064 caused a 50% reduction in the bile pool size (Fig. 3B). A smaller, 15% decrease occurred in wild-type mice (Fig. 3B). The large decrease in the bile pool size caused by GW4064 in *Asbt*$^{-/-}$ mice is even more significant, considering that the basal bile acid pool size is already 62% smaller in these animals (Fig. 3B).

The changes in bile acid pool size caused by either the lack of ASBT or GW4064 treatment were accompanied by alterations in its composition. In the basal state, *Asbt*$^{-/-}$ mice had a decreased ratio of TβMCA to TCA (Fig. 3B) (4). These data are consistent with an increased expression of CYP8B1, which catalyzes a key step in the formation of TCA, in *Asbt*$^{-/-}$ mice. Treatment with GW4064, which reduces CYP8B1 levels, changed the TβMCA/TCA ratio from 0.11 to 0.19. Similarly, GW4064 administration to wild-type mice shifted the TβMCA/TCA ratio from 1.06 to 1.49 (Fig. 3B). Because TβMCA is more hydrophilic than TCA, GW4064 caused a significant decrease in the hydrophobicity index of the bile acid pool in both genotypes (from 0.07 ± 0.02 to −0.02 ± 0.01 in wild-type mice and from 0.19 ± 0.07 to 0.06 ± 0.03 in *Asbt*$^{-/-}$ mice; $P < 0.05$).

An estimation of the fractional turnover rate of bile acids can be calculated by dividing the daily fecal bile acid excretion by the bile acid pool size (4). As shown in **Table 1**, the fractional turnover rate did not change after GW4064 treatment in wild-type animals. By contrast, the fractional turnover rate was increased by 24-fold in the *Asbt*$^{-/-}$ mice under basal conditions and was reduced by >60% after GW4064 administration. Although the large increase in fractional turnover rate in the *Asbt*$^{-/-}$ mice is consistent with increased *Cyp7a1* expression and decreased intestinal bile acid absorption, the mechanism by which the FXR agonist reduced the turnover rate in *Asbt*$^{-/-}$ mice is not entirely known. Together, these data demonstrate that FXR activation reverses key pathological measurements of bile acid malabsorption in the *Asbt*$^{-/-}$ model of the disease.

Effects of FXR loss and gain of function on hepatic lipid metabolism in *Asbt*$^{-/-}$ mice

The FXR pathway regulates not only bile acid homeostasis but also cholesterol and triglyceride concentrations (13). Therefore, we examined the effect of GW4064 treatment on hepatic and serum lipid levels. There were no differences between wild-type and *Asbt*$^{-/-}$ mice in basal hepatic or serum triglyceride and cholesterol concentrations (**Fig. 4**). However, treatment with GW4064 led to significant decreases in liver triglyceride concentrations in both wild-type and *Asbt*$^{-/-}$ mice and a decrease in serum triglyceride levels in *Asbt*$^{-/-}$ mice (Fig. 4). Similar triglyceride-lowering effects of GW4064 have been reported previously (26). GW4064 significantly decreased serum cholesterol levels and caused a trend toward decreased hepatic cholesterol concentrations in *Asbt*$^{-/-}$ mice. Given the prominent role of bile acids in intestinal cholesterol absorption (27), the marked reductions in total bile acid pool size and bile acid hydrophobicity might

TABLE 1. Fractional turnover rate of bile acids in wild-type and *Asbt*$^{-/-}$ mice after vehicle or GW4064 treatment

Treatment	*Asbt*$^{+/+}$	*Asbt*$^{-/-}$
Vehicle	0.18 ± 0.08	4.24 ± 0.44[a]
GW4064	0.20 ± 0.04	2.53 ± 0.15[a]

Fractional turnover rate was calculated as daily fecal bile acid excretion divided by the bile acid pool size and is expressed as pools/day. Data are expressed as means ± SEM.
[a] $P < 0.01$ versus wild-type mice.

