Activation of intestinal peroxisome proliferator-activated receptor-α increases high-density lipoprotein production

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Aims
Peroxisome proliferator-activated receptor (PPAR)-α is a transcription factor controlling lipid metabolism in liver, heart, muscle, and macrophages. Peroxisome proliferator-activated receptor-α activation increases plasma HDL cholesterol and exerts hypotriglyceridaemic actions via the liver. However, the intestine expresses PPAR-α, produces HDL and chylomicrons, and is exposed to diet-derived PPAR-α ligands. Therefore, we examined the effects of PPAR-α activation on intestinal lipid and lipoprotein metabolism.

Methods and results
The impact of PPAR-α activation was evaluated in term of HDL-related gene expression in mice, ex vivo in human jejunal biopsies and in Caco-2/TC7 cells. Apolipoprotein-AI/HDL secretion, cholesterol esterification, and trafficking were also studied in vitro. In parallel to improving plasma lipid profiles and increasing liver and intestinal expression of fatty acid oxidation genes, treatment with the dual PPAR-α/δ ligand GFT505 resulted in a more pronounced increase in plasma HDL compared with fenofibrate in mice. GFT505, but not fenofibrate, increased the expression of HDL production genes such as apolipoprotein-AI and ATP-binding cassette A1 transporter in murine intestines. A similar increase was observed upon PPAR-α activation of human biopsies and Caco-2/TC7 cells. Additionally, HDL secretion by Caco-2/TC7 cells increased. Moreover, PPAR-α activation decreased the cholesterol esterification capacity of Caco-2/TC7 cells, modified cholesterol trafficking, and reduced apolipoprotein-B secretion.

Conclusion
Peroxisome proliferator-activated receptor-α activation reduces cholesterol esterification, suppresses chylomicron, and increases HDL secretion by enterocytes. These results identify the intestine as a target organ of PPAR-α ligands with entero-hepatic tropism to reduce atherogenic dyslipidaemia.

Keywords
PPAR-α • Intestine • HDL • Dyslipidaemia

Introduction
High levels of low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol are risk factors for cardiovascular disease. In association with lifestyle intervention, LDL cholesterol-lowering therapy with statins is highly efficient to reduce cardiovascular risk, but has only modest effects on HDL cholesterol. Furthermore, low HDL cholesterol is an independent risk factor, which contributes to the persistent residual cardiovascular risk in statin-treated patients. Therefore, raising HDL may be a promising strategy to attenuate the residual cardiovascular risk in statin-treated patients.

In enterocytes, dietary lipids are packaged with apolipoprotein-B48 into chylomicrons secreted into the lymph. Several studies demonstrated that post-prandial chylomicrons contribute to lipid accumulation in the arterial wall and to atherogenesis. Animal studies have shown that the intestine produces HDL. Indeed, intestinal-specific deletion of ATP-binding cassette A1 transporter

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(ABCA1) in mice results in a 30% decrease in HDL cholesterol levels. Furthermore, exercise-training enhances HDL cholesterol in rats in correlation with increased intestinal ABCA1 mRNA expression. Interestingly, human intestinal mucosa was shown to produce apolipoprotein-AI (apoAI) and HDL.

Peroxisome proliferator-activated receptor-α is a transcription factor belonging to the nuclear receptor superfamily and activated by fatty acids, eicosanoids, and bile acids. Peroxisome proliferator-activated receptor-α controls lipid and glucose metabolism in several tissues and cell types including liver, heart, kidney, muscle, and macrophages. Peroxisome proliferator-activated receptor-α activation enhances hepatic fatty acid oxidation and peripheral triglyceride (TG) clearance, thus reducing hypertriglyceridaemia. Peroxisome proliferator-activated receptor-α increases hepatic apoAI synthesis and ABCA1 expression, resulting in increased plasma HDL cholesterol. In addition, PPAR-α activation controls cholesterol trafficking in human macrophages and raises cholesterol efflux via ABCA1 contributing to increased reverse cholesterol transport. Since diet-derived compounds (fatty acids and phospholipids) can activate PPAR-α and since the intestine is the site of dietary lipid absorption, it is highly exposed to PPAR-α ligands. The role of PPAR-α in the intestine has been addressed in only a few studies. Previous studies in rodents did not evidence pronounced effects of the PPAR-α ligand fenofibrate (FF) in the intestine contrary to the liver, possibly because of its rapid urinary excretion and hence relatively low intestinal exposure. However, a genome wide analysis of intestinal RNA of mice treated with Wy14643 revealed that PPAR-α controls numerous metabolic pathways and in particular lipid metabolism, pointing to a role for PPAR-α in this organ.

