Fibrates Suppress Bile Acid Synthesis via Peroxisome Proliferator–Activated Receptor-α–Mediated Downregulation of Cholesterol 7α-Hydroxylase and Sterol 27-Hydroxylase Expression

Sabine M. Post, Hélène Duez, Philippe P. Gervois, Bart Staels, Folkert Kuipers, Hans M.G. Princen

Abstract—Fibrates are hypolipidemic drugs that affect the expression of genes involved in lipid metabolism by activating peroxisome proliferator–activated receptors (PPARs). Fibrate treatment causes adverse changes in biliary lipid composition and decreases bile acid excretion, leading to an increased incidence of cholesterol gallstones. In this study, we investigated the effect of fibrates on bile acid synthesis. Ciprofibrate and the PPARα agonist Wy14,643 decreased bile acid synthesis in cultured rat hepatocytes and suppressed cholesterol 7α-hydroxylase and sterol 27-hydroxylase activities, paralleled by a similar reduction of the respective mRNAs. Treatment of rats with 0.05% (wt/wt) ciprofibrate decreased cholesterol 7α-hydroxylase enzyme activity and mRNA. The functional involvement of PPARα in the suppression of both enzymes was proven with the use of PPARα-null mice. In wild-type mice, ciprofibrate reduced cholesterol 7α-hydroxylase and sterol 27-hydroxylase enzyme activities and mRNA. The decrease in mRNA of both enzymes is regulated transcriptionally and posttranscriptionally, respectively, resulting in a decline in the output of fecal bile acids (~45%) and a 3-fold increase in fecal cholesterol secretion. These effects were completely abolished in PPARα-null mice. A decreased bile acid production by PPARα-mediated downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase may contribute to the increased risk of gallstone formation after fibrate treatment. (Arterioscler Thromb Vasc Biol. 2001;21:1840-1845.)

Key Words: PPARα-null mice ■ rats ■ hepatocytes ■ cholesterol excretion

Fibrates are drugs widely used in the treatment of hyperlipidemia.1 These drugs lower triglyceride levels and increase HDL cholesterol levels in hyperlipidemic patients2,3 and reduce the risk of coronary heart disease in patients with low HDL cholesterol levels.4

Fibrates act by activation of nuclear receptors, termed peroxisome proliferator–activated receptors (PPARs). After heterodimerization with the retinoid X receptor, they alter the transcription of specific genes controlling lipoprotein metabolism by binding to a distinct response element, the peroxisome proliferator response element, which consists of a direct repeat of the AGGTCA consensus sequence separated by 1 or 2 nucleotides (DR-1, DR-2).1,5,6 Three different types of PPARs have been identified, termed α, δ (also called β), and γ; each is encoded by a separate gene and shows a distinct distribution pattern.5 PPARα is highly expressed in the liver, and its activation results in an increased fatty acid catabolism.1

Fibrate treatment causes adverse changes in biliary lipid composition and decreases the excretion of bile acids, leading to supersaturation of gall bladder bile and, consequently, an increased incidence of cholesterol gallstones in patients on long-term therapy.7–11 Bile acid synthesis and secretion together with the excretion of free cholesterol into the bile constitute the major route for elimination of cholesterol from the mammalian body.12 The classic or neutral route in bile acid biosynthesis in rats and humans is initiated by 7α-hydroxylation of cholesterol catalyzed by the rate-limiting enzyme cholesterol 7α-hydroxylase, which is located in the smooth endoplasmic reticulum.13 An alternative pathway is operational as well, contributing considerably to the total bile acid synthesis in humans,14 rats,15 and rabbits16 and in cultured human and rat hepatocytes.17 The latter so-called acidic pathway is initiated by conversion of cholesterol by sterol 27-hydroxylase, which is located in the inner mitochondrial membrane.13 A decreased enzyme activity of cholesterol 7α-hydroxylase has been found in humans10,18 and rats19,20 treated with fibrates. In contrast, some studies in rodents did not show an effect on cholesterol 7α-hydroxylase on fibrate treatment.19,21 Recently, divergent data on the effect of PPARα agonists on cholesterol 7α-hydroxylase transcription in promoter-reporter studies have been described.22,23 The
mechanism of action and the potential role of PPARα in the downregulation of cholesterol 7α-hydroxylase by fibrates remain to be clarified. Furthermore, the effect of fibrates on sterol 27-hydroxylase expression has not been established.