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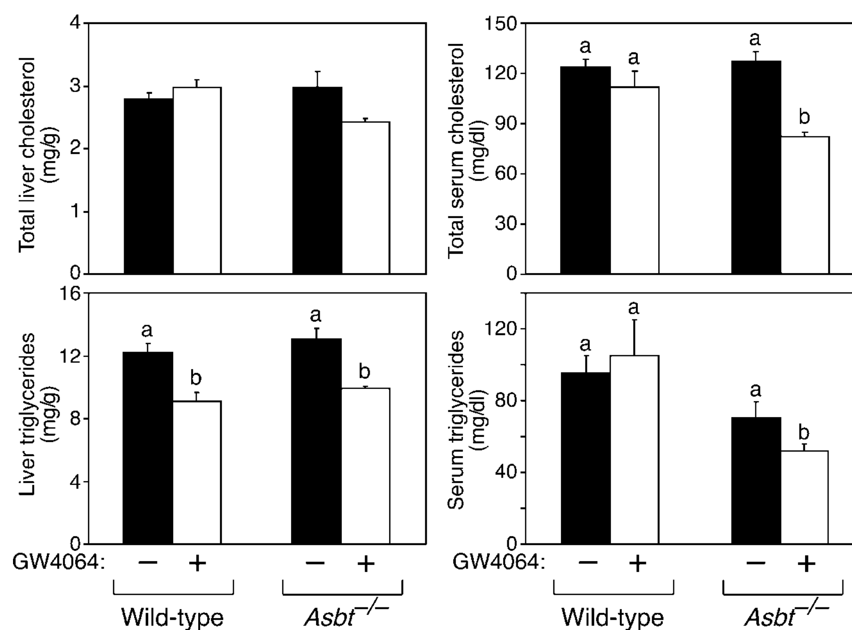

Fig. 4. Lipid profiles in wild-type and *Asbt*$^{-/-}$ mice treated with GW4064. Mice were treated for 6 days with vehicle (black bars) or GW4064 (white bars) and analyzed for hepatic and serum triglyceride and cholesterol levels. The same mice used for Figs. 1–3 were analyzed. Data represent means ± SEM. Different lowercase letters indicate statistical significance ($P < 0.05$) between groups.

account for the cholesterol-lowering actions of GW4064 in *Asbt*$^{-/-}$ mice.

Effects of ASBT and FXR agonist on liver weight

Asbt$^{-/-}$ mice had a 32% reduction in body weight compared with wild-type mice (**Table 2**). Interestingly, despite their small size, *Asbt*$^{-/-}$ mice had a reduced liver-to-body weight ratio (Table 2). Because bile acids promote hepatocyte proliferation and liver regeneration through an FXR-dependent pathway (28), the small liver size in *Asbt*$^{-/-}$ mice could be related to their reduced bile acid pool. Neither wild-type mice nor *Asbt*$^{-/-}$ mice had changes in body weight after treatment with GW4064 (Table 2). However, treatment with GW4064 led to increased liver weight in both groups. The increase in liver weight in GW4064-treated *Asbt*$^{-/-}$ mice resulted in liver-to-body weight ratios comparable to those of wild-type mice (Table 2). These data reveal a role for FXR in regulating liver growth under conditions of impaired enterohepatic circulation.

FGF15 reduces fecal bile acid excretion in *Asbt*$^{-/-}$ mice

Asbt$^{-/-}$ mice had a pronounced reduction in gallbladder volume compared with wild-type mice under fasting conditions (0.07 ± 0.01 vs. 0.19 ± 0.04 μl/g body weight, respectively; $P < 0.01$). The smaller fasting gallbladder volume in *Asbt*$^{-/-}$ mice is likely a consequence of low mRNA levels of intestinal FGF15 (Fig. 2), which is required for gallbladder filling (29). Because FGF15 is also required for efficient FXR-mediated repression of bile acid synthesis, we tested whether FGF15 administration reverses excess fecal bile acid excretion in *Asbt*$^{-/-}$ mice. Infection of *Asbt*$^{-/-}$ mice with an FGF15-expressing adenovirus resulted in robust FGF15 mRNA levels in liver, and a corresponding decrease in *Cyp7a1* mRNA was observed (**Fig. 5A**). Significantly decreased serum cholesterol levels and a trend toward decreased hepatic cholesterol concentrations were observed in *Asbt*$^{-/-}$ mice infected with FGF15-expressing adenovirus (Fig. 5B). Also, fecal bile acid excretion was reduced by ~80% in mice infected with

TABLE 2. Body weight, liver weight, and liver-to-body weight ratio in wild-type and *Asbt*$^{-/-}$ mice after vehicle or GW4064 treatment