We thus investigated whether intestinal PPAR-α activation regulates HDL production. Treatment of mice with two different PPAR agonists, FF, a pure PPAR-α agonist and GFT505, a PPAR-α/δ modulator, which, unlike FF, undergoes extensive enterohepatic cycling, resulted in comparable hypotriglyceridaemic effects. However, only GFT505 treatment increased apoAI and ABCA1 mRNA levels in the murine intestine, an effect which was associated with a more pronounced increase in plasma HDL levels. These effects were not observed in PPAR-α-deficient mice. Using the human Caco-2/TC7 model cultured on porous filters, we found that PPAR-α activation reduces the secretion of chylomicrons while enhancing HDL production probably by increasing ABCA1 expression and apoAI secretion, and by reducing cholesterol esterification. The physiological relevance of these regulatory processes was verified in human jejunal biopsies. Collectively, our data suggest that the intestine is a target organ for entero-hepato-tropic PPAR-α ligands to increase HDL, an effect which may result in a reduction in the residual cardiovascular risk.

**Methods**

For details, see Supplementary material online, Methods.

**Animal study**

Wild-type (+/+) and homozygous (−/−) PPAR-α-deficient female mice in the apoE2-KI background (12-week-old) fed a western diet were treated for 14 days with GFT505 (10 or 30 mpk) or FF (200 mpk) or carboxy methyl cellulose (0.5%).

**Human intestine culture**

Intestinal biopsies were recovered during gastric bypass surgery from obese patients enrolled in the ABOS study (ClinicalTrials.gov, NCT01129297).

**Caco-2/TC7 cell culture and peroxisome proliferator-activated receptor-α knockout**

Caco-2/TC7 were grown as described. For stable PPAR-α invalidation and culture details, see Supplementary material online, Methods.

**High-density lipoprotein preparation**

High-density lipoprotein (d = 1.12–1.21 g/mL) from human plasma and basolateral media of Caco-2/TC7 were prepared by sequential ultracentrifugations. For details in preparation, electron microscopy, and apolipoprotein quantification, see Supplementary material online, Methods.

**Post-prandial micelle preparation**

Synthetic micelles are prepared as described in Béaslas et al.

**Confocal microscopy**

For details, see Supplementary material online, Methods and Hennuyer et al.

**Cholesterol esterification assay**

Caco-2/TC7 were incubated with [1H] cholesterol micelles (7.5 μCi/ well), lipids were extracted and separated by TLC.

**Macrophage cell culture and cholesterol efflux**

Mononuclear cells were isolated from the blood of healthy donors, cholesterol loaded with [3H] cholesterol AcLDL, and efflux assays performed as described.

**Statistics**

For details, see Supplementary material online, Methods.

**Results**

Peroxisome proliferator-activated receptor-α activation in mice and in human jejunal biopsies increases the expression of genes involved in intestinal high-density lipoprotein production

