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## On Fibrates and Cholestasis: A review

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### Abstract

Cholestasis, including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), results from an impairment or disruption of bile production and causes intracellular retention of toxic bile constituents, including bile salts. If left untreated, cholestasis leads to liver fibrosis and cirrhosis, which eventually results in liver failure and the need for liver transplantation. Currently, the only therapeutic option available for these patients is ursodeoxycholic acid (UDCA), which slows the progression of PBC, particularly in stage I and II of the disease. However some patients have an incomplete response to UDCA therapy, while other more advanced cases often remain unresponsive. For PSC, UDCA therapy does not improve survival, and recommendations for its use remains controversial. These considerations emphasize the need for alternative therapies.

Hepatic transporters, located along basolateral (sinusoidal) and apical (canalicular) membranes of hepatocytes, are integral determinants of bile formation and secretion. Nuclear receptors are critically involved in the regulation of these hepatic transporters and are natural targets for therapy of cholestatic liver diseases. One of these nuclear receptors is peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) which plays a central role in maintaining cholesterol, lipid and bile acid homeostasis by regulating genes responsible for bile acid synthesis, and transport in humans, including Cytochrome P450 (CYP) isoform 7A1 (CYP7A1), CYP27A1, CYP8B1, UGT1A1, 1A3, 1A4, 1A6, SULT2A1, MDR3, and ASBT. The expression of many of these genes is altered in cholestatic liver diseases but few have been extensively studied or had the mechanism of PPAR $\alpha$  effect identified. In this review we examine what is known about these mechanisms and consider the rationale for the use of PPAR $\alpha$  ligand therapy in various cholestatic liver disorders.

### I. Introduction

Hepatic bile salt secretion and bile formation are essential functions of the mammalian liver. Cholestasis, a condition where the production of bile is impaired, results in intracellular retention of toxic bile constituents, including bile salts (1). Hepatocytes are polarized epithelial cells with basolateral (sinusoidal) and apical (canalicular) domains (2), where several liver-specific transporters enable vectorial movement of endogenous and exogenous compounds from blood into bile (3). Canalicular secretion of bile components represents the rate-limiting step in bile formation (2). Bile acids, glutathione conjugates, and xenobiotics

are removed from hepatocytes and concentrated into the bile by canalicular efflux transporters in an ATP-dependent manner. Several transporters that are members of the ATP-binding cassette (ABC) superfamily are expressed along the canalicular membrane of hepatocytes, where they are involved in the secretion of bile constituents. Consequently, hepatic transporters play important roles in bile formation. The multidrug resistance protein 3 (MDR3/Mdr2 in rodent), encoded by the ABC protein subtype B4 (*ABCB4*) gene, is the major determinant of biliary phosphatidylcholine (PC) secretion (4), where it functions as a floppase and translocates PC from the inner to the outer leaflet of the canalicular membrane of hepatocytes for bile salt extraction (2). The bile salt export pump (BSEP/Bsep), encoded by the *ABCB11* gene, and first identified as the sister of P-glycoprotein (5), is essential for biliary secretion of bile salts, while the heterodimer of *ABCG5* and *ABCG8* secretes cholesterol into bile (6). Substrates of these transporters (bile salts, PC and cholesterol) form mixed biliary micelles which reduce the biliary detergent activity of the bile salts and maintain cholesterol homeostasis (7). Indeed, mutations in these transporters result in several types of inherited disorders (8), known as progressive familial intrahepatic cholangitis (PFIC) type 1, 2, and 3. Mutations in *MDR3* also cause several liver disorders in addition to PFIC3 ranging from gallstone formation, to drug induced liver disease, intrahepatic cholestasis of pregnancy and even some forms of progressive cholestatic liver disease in adults (9).

A growing body of literature supports the notion that nuclear receptors are critically involved in the regulation of hepatic transporters, findings that have prompted the investigation of nuclear receptors as therapeutic targets for cholestatic liver diseases. In particular, fenofibrate, the peroxisome proliferator-activated receptor-alpha (PPAR $\alpha$ ) agonist is increasingly used to treat patients with chronic cholestatic liver disease who are refractory to ursodeoxycholic acid (UDCA) monotherapy. In this review we examine the data supporting the claim of PPAR $\alpha$  as an alternative pharmacological target for the treatment of cholestatic disorders and provide insight into the mechanism(s) by which PPAR $\alpha$  agonists may improve cholestatic liver injury.