Mouse and Treatment	Body Weight, Day 0	Body Weight, Day 6	Liver Weight, Day 6	Liver-to-Body Weight Ratio on Day 6
		mg		
Asbt$^{+/+}$ vehicle	30.1 ± 0.7	28.6 ± 1.1	1.18 ± 0.07	4.12 ± 0.11
Asbt$^{+/+}$ GW4064	30.2 ± 1.3	29.6 ± 1.0	1.45 ± 0.10	4.82 ± 0.46
Asbt$^{-/-}$ vehicle	19.3 ± 1.5[a]	19.0 ± 1.4[a]	0.68 ± 0.06[a]	3.46 ± 0.22
Asbt$^{-/-}$ GW4064	21.8 ± 1.1[a]	20.9 ± 0.7[a]	0.92 ± 0.03	4.53 ± 0.16

Data are expressed as means ± SEM.
[a] $P < 0.01$ versus *Asbt*$^{+/+}$ vehicle.

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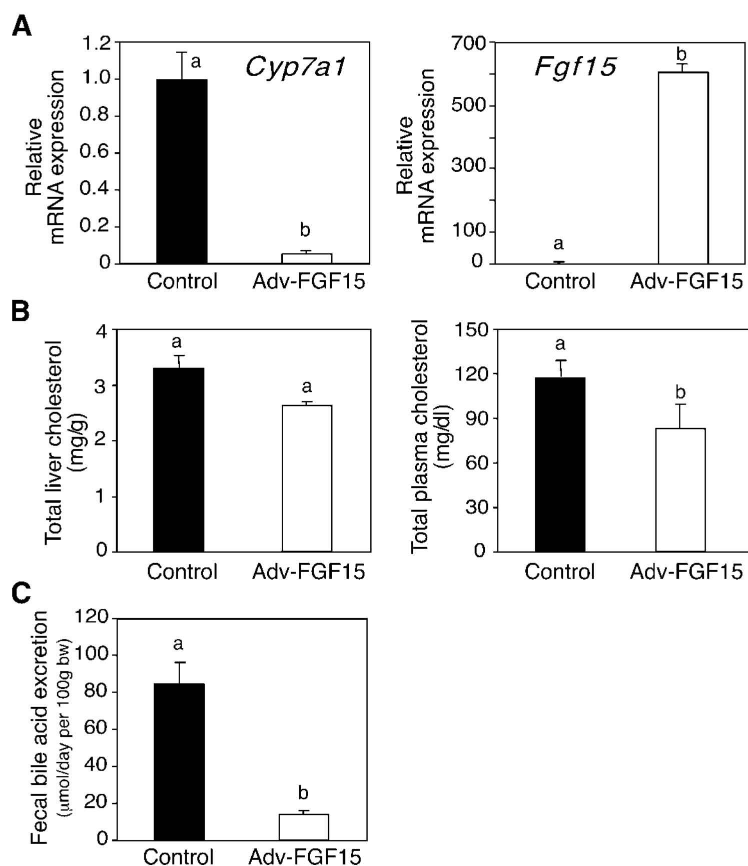

Fig. 5. FGF15 phenocopies the effects of an FXR agonist on bile acid metabolism in *Asbt*$^{-/-}$ mice. Six male *Asbt*$^{-/-}$ mice were injected in the jugular vein with either control adenovirus or an FGF15-expressing adenovirus (Adv-FGF15). A, B: Mice were euthanized at 5 days after injection and analyzed for mRNA expression analysis in the liver (A) and hepatic and serum cholesterol levels (B) by quantitative PCR. C: Feces were collected for 3 days before euthanasia for fecal bile acid excretion measurements. Data represent means ± SEM. Different lowercase letters indicate statistical significance ($P < 0.05$) between groups.

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the FGF15-expressing adenovirus (Fig. 5C). Notably, there was no increase in liver weight of *Asbt*$^{-/-}$ mice after infection with FGF15-expressing adenovirus (data not shown), indicating that other FXR actions are required to promote liver growth.