To determine whether PPAR-α activation regulates HDL production in the small intestine, apoE2-KI mice, which display a similar lipid response to PPAR-α agonists as humans, were fed a western diet with daily oral administration of FF or the dual PPAR-α/δ agonist GFT505 for 14 days. As reported, FF decreased plasma TGs and total cholesterol (Table 1). Similarly, GFT505 lowered plasma TG and total cholesterol, whereas plasma HDL cholesterol increased ~2.5-fold upon treatment with FF, the increase in HDL cholesterol was significantly more...
pronounced upon GFT505 (Table 1). Fenofibrate and GFT505 induced the hepatic expression of PPAR-α target genes, such as acyl coenzyme A oxidase-1 (ACOX1) at a similar extent (Supplementary material online, Figure S1) indicating equipotent dosing. The effects of GFT505 on TG and HDL cholesterol were abolished in the PPAR-α-deficient apoE2-KI mice, demonstrating that the effects are PPAR-α dependent (Supplementary material online, Table S1). Interestingly, a decrease, albeit less pronounced, in total and non-HDL cholesterol was maintained in GFT505-treated PPAR-α-deficient apoE2-KI mice, suggesting a contribution of its PPAR-δ activity on these lipid parameters (Supplementary material online, Table S1). GFT505-treated mice displayed a PPAR-α-dependent higher ABCA1 and apoAI gene expression in the small intestine compared with untreated mice (Figure 1A and B), whereas FF did not regulate ABCA1 nor apoAI mRNA expression (Figure 1C and D). Treatment of mice with GW0742, a pure PPAR-δ agonist, did not modify ABCA1 nor ApoAI gene expression (not shown).

To determine whether PPAR-α activation also regulates these genes in the human intestine, human jejunal biopsies were treated with GFT505 and a synthetic PPAR-α ligand, GW7647, for 18 h. Both compounds significantly increased ABCA1 and apoAI mRNA expression (Figure 1E and F).

**Peroxisome proliferator-activated receptor-α activation increases the production of high-density lipoprotein in Caco-2/TC7**

Based on observations in mice, we hypothesized that the up-regulation of ABCA1 and apoAI gene expression observed upon PPAR-α activation would translate in increased intestinal HDL production. To test this, we used an in vitro model of the human intestinal barrier, polarized Caco-2/TC7 cells grown on porous filters. Peroxisome proliferator-activated receptor-α expression was knocked-down (ShPPAR-α) or not (ShControl) by lentiviral infection and cells were subsequently incubated with GW7647. High-density lipoproteins secreted by Caco-2/TC7 were isolated by ultracentrifugation and analysed by electron microscopy. Peroxisome proliferator-activated receptor-α activation increased the number of HDL secreted at the basolateral side of Caco-2/TC7 (Figure 2A). Apolipoprotein-AI secreted in the HDL fraction increased when non-infected Caco-2/TC7 and ShControl-infected cells were treated with GW7647, whereas apoAI secretion was not modified upon treatment of ShPPAR-α-infected cells by GW7647 (Figure 2B), demonstrating that this effect is PPAR-α dependent. Interestingly, the quantity of apoAI in the chylomicron fraction was not modified (not shown). To evaluate the HDL functionality, we investigated their capacity to promote cholesterol efflux from macrophages. Human monocyte-derived macrophages were cholesterol loaded with [3H] cholesterol AcLDL and subsequently incubated with HDL secreted by Caco-2/TC7 treated with GW7647 for 24 h. Equivalent volumes of isolated HDL from non-infected or ShControl-infected Caco-2/TC7 treated with GW7647-enhanced macrophage cholesterol efflux compared with HDL isolated from vehicle-treated cells (Figure 2C). High-density lipoprotein from ShPPAR-α-infected cells treated with GW7647 did not show enhanced efflux capacity compared with HDL from untreated cells. ATP-binding cassette A1 transporter gene expression increased upon GW7647 treatment in a PPAR-α-dependent manner (Figure 2D). A similar up-regulation was observed with GFT505 (Supplementary material online, Figure S2). In contrast to the in vivo and ex vivo response, apoAI mRNA was not induced by PPAR-α agonists in Caco-2/TC7 (not shown).