## II. Peroxisome Proliferator-Activated Receptor (PPAR)

Discovered in 1990, PPARs are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily (10). Three distinct PPAR isoforms:  $\alpha$ ,  $\beta/\delta$ , and  $\gamma$ , are encoded by distinct genes and show different distribution patterns. All PPARs share the typical structure of other members in this family (Figure 1). Upon ligand activation, PPARs regulate gene transcription by forming a heterodimer with the retinoid x receptor and bind to specific DNA-response elements containing direct repeats of the consensus sequence AGGTCA separated by one or two nucleotides located within the regulatory regions of target genes (11). Activation of PPAR by an appropriate ligand results in the recruitment of co-activators and the loss of co-repressors which remodel the chromatin and activate gene transcription (11).

Activation of PPAR $\alpha$ , results in proliferation of peroxisomes in rodents but not humans (12). The molecular basis for this species difference is attributed to a murine-specific micro-RNA let-7c signaling cascade (13). PPAR $\alpha$  is highly expressed in tissues including liver,

muscle, kidney, and heart where it stimulates the  $\beta$ -oxidative degradation of fatty acids (22), and regulates the transcription of several genes involved in lipid metabolism (14). The phenotype of the fasted PPAR $\alpha$  knock-out mouse is hypoglycaemia, hypoketonaemia, hypertriglyceridaemia and hepatic steatosis (15).

PPAR is the molecular target for the fibrate hypolipidemic agents, including fenofibrate, gemfibrozil, and clofibrate, which are FDA-approved for the treatment of dyslipidemia, though each fibrate differs in its specificity for the different PPAR subtypes,  $\alpha$ ,  $\beta/\delta$ , and  $\gamma$  (16), presented in Table 1. Another fibrate, bezafibrate, activates all three PPAR isoforms at equivalent molar concentrations, whereas fenofibrate exhibits approximately a 10-fold selectivity for PPAR- $\alpha$  vs. - $\gamma$  (16). Fenofibrate activates PPAR $\alpha$  by binding to PPAR response elements (PPREs) in the upstream regions of target genes (17). The synthetic compound Wy-14,643 is also a PPAR $\alpha$  ligand, often used in *in vitro* testing.

### III. PPAR $\alpha$ : Regulation of Bile Acid (BA) Synthesis

Ligand-activated PPAR $\alpha$  contributes to a range of actions including cholesterol and BA homeostasis, summarized in Table 2. Also, fenofibrate significantly reduced serum levels of UDCA as well as toxic primary and secondary bile acids, including CDCA, deoxycholic acid, and lithocholic acid in non-cholestatic adult volunteers (18). PPAR $\alpha$  primarily down-regulates BA synthesis through inhibition of the BA-synthesizing enzymes, cytochrome P450 cholesterol 7 $\alpha$ 1-hydroxylase (CYP7A1), the rate-limiting step in bile acid synthesis, and cytochrome sterol 27-hydroxylase (CYP27A1). Ciprofibrate and Wy-14,643 reduced CYP7A1 and CYP27A1 mRNA expression in parallel with reduction in their respective hydroxylase activities (19). Wy-14,643 suppresses *Cyp7a1* gene promoter activity (28) via interruption of hepatocyte nuclear factor4-mediated activation of CYP7A1 (20), while ciprofibrate induces the promoter activity of human apical sodium-dependent bile salt transporter (*ASBT*) gene in Caco2 cells (30). In contrast, ligand-activated PPAR $\alpha$  stimulates the expression and activity of sterol 12 $\alpha$ -hydroxylase (CYP8B1), a hepatic microsomal enzyme that acts as a branch point in the bile acid synthetic pathway that determines the cholic acid (CA):chenodeoxycholic acid (CDCA) ratio (21). Treatment of wild-type animals with Wy-14,643 increased CA formation in a PPAR $\alpha$ -dependent manner, that was blocked in *Ppara*-null mice (21). Additionally, recent findings indicate that PPAR $\alpha$  also regulates BA detoxification via up-regulation of CYP3A4 (22), UGT2B4 (23), UGT1A1, 1A3, 1A4, 1A6 (24), SULT2A1 (25), and *ASBT* (26). Murine PPAR $\alpha$  also plays a crucial role in BA synthesis, but reduces phospholipid concentration and mRNA expression of *Abcb4*, *Abca1*, *Abcg5*, and *Abcg8* in *Ppara*-null mice. (27). These data suggest that PPAR $\alpha$  activation decreases BA synthesis and bile salt secretion into bile. Furthermore, PPAR $\alpha$  activators, i.e. fenofibrate, enhanced human hepatic glucuronidation activity and expression of the uridine 5'-diphospho-glucuronosyltransferase (UGT) family of enzymes, specifically *UGT2B4* (23). *SULT2A1* catalyzes the sulfation of BAs which facilitates the elimination of the toxic secondary bile acid lithocholic acid (28), thereby reducing cholestasis. Transcriptional regulation of *SULT2A1* by PPAR $\alpha$  occurs at PPREs located -5949 to -5929 bp upstream of the transcription start site (25). A thorough analysis of the *UGT1* locus (24) revealed that PPAR $\alpha$  positively regulates not only liver *UGT1A1*, but also *1A3*, *1A4*, and *1A6* isoforms. More recently, PPAR $\alpha$  was shown to directly regulate *CYP3A4* transcription as well as