In the present study, we further examined in rats in vivo and in cultured rat hepatocytes the effect of fibrates in the regulation of bile acid synthesis and especially on the expression of cholesterol 7α-hydroxylase and sterol 27-hydroxylase. The functional role of PPARα in the regulation of bile acid synthesis by fibrates was studied in PPARα-null (PPARα−/−) mice.

Our data indicate that fibrates suppress bile acid biosynthesis in rodents via a PPARα-mediated downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase expression.

Methods

Material and Animals

Ciprofibrate, fenofibric acid, and gemfibrozil were kindly provided by Dr Ritceo (Sanofi Winthrop, Maassluis, the Netherlands), Dr Edgar (Laboratoires Fournier, Daix, France), and Dr Bierman (Warner-Lambert, Hoofddorp, the Netherlands), respectively. Beza-fibrate was obtained from Boehringer-Mannheim. BRL49653 was a gift from Dr Berthenon (Lipha Merck, Lyon, France). Materials used for the isolation and culturing of rat hepatocytes and for assaying cholesterol 7α-hydroxylase and sterol 27-hydroxylase were obtained from sources described previously.24,25

Male Wistar rats weighing 250 to 350 g were used throughout and were maintained on standard chow and water ad libitum. In vitro experiments were as follows: Two days before the hepatocyte isolation, the animals were fed a diet supplemented with 2% (wt/wt) cholestyramine (Questran, Bristol Myers B.V.) to obtain a sufficient level of expression of cholesterol 7α-hydroxylase and sterol 27-hydroxylase. For the preparation of hepatocytes, the animals were killed between 9:00 and 10:00 AM. In vivo experiments were as follows: Male Wistar rats were treated for 14 days with ciprofibrate (0.05% [wt/wt]) in standard rat chow. After the treatment period, the rats were fasted overnight. Male Sv129 homozygous wild-type (+/+ ) and PPARα−/− mice (10 to 12 weeks of age), which were kindly provided by Dr Gonzalez, Laboratory of Metabolism, National Cancer Institute, National Institutes of Health, Bethesda, Md,26 were fed for 17 days with standard mice chow mixed with 0.05% (wt/wt) ciprofibrate. After the treatment period, the animals were fasted for 4 hours, weighed, and euthanized. For isolation of RNA, microsomes and mitochondria livers were removed immediately, weighed, rinsed with 0.9% (wt/vol) NaCl, and frozen in liquid nitrogen. None of the treatments caused changes in the food intake. Institutional guidelines for animal care were observed in all experiments.

Rat Hepatocyte Isolation and Culture

Hepatocytes were isolated and cultured as described previously by using Williams E medium (ICN) supplemented with 10% FCS.24 Various fibrates and PPARα agonist Wy14,635 (Alexis), dissolved in dimethyl sulfoxide (final concentration of dimethyl sulfoxide in the medium was 0.1% [vol/vol]), were added to the medium between 18 and 42 hours of culture age, unless otherwise stated. Cells were harvested at the same time after a 42-hour culture period for measurement of enzyme activities and mRNA levels. Cell viability was assessed by ATP measurements and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays as described previously.24 The total amount of protein and DNA in all cell culture experiments after incubation with fibrates and Wy14,635 was measured and did not change.

Quantification of Bile Acid Mass Production

Mass production of bile acids by rat hepatocytes was measured by gas-liquid chromatography after a preincubation period of 8 hours (from 18 to 26 hours of culture age), during the following 24-hour culture period from 26 to 50 hours in Williams E medium containing 10% FCS in the presence or absence of ciprofibrate or Wy14,643, as described previously.24

Enzyme Activity of Cholesterol 7α-Hydroxylase and Sterol 27-Hydroxylase

Enzyme activities of cholesterol 7α-hydroxylase and sterol 27-hydroxylase in cell homogenates and isolated liver microsomes and mitochondria were determined as described previously,27 measuring the mass conversion of cholesterol into 7α- and 27-hydroxycholesterol.