**Peroxisome proliferator-activated receptor-α activation modulates cholesterol distribution, increases cytoplasmic lipid droplet formation, and reduces apolipoprotein secretion in Caco-2/TC7**

To test the effect of PPAR-α activation on intestinal cholesterol absorption known to occur in sequential steps, from uptake at the brush border membrane and transport into the cell to packaging and secretion of lipoproteins at the basolateral side of enterocytes, Caco-2/TC7 were incubated for 24 h with [3H] cholesterol micelles and activated with GW7647 24 h before and 24 h after cholesterol loading. The cholesterol content in the apical membrane, the cellular compartment, and the basolateral medium of Caco-2/TC7 was not modulated by GW7647 (not shown), suggesting that PPAR-α regulates neither total cholesterol uptake nor efflux by enterocytes. Next, GW7647-treated Caco-2/TC7 were incubated with fluorescent NBD cholesterol-containing micelles for 4 h, followed by non-fluorescent micelles for an additional 4 h period. Quantitative analysis of fluorescence intensity at each optical slice showed that, without affecting the total amount of absorbed cholesterol (assessed by radioactive assay), GW7647 treatment modifies cholesterol distribution-inducing retention of cholesterol in the subapical compartments (Figure 3A). Interestingly, as shown by confocal microscopy (Figure 3B), GW7647 also increased the size of cholesterol-containing lipid droplets in the apical and basolateral compartments.

Since PPAR-α activation in Caco-2/TC7 does not affect the total amount of cholesterol uptake and efflux, we hypothesized that PPAR-α activation may decrease apoB-containing lipoprotein...
secretion to counterbalance the increase of secreted HDL. Indeed, GW7647 decreased apoB secretion in the basolateral compartment of Caco-2/TC7 (Figure 3C) as previously shown.  

Peroxisome proliferator-activated receptor-α activation decreases cholesterol esterification capacity of Caco-2/TC7

Cholesterol trafficking from the plasma membrane to the endoplasmic reticulum is a limiting step for its esterification and subsequent secretion in chylomicrons. To address whether, by interfering with cholesterol trafficking, PPAR-α reduces cholesterol esterification, Caco-2/TC7 were incubated for 24 h with [\(^{3}H\)]cholesterol micelles and activated with GW7647 before and 24 h after cholesterol loading. Peroxisome proliferator-activated receptor-α activation decreased the quantity of [\(^{3}H\)]cholesteryl esters (CE) assayed by TLC both in the cells (Figure 4A) and secreted in the basolateral compartment (Figure 4B). The decreased CE production does not result only from a perturbation of cholesterol trafficking since ACAT-2 (acyl coenzymeA:cholesterol acyltransferase-2) gene expression was also decreased (Figure 4C).
Peroxisome proliferator-activated receptor-α activation increases the expression of lipid droplet formation genes in Caco-2/TC7 cells

To investigate the mechanism behind the increase in the cytoplasmic lipid droplet size upon PPAR-α activation (Figure 3B), we analysed the expression of lipid droplet-associated proteins. Peroxisome proliferator-activated receptor-α activation increased mRNA levels of perilipin-2 (PLIN2), which coats lipid droplets with its partner ABHD5 (AB hydrolase domain-containing-5) (Figure 5A).36 In line, ABHD5 gene expression was also increased (Figure 5B). Furthermore, the increase in PLIN2 was strongly reduced and the increase in ABHD5 was totally abolished in ShPPAR-α-infected cells treated with GW7647 (Supplementary material online, Figure S3A and B). In addition, PLIN2 and ABHD5 mRNA levels increased only in intestines of GFT505-treated PPAR-α+/+, but not PPAR-α−/− apoE2-KI mice (Supplementary material online, Figure S3C and D). The increased PLIN2 and ABHD5 gene expression was also observed, albeit less pronounced, in human jejunal biopsies treated with GW7647 or GFT505 (Figure 5C and D).