*CYP1A1, 1A2, 2B6, and 2C8* (22). These findings introduce potential drug-drug interactions between PPAR $\alpha$  agonists and CYP450 regulators.

## IV. PPAR: Regulation of Bile Excretory Function

### a. Efflux Transporter MDR3/Mdr2

MDR3 (ABCB4) is predominantly expressed in the liver (29) and localized to the canalicular membrane of hepatocytes, where it is the major determinant of biliary PC secretion (4). The functional importance of MDR3 was first demonstrated in *Mdr2* knockout mice which lack biliary phospholipids and develop bile duct injury and progressive liver disease (30), closely resembling PSC in humans (31). We and others (7, 32) observed a linear relationship between biliary PC concentration and *Mdr2* gene expression (Figure 2). Clinically, mutations and polymorphisms of MDR3 contribute to several types of cholestatic liver injury, including PFIC-3, intrahepatic cholestasis of pregnancy, low phospholipid cholelithiasis, drug-induced and idiopathic chronic cholestasis in adults (33). Thus, MDR3 represents an important pharmacological target.

The observation that bezafibrate improved serum alkaline phosphatase (ALP) in patients treated for hyperlipidemia (34) introduced the possibility that fibrates could be beneficial for patients with cholestatic liver disease. Since then, case reports and pilot studies demonstrated the efficacy of bezafibrate and fenofibrate, reviewed in (35), in reducing biomarkers of cholestasis and liver function abnormalities in patients with PBC or PSC experiencing an incomplete response to UDCA monotherapy (13–15 mg/kg/day). However, most studies test bezafibrate, a non-specific PPAR agonist not FDA-approved nor clinically available in the United States, compared to fenofibrate, a specific FDA approved PPAR $\alpha$  agonist. Despite *in vitro* and animal findings, and clinical studies showing efficacy, the mechanism(s) by which fibrates reduce biochemical markers of cholestasis remains unclear. Bezafibrate has been reported to act as a dual PPAR $\alpha$  and  $\gamma$  and pregnane X receptor (PXR) agonist (36), albeit at super-physiological doses. We examined the mechanism by which fenofibrate modulates MDR3 expression and found that activation of PPAR $\alpha$  by fenofibrate directly up-regulates human MDR3 expression by binding to specific PPREs located on the gene's promoter (37). *In silico* analysis of the 5'-upstream region of human MDR3 gene identified 21 putative PPREs. Reporter gene assays identified three novel PPREs located 6–10 kb upstream of the transcription start site of the MDR3 promoter. Further, fenofibrate increased the canalicular excretion of fluorescently labeled PC when incubated with isolated rat hepatocytes grown in collagen sandwich cultures (37). This is the first evidence that the human *MDR3* gene is directly trans-activated by PPAR $\alpha$  and strongly suggests that PPAR $\alpha$  up-regulates the expression of MDR3 and facilitates hepatic export of phospholipids. Together, these findings provide a molecular and physiologic mechanism by which fenofibrate may improve symptoms and liver function in patients with chronic cholestatic liver disease.

Others have reported that bezafibrate increases MDR3 localization and NBC-PC within pseudo-canalculi of HepG2 cells although the specificity for canalicular secretion of PC was not clear since bezafibrate also increased mRNA expression of *MRP2* and *BSEP* (38). In contrast, when primary rat hepatocytes were cultured in a collagen sandwich and treated

with fenofibrate there was a 2-fold increase in fluorescent intensity of NBD-PC secreted into the canalicular lumen closely mimicking the *in vivo* situation (37). These results strongly suggest that fenofibrate improves biochemical markers of cholestasis by enhancing biliary excretion of PC.