RNA Isolation, Blotting, and Hybridization Procedures

Isolation of total RNA, electrophoresis, Northern blotting, probes, and hybridization techniques were performed as described previously.24 The GAPDH mRNA or 18S rRNA was used as an internal standard to correct for differences in the amount of total RNA applied onto the gel. mRNA levels were quantified as described previously.25

Isolation of Nuclei and Transcriptional Rate Assay

To obtain a sufficient level of expression of cholesterol 7α-hydroxylase, we euthanized untreated mice and mice treated for 14 days with 0.05% (wt/wt) of ciprofibrate at 12:00 noon. From the livers of these animals, nuclei were prepared, and nuclear runoff experiments were performed as recently described.27

Fecal Sterol Analysis

Wild-type or PPAR−/− mice treated with or without 0.05% (wt/wt) ciprofibrate (n=6 per group) were housed individually, and total fecal production during 3 days (from day 12 until day 14) was separated from the wood shavings. Aliquots of lyophilized feces were used for determination of neutral and acidic sterol content by gas-liquid chromatographic procedures.25

Statistical Analysis

Data were analyzed statistically by using the Student paired t test, comparing the effects of fibrates versus control in hepatocytes from the same isolation (n independent hepatocyte isolations), or unpaired t test (rats and mice) with the level of significance selected to be P<0.05. Values are expressed as mean±SD

Results

Ciprofibrate and Wy14,643 Decrease Bile Acid Mass Production in Rat Hepatocytes

Incubation of hepatocytes with 300 μmol/L ciprofibrate resulted in a 66% reduction in bile acid mass production
(Figure 1). Because fibrates are PPARα activators, we tested the effect of the specific PPARα ligand Wy14,643. Incubation with 100 μmol/L Wy14,643, compared with ciprofibrate, resulted in a similar decrease (−61%) in bile acid mass production (Figure 1). The major bile acids formed were cholic acid and β-muricholic acid, in a ratio of ∼20:80.28 This ratio did not change on incubation with both compounds. The concentrations used in these experiments (up to 1000 μmol/L ciprofibrate and 100 μmol/L Wy14,643) did not have adverse effects on cell viability as indicated by measurements of cellular MTT and ATP and are mean±SD of independent experiments with hepatocytes from 3 or 4 rats. Absolute activities of cholesterol 7α-hydroxylase and sterol 27-hydroxylase in cell homogenates in control cells were 584±194 and 80±7 pmol/h per milligram cell protein, respectively. *P<0.05 and **P<0.005 vs respective control.

Fibrates and Wy14,643 Suppress Cholesterol 7α-Hydroxylase and Sterol 27-Hydroxylase Activity and mRNA Levels in Rat Hepatocytes

To assess the level at which ciprofibrate and Wy14,643 decrease bile acid mass production, enzyme activities and mRNA levels of cholesterol 7α-hydroxylase and sterol 27-hydroxylase were determined. Ciprofibrate and Wy14,643 suppressed cholesterol 7α-hydroxylase (−69% and −60%, respectively) and sterol 27-hydroxylase (both −49%) activities (Figure 2); these values paralleled well with suppression of its mRNA, being −62% and −52%, respectively, for 300 μmol/L ciprofibrate and −53% and −51%, respectively, for 100 μmol/L Wy14,643 (Table 1). Ciprofibrate dose-dependently suppressed cholesterol 7α-hydroxylase and sterol 27-hydroxylase mRNA levels (Figure 3). In contrast, mRNA levels of GAPDH and 18S ribosomal RNA, used as

Table 1. Effect of Different Clinically Used Fibrates and the PPARα Ligand Wy14,643 on mRNA Levels of Cholesterol 7α-Hydroxylase and Sterol 27-Hydroxylase

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Control</th>
<th>Ciprofibrate (300 μmol/L)</th>
<th>Gemfibrozil (300 μmol/L)</th>
<th>Bezafibrate (300 μmol/L)</th>
<th>Fenofibrate (300 μmol/L)</th>
<th>Wy14,643 (100 μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol 7α-Hydroxylase, % of Control</td>
<td>100</td>
<td>38±13* (4)</td>
<td>90±25 (4)</td>
<td>36±15† (3)</td>
<td>73±10† (4)</td>
<td>47±20* (6)</td>
</tr>
<tr>
<td>Sterol 27-Hydroxylase, % of Control</td>
<td></td>
<td>100</td>
<td>48±17† (4)</td>
<td>71±10† (4)</td>
<td>43±7* (3)</td>
<td>49±23* (6)</td>
</tr>
</tbody>
</table>

*P<0.01, †P<0.05, and ‡P<0.001 for control vs treated cells.