DISCUSSION

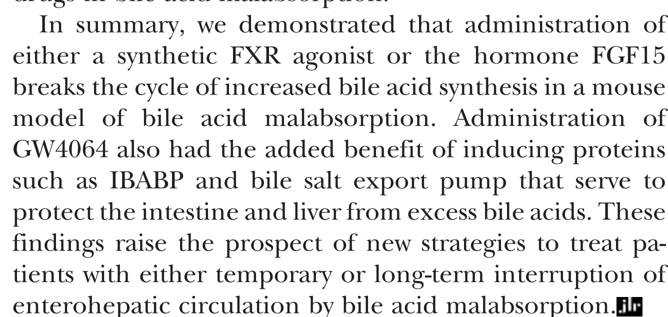
There is increasing evidence that bile acid malabsorption is a common cause of chronic diarrhea in conditions ranging from short bowel syndrome to inflammatory bowel disease. Bile acid malabsorption is generally treated with cholestyramine, a resin that sequesters bile acids in the intestine and thus protects the bowel from exposure to the increased levels of colonic bile acids seen in these patients. However, cholestyramine and other resins are unpalatable and have adverse side effects that include constipation, vitamin deficiency (30), and hypertriglyceridemia (31). Moreover, by sequestering bile acids in intestine, cholestyramine interrupts the normal feedback repression of hepatic bile acid synthesis, resulting in increased bile acid production.

In this study, we examined the potential therapeutic utility of FXR agonists and FGF15 in the *Asbt*$^{-/-}$ mouse model of bile acid malabsorption. *Asbt*$^{-/-}$ mice were unable to reabsorb bile acids in the ileum (4), resulting in impaired FXR activity in both intestine and liver. The changes in gene expression included marked decreases of *Fgf15* and *Shp* in ileum and liver, respectively. Because both FGF15 and SHP are crucial components of the feedback regulatory loop, there was a corresponding increase in *Cyp7a1* mRNA and bile acid synthesis in these mice. Notably, treatment of *Asbt*$^{-/-}$ mice with the synthetic FXR agonist GW4064 reactivated the FXR pathway, inducing the expression of *Fgf15* in intestine and *Shp* in liver. This resulted in the suppression of *Cyp7a1* followed by decreased bile acid pool size and fecal bile acid excretion. Downregulation of *Cyp7a1* and reduction of fecal bile acid excretion were also accomplished by the introduction of FGF15 directly into the livers of *Asbt*$^{-/-}$ mice. Together, these data suggest that reactivation of the FXR-FGF15 signaling cascade may have important therapeutic potential in diseases associated with bile acid malabsorption.

This study also highlights the quantitative importance of FXR in suppressing de novo bile acid synthesis. Because *Asbt*$^{-/-}$ mice are unable to reabsorb bile acids in the intestine, the newly synthesized bile acids constitute the entire bile acid pool, whereas they account for only 5% of the bile acid pool in normal mice (2). Activation of FXR by GW4064 in *Asbt*$^{-/-}$ mice reduced the bile acid pool size by 50%. This was reflected in the fractional turnover rate of bile acids, which was decreased by >60% after GW4064 administration. To our knowledge, this is the first in vivo study showing the relative pharmacological importance of the repression of bile synthesis by FXR.

Activation of the FXR pathway via selective specific agonists has been proposed as a therapeutic tool in biliary

diseases such as cholesterol gallstone disease (24) and cholestasis (32, 33). FXR agonists also protect the intestinal mucosa from bacterial infection and inflammatory insults (34). Recently, it was demonstrated that FGF15 is a key hormonal regulator of gallbladder filling (29), which would decrease the amount of intestinal bile acid during the interprandial cycles. These observations, together with our data on the *Asbt*$^{-/-}$ mice, support the potential therapeutic action of selective FXR agonists and FGF15 in the management of temporary or long-term clinical manifestations of bile acid malabsorption. Interestingly, in certain conditions, FXR agonists are able to decrease circulating and hepatic triglyceride levels (26), thus protecting against one of the major adverse side effects of cholestyramine and other resins (31), which are the actual major drugs in bile acid malabsorption.



In summary, we demonstrated that administration of either a synthetic FXR agonist or the hormone FGF15 breaks the cycle of increased bile acid synthesis in a mouse model of bile acid malabsorption. Administration of GW4064 also had the added benefit of inducing proteins such as IBABP and bile salt export pump that serve to protect the intestine and liver from excess bile acids. These findings raise the prospect of new strategies to treat patients with either temporary or long-term interruption of enterohepatic circulation by bile acid malabsorption.

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