Results vary on the effects of fibrates on *Mdr2* mRNA expression, i.e. ciprofibrate and Wy-14,643 treatment up-regulate *Mdr2* mRNA expression in primary hepatocytes and liver tissue of wild-type but not *Ppara*-null mice, yet, wild-type mice displayed an increase in bile flow in spite of reduced biliary phospholipid and bile salt concentrations (39). Others (40) reported that a 0.5% fenofibrate diet did not increase biliary phospholipid output in wild-type mice, despite increased *Mdr2* mRNA levels, while clofibrate and ciprofibrate increased biliary phospholipid levels in wild-type animals, but not in *Ppara*-null mice. Interestingly, the effects of clofibrate and ciprofibrate on phospholipid output occurred independently of changes in bile acid output and fibrate treatment did not alter the BA pool composition (40). However, *in silico* analysis of the mouse *Abcb4* promoter reveals 25 Ppres located within the 10 kb upstream region (37). In particular, three Ppres in the 6–10 kb upstream region were located very close to the three PPREs described in the human *ABCB4* promoter (37). These findings corroborate the conclusion that  $\text{Ppara/PPAR}\alpha$  directly regulates *Abcb4/ABCB4* expression in both rodents and humans. Opposing effects of fibrates may be the result of species-specificity or the variable affinity of fibrates for  $\text{PPAR}\alpha/\text{Ppara}$ , as previously noted (19). While these studies suggest a direct role for *MDR3/Mdr2* by  $\text{PPAR}\alpha$  activation, additional effects of  $\text{PPAR}\alpha$  activation, via independent yet additive pathways, i.e. lipid metabolism, CYP450-, and UGT-mediated drug metabolism and BA synthesis, likely contribute to the benefit of fenofibrate therapy observed in patients with chronic cholestatic liver disease.

## V. Additional Effects of $\text{PPAR}\alpha$

### a. Efflux Transporters *Mrp3* and *Mrp4*

Hepatic transporters have crucial roles in (ATP-dependent) BA and substrate efflux into the systemic circulation. *MRP4/Mrp4*, a member of the multidrug resistance-associated gene family, expressed on the basolateral membrane of hepatocytes undergoes an adaptive up-regulation in response to cholestatic injury or BA feeding (41). *Mrp4*-null mice show greater liver injury following BDL significant reductions in serum BA levels, and increased *Mrp3* protein expression. *MRP3* is also up-regulated during human cholestasis (42). Up-regulation of these basolateral export pumps presumably function as an adaptive compensatory mechanism to minimize the damaging cellular effects of cholestasis. These findings have led to the idea that pharmacological up-regulation of efflux transporters on the basolateral membrane, particularly *MRP3* and *MRP4*, might be of therapeutic benefit. Indeed treatment with the  $\text{PPAR}\alpha$  agonist clofibrate increases *Mrp3* and *Mrp4* mRNA and protein expression (43). Whether human *MRP3/4* expression is affected by fibrates remains to be determined. However, bezafibrate, a dual  $\text{PPAR}$  and  $\text{PXR}$  agonist, increased mRNA expression of *NTCP*, *CYP3A4*, *MDR1*, *MDR3*, and *MRP2*, while down-regulating expression of *CYP7A1* and *CYP27A1* in human hepatoma cells (36). Up-regulation of these transporters may provide additional benefit in reducing cholestatic liver injury.

## b. Regulation of the Pro-inflammatory Response

PPAR $\alpha$  also interferes with pro-inflammatory transcription factor pathways by trans-repression (21). PPAR $\alpha$  negatively interferes with transcription factor signaling, including nuclear factor- $\kappa$ B (NF- $\kappa$ B) (43), activator protein 1, signal transducers and activators of transcription. PPAR $\alpha$  activation by fibrates and Wy-14,643 induced human mRNA and protein expression of the inhibitory protein I $\kappa$ B $\alpha$  in a PPAR $\alpha$ -dependent manner, thereby reducing p65-mediated gene activation of the pro-inflammatory cytokine II-1 $\beta$  (43). A significant increase in *Tnfa* mRNA expression was observed in *Ppara*-null mice (27). Human endothelial cells stimulated with cytokines and treated with fenofibrate or Wy-14,643, showed a significant reduction in vascular cell adhesion molecular-1 (VCAM-1) gene expression accompanied by reduced VCAM-1 promoter activity via inhibition of NF- $\kappa$ B translocation, thereby reducing leukocyte adhesion and inhibition of subsequent trans-endothelial migration (44). Whether fibrates exert their beneficial effect on cholestatic liver function by also regulating anti-inflammatory pathways seems likely but remains to be determined.