Values are a percentage of control and are mean±SD of independent experiments using hepatocytes from 3 to 6 rats (indicated between parentheses). Rat hepatocytes were incubated in the presence or absence of different fibrates or Wy14,643 for 24 hours. mRNA levels were assessed as described in Methods.
internal standards, were not affected. The reduction of the bile acid synthetic enzymes in cultured hepatocytes by fibrates and Wy14,643 is indicative of a direct effect of these compounds on the hepatocyte.

To investigate whether the downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase is a general characteristic of fibrates rather than a specific effect of ciprofibrate, we also studied the effect of other fibrates on mRNA levels of these enzymes (Table 1). Among the compounds tested, gemfibrozil appeared to be less active in the suppression of mRNA levels of both enzymes.

In addition to their PPARα-activating capacity, fibrates also activate PPARγ, although much more weakly. Therefore, we tested the effect of a high-affinity ligand for PPARγ, the thiazolidinedione, BRL49653. This ligand has (almost) no PPARα-agonizing activity. BRL49653 (10 μmol/L) was unable to suppress cholesterol 7α-hydroxylase (105±21%, n=4) and sterol 27-hydroxylase (97±25%, n=4) mRNA levels. This indicates that the suppressive effect of fibrates on both enzymes requires PPARα and not PPARγ activation.

Ciprofibrate Suppresses Cholesterol 7α-Hydroxylase Enzyme Activity and mRNA Levels In Vivo in Rats

To validate the effects of fibrates obtained in rat hepatocytes, we determined the effect of ciprofibrate on the major enzymes involved in bile acid synthesis in vivo in rats. Ciprofibrate (0.05% [wt/wt]) decreased cholesterol 7α-hydroxylase enzyme activity (−87±1%, P<0.005) and mRNA levels (−69±19%, P<0.05). The control value for the enzyme activity was 0.7±0.2 nmol/h per milligram protein. In contrast to the results in vitro in rat hepatocytes, we did not detect significant effects on sterol 27-hydroxylase.

PPARα−/− mice Are Refractory to the Suppressive Effects of Ciprofibrate on Cholesterol 7α-Hydroxylase and Sterol 27-Hydroxylase Expression

The effect of fibrates and the PPARα ligand Wy14,643 on cholesterol 7α-hydroxylase and sterol 27-hydroxylase implies a role for PPARα in the regulation of expression of both enzymes. To assess the direct involvement of PPARα in the regulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase, wild-type and PPARα−/− mice were treated with or without 0.05% (wt/wt) ciprofibrate. In wild-type mice, ciprofibrate reduced cholesterol 7α-hydroxylase and sterol 27-hydroxylase enzyme activities (−78% and −29%, respectively; Figure 4A), paralleled by a similar reduction of the respective mRNAs (−65% and −48%, Figure 4B and 4C). The decrease in the mRNA level of cholesterol 7α-hydroxylase in the wild-type mice was due to the suppression of gene transcription (Figure 4D). In contrast, sterol 27-hydroxylase gene transcription was not affected by fibrate treatment, indicating posttranscriptional regulation by ciprofibrate. As a control, the gene transcription of acyl coenzyme A oxidase, the rate-limiting enzyme in peroxisomal β-oxidation, the induction of which by fibrates is strictly PPARα-mediated, showed a strongly increased transcription in the wild-type but not in the PPARα−/− mice (Figure 4D).

The downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase resulted in a decline in the total output of fecal bile acids (−45%, Table 2). The fecal bile acid composition did not change on ciprofibrate treatment. The bile acids present in the feces were predominantly deoxycholate (40%), muricholate (α, β, and ω; 36%), and cholate (14%), with minor amounts of lithocholate, chenodeoxycholate, hyodeoxycholate, and ursodeoxycholate. Concomitantly, the fecal cholesterol output was increased 3-fold. In contrast, in PPARα−/− mice, these effects of ciprofibrate were completely absent (Figure 4 and Table 2). Food intake

![Figure 4](http://atvb.ahajournals.org/)

**Figure 4.** Effect of ciprofibrate on cholesterol 7α-hydroxylase and sterol 27-hydroxylase enzyme activity, mRNA, and transcriptional activity in wild-type (WT) and PPARα−/− mice. Cholesterol 7α-hydroxylase (closed bars) and sterol 27-hydroxylase (open bars) enzyme activity (A), mRNA levels (B and C), and transcriptional activity (D) were measured in WT and PPARα−/− mice treated with or without 0.05% (wt/wt) ciprofibrate. A and B. Values shown are expressed as a percentage of values obtained in WT mice on a control (chow) diet and are mean±SD of 8 mice. *P<0.05 compared with WT mice treated without ciprofibrate. C and D, Autoradiographs show representative blots (n=8 per group in panel C and n=4 per group in panel D) of the empty vector pUC19 (Vec), acyl coenzyme A oxidase (ACO), GAPDH, cholesterol 7α-hydroxylase (7αOH), and sterol 27-hydroxylase (27OH).

| Table 2. Effects of Ciprofibrate on Fecal Bile Acid and Cholesterol Secretion in WT and PPARα−/− Mice |
|---------------------------------|----------------|----------------|
| Bile Acids, μmol/d | Cholesterol, μmol/d |
| WT | 3.65±1.00 | 1.71±1.91 |
| WT + 0.05% ciprofibrate | 2.28±0.41* | 6.13±0.40† |
| PPARα−/− | 3.92±0.87 | 1.86±0.95 |
| PPARα−/− + 0.05% ciprofibrate | 3.41±1.60 | 2.79±1.05 |

WT indicates wild type. Values are mean±SD of individual feces samples of 6 mice. Fecal cholesterol and bile acid output in WT and PPARα−/− mice treated with or without 0.05% (wt/wt) ciprofibrate was determined as described in Methods.

*P<0.005 and †P<0.01 vs WT mice treated without ciprofibrate.
and feces production did not differ between the groups (data not shown). These results indicate that PPARα is involved in the fibrate-suppressed expression of cholesterol 7α-hydroxylase and sterol 27-hydroxylase in wild-type mice.

Discussion

In the present study, we showed that fibrates decrease bile acid synthesis by downregulation of cholesterol 7α-hydroxylase gene expression and sterol 27-hydroxylase mRNA levels in rodents, leading to a decreased bile acid secretion. Activation of the nuclear receptor PPARα by fibrates mediates the suppression of expression of both proteins: a direct involvement of PPARα was demonstrated by using PPARα−/− mice.

Our finding that fibrates suppress cholesterol 7α-hydroxylase gene expression in rats and mice parallels the findings in human studies, which show a lower enzyme activity of cholesterol 7α-hydroxylase concomitantly with a decrease in the amount of bile acids excreted during fibrate treatment.10,11,24 Additionally, we found that downregulation of sterol 27-hydroxylase may also contribute to reduction in bile acid synthesis. Whether sterol 27-hydroxylase is also reduced in humans treated with fibrates is not yet known. Nevertheless, a decreased bile acid synthesis by fibrate treatment in humans can contribute to the observed increase in the biliary lithogenicity index.9,11,31

The decrease in mRNA levels of cholesterol 7α-hydroxylase and sterol 27-hydroxylase was not a specific effect of ciprofibrate but rather a general characteristic of fibrates, inasmuch as all the fibrates tested showed suppression of both genes. Among the compounds tested, gemfibrozil appeared to be less active in the suppression of mRNA levels of both enzymes. No effect was observed in cultured rat hepatocytes with the high-affinity ligand for PPARγ, the thiazolidinedione BRL49653, indicating that PPARγ is not involved in the repression of cholesterol 7α-hydroxylase and sterol 27-hydroxylase expression. However, it should be noted that PPARγ levels are low in the liver.5