## c. Crosstalk with Nuclear Farnesoid X Receptor (FXR)

Alternative pathways of human MDR3 regulation have also been reported. FXR response elements exist in the proximal region of the human *MDR3* promoter and *MDR3* mRNA levels increase following treatment with CDCA (45). Despite these findings, FXR may not be a direct activator of *Acb4* regulation since mice with a homozygous deletion of the *Fxr* gene still respond to a CA-enriched diet with an increase in *Mdr2* mRNA (46). Thus, FXR-mediated effects may occur indirectly via PPAR $\alpha$  activation. Combination treatment with CDCA and GW7647, a PPAR $\alpha$  agonist, enhance PPAR $\alpha$  activation compared to either agent alone (47). In contrast, treatment of primary human hepatocytes with fenofibrate increases MDR3 mRNA and protein expression greater than CDCA but together are not synergistic (37). Interestingly, many of the actions reported by PPAR $\alpha$ , i.e. up-regulation of UGT2B4 and CYP7A1, are also described for FXR (48).

## VI. Clinical Experience with Fibrates

Fibrates reduce serum triglyceride levels by at least 30% with a modest increase in high-density lipoprotein (HDL) in patients with hypertriglyceridemia (49). These effects are mediated in the liver through increased lipoprotein lipolysis and fatty acid uptake, decreased triglyceride production, and increased low-density lipoprotein (LDL) removal and reverse cholesterol transport. The effect of fibrates on lipoproteins is in large part triggered by fibrate activation of PPAR $\alpha$ , which binds to a PPRE in the promoter of the lipoprotein lipase gene in humans (50).

Human studies in cholestasis have not been conducted with clofibrate, a drug which is no longer in clinical use. Gemfibrozil, though clinically used for treatment of hypertriglyceridemia, has also not been studied in human cholestatic disorders. Once early pharmacology studies observed that bezafibrate reduced serum liver-specific ALP and  $\gamma$ -glutamyl transferase levels in humans (51), Iwasiki *et al.* (52), demonstrated a 62.5% reduction in serum ALP for patients with PBC and persistent cholestasis despite UDCA.

Since then, various studies confirmed this observation in PBC (53–66), and also reported ALP reductions in three patients with PSC (57). A prospective, randomized, multicenter study from Japan demonstrated improvement in cholestasis both with bezafibrate monotherapy and combination therapy with UDCA (55). Adverse effects included three instances of elevated serum creatinine kinase and one case of self-limited myalgia. A recent study in a Western patient population (60) further demonstrated the role of bezafibrate as an effective adjuvant therapy for pre-cirrhotic PBC patients treated with UDCA who have persistent cholestasis. In this trial there were isolated instances of mild symptoms, of nausea and heartburn, resulting in a 13% rate of adverse effects, but no reports of myalgias or rhabdomyolysis (60). However, bezafibrate is not clinically available in the United States.

Fenofibrate has been increasingly evaluated for cholestatic liver diseases. An initial report (67) showed similar reductions in cholestasis as seen with bezafibrate for PBC. Subsequent studies evaluated fenofibrate as adjunct to UDCA for treatment of refractory cholestasis in PBC, reviewed in (35). One study reported adverse effects consisting of limited heartburn, nausea, arthralgias, and transient aminotransferase elevations to 2–5x upper limit of normal (68). Two others reported mild, transient pruritus and liver enzyme elevations (67, 69). One trial compared fenofibrate to bezafibrate and reported a similar effectiveness in ALP reduction (75), although fenofibrate was superior in reducing serum LDL and uric acid levels. Of note, in a large randomized study for cardiovascular prevention in type 2 diabetes, the median plasma creatinine was reversibly increased by 12% in the fenofibrate arm (76). The potential nephrotoxic effect of fenofibrate remains controversial with multiple studies supporting (70, 71) and refuting (72, 73) these findings. One potential mechanism for acute kidney injury may be PPAR $\alpha$ -induced blockade of prostaglandin-mediated renal vasodilation, resulting in vasoconstriction (74). Monitoring serum creatinine is recommended prior to initiation of a fibrate and throughout therapy with dose reduction if there is renal impairment (75).