Whereas the effects of fibrates obtained in cultured rat hepatocytes on cholesterol 7α-hydroxylase enzyme activity and mRNA levels were comparable to the in vivo effect in rats, we did not detect significant changes in sterol 27-hydroxylase by ciprofibrate in rats. The reason for this discrepancy is unknown, but the finding was consistently made in all rats and may be related to a species difference in the sensitivity of the sterol 27-hydroxylase gene toward the effects of fibrates in vivo, because wild-type mice responded well to ciprofibrate treatment by suppression of sterol 27-hydroxylase and cholesterol 7α-hydroxylase activity and mRNA levels. This effect of ciprofibrate on mRNA levels and enzyme activity was completely abolished in PPARα−/− mice, showing the direct involvement of PPARα in the downregulation by fibrates. The decrease in mRNA levels of cholesterol 7α-hydroxylase in the wild-type mice treated with ciprofibrate was caused by a decreased transcription of the gene mediated by PPARα. No effect was found on transcriptional activity of the sterol 27-hydroxylase gene, indicating that the decrease in mRNA levels results from an effect of ciprofibrate on the stability of sterol 27-hydroxylase mRNA. Such a regulatory mechanism by a fibrate has also been shown for the LDL receptor, although in the opposite way.22 Our data on the downregulation of cholesterol 7α-hydroxylase gene expression are in line with promoter-reporter studies with the human and rat promoter in HepG2 cells.22,33 Marrapodi and Chiang22 showed that PPARα and the PPARα agonist Wy14,643 decreased cholesterol 7α-hydroxylase promoter activity by reducing the availability of hepatocyte nuclear factor-4, a transcription factor involved in the basal expression of cholesterol 7α-hydroxylase, which may explain the mechanism of suppression of cholesterol 7α-hydroxylase by PPARα agonists. On the other hand, the possibility that the negative effect of fibrates is due to stimulation of the negative nuclear receptor Rev-erba by PPARα cannot be excluded. Opposite data on the regulation of the human and murine cholesterol 7α-hydroxylase promoter, with the use of promoter-reporter studies in McArdle RH-777 cells, were also reported.23 In addition, no effect on cholesterol 7α-hydroxylase mRNA levels35 were reported from a study with mice that at the same time showed increased levels of sterol 12α-hydroxylase after treatment with the PPARα agonist Wy14,643. In our mice, we also measured sterol 12α-hydroxylase mRNA levels and found that ciprofibrate significantly (P<0.001) increased 12α-hydroxylase in the wild-type mice (100±17% [control diet] versus 178±27% [ciprofibrate diet]) but not in the PPARα−/− mice. The reason for these divergent data on cholesterol 7α-hydroxylase by fibrates or other PPARα agonists is unclear but may be related to the dosage, duration of the treatment, or the experimental system that was used. However, it should be noted that by a more physiological approach, our finding of suppression of cholesterol 7α-hydroxylase by fibrates was consistently found in vitro and in vivo and in different species at the level of gene transcription, mRNA, and enzyme activity.

The downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase in wild-type mice resulted in a decrease in total fecal bile acid mass. Concomitantly, the total amount of cholesterol in the feces of ciprofibrate-treated mice was 3-fold higher than that in the control group. The latter increase may result from a reduction in the intestinal bile acid pool size, leading to a reduced cholesterol absorption. Furthermore, a reduction in cholesterol absorption can lead to a rise in intestinal sterol synthesis, resulting in a higher endogenous cholesterol secretion.36

A direct involvement of PPARα in the expression of different genes in lipid metabolism has been reported, with suppression as well as induction of gene transcription being shown. Whereas (see review1) the genes encoding human apoA-I and apoA-II and the genes involved in fat metabolism (lipolysis of triglycerides and uptake and β-oxidation of fatty acids) are positively regulated, the human apoC-III gene and genes involved in the synthesis of fatty acids are negatively regulated. Our finding that the expression of cholesterol 7α-hydroxylase and sterol 27-hydroxylase is decreased on activation of PPARα indicates that PPARα is directly involved not only in the metabolism of triglycerides and fatty acids but also in the metabolism of cholesterol, although in the opposite way.

In conclusion, we have found that fibrates inhibit bile acid synthesis via PPARα-mediated downregulation of cholesterol 7α-hydroxylase and sterol 27-hydroxylase, which may con-
tribute to the formation of gallstones in patients after long-term therapy with fibrates.

Acknowledgments

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