#### **a. Potential Clinical Drug-drug Interactions Involving Fibrates**

Most drug-drug interactions involving fibrates are attributed to either competition for protein binding, primarily to albumin, or CYP3A4 metabolism (76). Clinically important potential drug interactions involving fenofibrate are listed in Table 3. All fibrates, but particularly gemfibrozil, displace warfarin from albumin and prolong the prothrombin time. Therefore, warfarin doses should be reduced by at least 30% and INR levels must be frequently monitored (76). Competition for the CYP3A4 enzyme may result in increased sensitivity to statin toxicity, particularly with hydrophobic drugs such as lovastatin when taken with gemfibrozil (77). However, a recent comprehensive review of fibrate toxicity in the cardiology literature suggests that with monitoring it is safe to co-administer statins and fibrates in the clinical setting of refractory hyperlipidemia (75). This has relevance to emerging evidence to support the role of FXR agonist obeticholic acid (OCA) for refractory cholestasis in PBC (78, 79), since OCA increases serum LDL levels consistent with its mechanism of action (80). No studies to date have evaluated fibrates in conjunction with FXR agonists for the treatment of cholestasis.

Fenofibrate can increase the lithogenicity of bile (81) and thus patients with pre-existing gallbladder disease are advised against its use (82). However, as opposed to clofibrate and gemfibrozil, there is no evidence that fenofibrate therapy induces formation of new gallstones (81, 82). Interestingly, the Physicians' Desk Reference specifically mentions PBC as a contraindication to use of fenofibrate (82). This appears to be a reference to much older literature in which clofibrate exacerbated hypercholesterolemia in patients with biliary cirrhosis (83, 84). Similar findings have not been described in more recent clinical studies of bezafibrate or fenofibrate. Published data on fibrate use in refractory cholestasis has thus far been limited mostly to pre-cirrhotic patients without overt jaundice. Also, no formal pharmacokinetic studies have been performed with these fibrates in patients with hepatic impairment. Therefore, further information is needed on the metabolism and safety of fibrates in advanced liver disease due to cholestasis before recommendations could be made in this specific setting.

## VII. Conclusions

This review summarizes the current literature highlighting the beneficial actions of PPAR $\alpha$  in the context of chronic cholestatic liver disease in adults. A summary of these effects is illustrated in Figure 3. It is likely that fenofibrate ameliorates cholestatic liver disease through its transcriptional activation of *MDR3*, in addition to the other reported beneficial actions of PPAR $\alpha$  activation in liver. Altogether, these findings strongly support the use of PPAR $\alpha$  agonists such as fenofibrate, as therapeutic alternatives for adult patients with cholestatic liver diseases, specifically those with an incomplete therapeutic response to UDCA.

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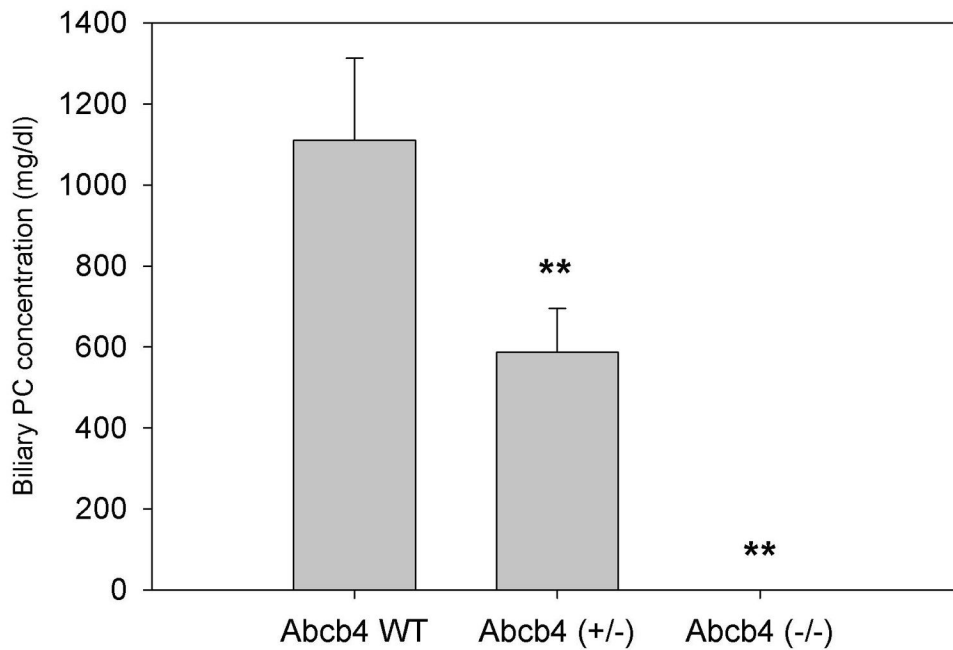
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**Figure 1.**

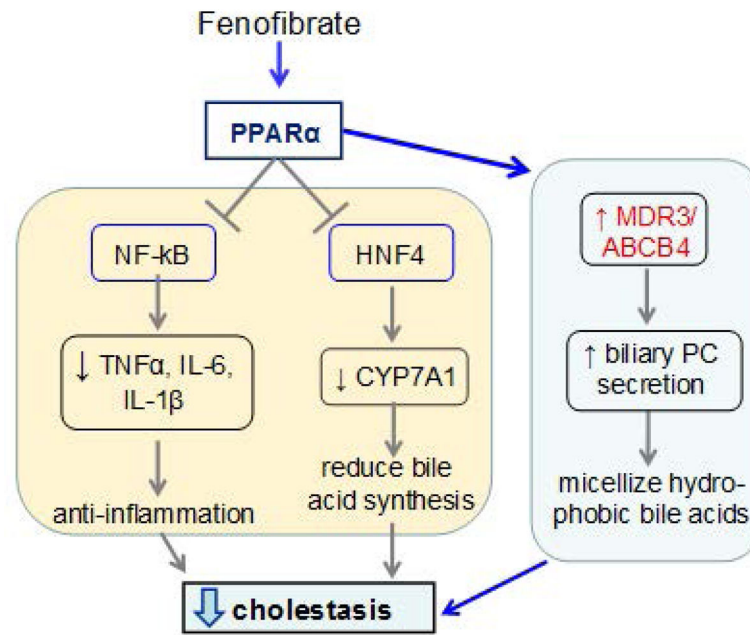
Typical structure of the functional domains of the human peroxisome proliferator-activated receptor (PPAR). **A/B**: Ligand-independent transactivation domain (AF-1), **C**: Ligand-dependent transactivation domain (AF-2), **D**: DNA binding domain (DBD), and **E**: Ligand binding domain (LBD).



**Figure 2. Biliary phosphatidylcholine (PC) is a function of *Abcb4* gene expression**

Bile was collected from age-matched mice that express the *Abcb4* gene (wild-type, WT), heterozygous expression (+/-), and homozygous deletion (-/-). Biliary PC concentration was determined using a colorimetric assay. Data are expressed as the mean  $\pm$  SD (n=3).

\*\*p<0.01 vs. WT.



**Figure 3.**  
Proposed pathway of fenofibrate-mediated reduction of cholestasis via PPAR $\alpha$  in the liver.

**Table 1**

Potency of human PPAR agonists, modified from Wilson TM et al. (16).

Ligand	Human receptor EC <sub>50</sub> (μM)		
	PPARα	PPARβ/δ	PPARγ
Wy-14,643	5	35	60
Clofibrate <sup>a</sup>	55	IA at 100	~500
Fenofibrate	30	IA at 100	300
Bezafibrate	50	20	60

<sup>a</sup> data is for the active metabolite, IA = inactive.

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**Table 2**Summary of key target genes involved in PPAR $\alpha$ -induced beneficial effects in cholestatic disorders.

Target gene(s)	Therapeutic effects	Ref.
Cyp7a1 and Cyp27a1	<ul style="list-style-type: none"> <li>Wy-14,643, ciprofibrate and fenofibric acid reduced mRNA levels and activity; decreased bile acid (BA) synthesis and fecal output</li> </ul>	(19)
ASBT/ <i>SLC10A2</i>	<ul style="list-style-type: none"> <li>Wy-14,643 trans-activated human promoter;</li> <li>Ciprofibrate induced mRNA levels</li> </ul>	(26)
Cyp8b1	<ul style="list-style-type: none"> <li>Wy-14,643 activated promoter and up-regulated hepatic mRNA; increased cholic acid (CA), decreased <math>\beta</math>-muricholic acid levels</li> </ul>	(21)
UGT2B4	<ul style="list-style-type: none"> <li>Wy-14,643 and fenofibric acid trans-activated human promoter; up-regulated hepatic mRNA levels and glucuronidation activity</li> </ul>	(23)
UGT1A1, 1A3, 1A4 and 1A6	<ul style="list-style-type: none"> <li>Wy-14,643 trans-activated promoters, increased mRNA and protein expression; up-regulated LCA-24G plasma concentrations</li> </ul>	(24)
SULT2A1	<ul style="list-style-type: none"> <li>Ciprofibrate and Wy-14,643 trans-activated human promoter; induced mRNA, protein and activity</li> </ul>	(25)
Bile acid synthesizing and metabolizing enzymes, and transporting proteins: Cyp7a1, Cyp7b1, Cyp8b1, Cyp27a1, and Hsd3b7; Ntcp, Oatp1 and 4, Abcb4, Baat, Bacs	<ul style="list-style-type: none"> <li>Bile acid homeostasis disrupted in Ppara-null mice fed a CA diet</li> </ul>	(27)
MDR3/ <i>ABCB4</i>	<ul style="list-style-type: none"> <li>Fenofibrate and Wy-14,643 trans-activated promoter; increased mRNA and protein; increased biliary PC excretion</li> </ul>	(37)
<i>Mdr2/Abcb4</i>	<ul style="list-style-type: none"> <li>Wy-14,643 and ciprofibrate up-regulated hepatic mRNA <i>Mdr1a/b</i> and protein expression; decreased <i>Bsep</i>, <i>Ntcp</i>, and <i>Oatp1</i> in WT</li> </ul>	(39)
<i>Mdr2</i>	<ul style="list-style-type: none"> <li>Clofibrate, ciprofibrate, fenofibrate and gemfibrozil increased hepatic gene expression; stimulated biliary phospholipid output</li> </ul>	(40)
Primary and secondary BAs	<ul style="list-style-type: none"> <li>Fenofibrate reduced human serum BA concentrations</li> </ul>	(18)

CYP7A1: Cholesterol 7 $\alpha$ -hydroxylase; CYP27A1: sterol 27-hydroxylase; ASBT/*SLC10A2*: Apical Sodium-dependent Bile Salt Transporter; Cyp8b1: Sterol 12 $\alpha$ -hydroxylase ; UGT: UDP-glucuronosyltransferase; SULT2A1: Hydroxysteroid sulfotransferase enzyme; Hsd3b7:Hydroxyl-delta-5-steroid dehydrogenase; Ntcp: sodium-taurocholate cotransporting polypeptide; Oatp: organic anion transporting peptide; Baat/*Slc27a5*: bile acid-CoA synthetase; Bacs:bile acid-coA amino acid *N*-acetyltransferase; *Mdr2*: Multidrug resistance drug transporter 2; MDR3/*ABCB4*: Multidrug resistance transporter 3/ATP-binding cassette protein subfamily B4

**Table 3**

Summary of potential clinical drug-drug interactions involving fenofibrate (82).

<b>Drug</b>	<b>Concern</b>	<b>Recommendation</b>
Warfarin	<ul style="list-style-type: none"> <li>Fenofibrate can prolong the PT/INR level</li> </ul>	<ul style="list-style-type: none"> <li>Reduce anticoagulant dose</li> <li>Monitor PT/INR frequently</li> </ul>
Calcineurin Inhibitors (CI), i.e. cyclosporine, tacrolimus	<ul style="list-style-type: none"> <li>CI-fenofibrate interaction may increase risk of nephrotoxicity</li> </ul>	<ul style="list-style-type: none"> <li>Use lowest effective dose</li> <li>Monitor renal function frequently</li> </ul>
HMG-CoA reductase inhibitors, i.e. statins	<ul style="list-style-type: none"> <li>Potential myalgias with older hydrophobic statins, i.e. lovastatin and gemfibrozil; No direct evidence of harm with fenofibrate</li> </ul>	<ul style="list-style-type: none"> <li>Monitor patients on statins and fenofibrate for myalgias</li> </ul>
Colchicine	<ul style="list-style-type: none"> <li>Potential rhabdomyolysis</li> </ul>	<ul style="list-style-type: none"> <li>Prescribe with caution</li> </ul>

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