Peroxisome proliferator-activated receptor-α activation increases fatty acid oxidation genes in human enterocytes and murine intestines

In addition to the decreased apoB secretion (Figure 3C) and in accordance with previous data showing that intestinal PPAR-α activation suppresses post-prandial lipidemia by increasing fatty acid oxidation,25,34 PPAR-α ligands increased mRNA levels of fatty
acid oxidation genes including carnitine palmitoyl transferase-1 (CPT-1A), ACOX1, and long-chain acyl-CoA synthetase family member 5 (ACSL5) (Figure 6A–C) in Caco-2/TC7. Carnitine palmitoyl transferase-1 and ACOX1 mRNA levels were increased in human biopsies treated with PPAR-\(\alpha\) ligands (Figure 6D and E). The effect of GW7647 on CPT-1A and ACSL5 was strongly reduced in treated ShPPAR-\(\alpha\)-infected cells and totally abolished for ACOX1 (Supplementary material online, Figure S4A–C).

GFT505 treatment increased the intestinal expression of fatty acid oxidation genes in a PPAR-\(\alpha\)-dependent manner in apoE2-KI mice (Supplementary material online, Figure S4A–C). GFT505 treatment increased the intestinal expression of fatty acid oxidation genes in a PPAR-\(\alpha\)-dependent manner in apoE2-KI mice (Supplementary material online, Figure S4A–C). The expression of fatty acid oxidation genes was induced in intestines of FF-treated mice, in contrast to the lack of regulation of HDL-related genes, suggesting that FF acts as a selective PPAR modulator in the intestine (Supplementary material online, Figure S4F–H).

Interestingly, PPAR-\(\alpha\) ligands increased cAMP responsive element binding protein-3 like-3 (CREB3L3) mRNA levels in Caco-2/TC7 (Supplementary material online, Figure S5A), a transcription factor involved in the regulation of TG metabolism for which mutations were recently associated with hypertriglyceridaemia in humans. The induction of CREB3L3 was observed in human biopsies treated with GW7647 and GFT505 (Supplementary material online, Figure S5B). Furthermore, PPAR-\(\alpha\) ligands did not regulate this gene in ShPPAR-\(\alpha\)-infected cells nor in the PPAR-\(\alpha\)-deficient mice (Supplementary material online, Figure S5C and D). Collectively, these results indicate that PPAR-\(\alpha\)
Figure 4 Peroxisome proliferator-activated receptor-α activation decreases cholesterol esterification in Caco-2/TC7. Caco-2/TC7 were incubated with [3H] cholesterol micelles (7.5 μCi/well) for 48 h. GW7647 (600 nM) was added 24 h before and during the [3H] cholesterol loading. Intracellular lipids (A) and lipids secreted in the basolateral compartment (B) were extracted and separated by TLC. Results are expressed as means of CE percent of total cholesterol (± SEM). Q-PCR analysis of acyl coenzymeA:cholesterol acyltransferase-2 (C) was performed on GW7647 (600 nM)-treated Caco-2/TC7 for 24 h. Values are expressed as means ± SD (t-test; *p < 0.05; **p < 0.01 vehicle vs. treatment).

Figure 5 Peroxisome proliferator-activated receptor-α activation increases cytoplasmic lipid droplet formation-associated genes in Caco-2/TC7 and in human jejunal biopsies. Q-PCR analysis of perilipin-2 (A and C) and AB hydrolase domain-containing-5 (B and D) was performed on RNA isolated from Caco-2/TC7 (A and B) and human jejunal biopsies (C and D) treated with GW7647 (600 nM) or GFT505 (1 μM) for 24 or 18 h, respectively. Values are expressed as means ± SD (t-test; *p < 0.05; **p < 0.01; ***p < 0.001 vehicle vs. treatment).
Activation increases the fatty acid oxidation pathway, the transcription factor CREB3L3 and increases the lipid droplet size.

**Discussion**

In addition to the liver, the intestine has emerged more recently as a central organ participating in lipid metabolism by regulating lipid absorption, trafficking and lipoprotein metabolism through its involvement in the production of chylomicrons, HDL and in trans-intestinal cholesterol excretion. Thus, both the liver and the intestine are involved in the regulation of whole body lipoprotein metabolism and play a role in the pathophysiology of atherogenic dyslipidaemia. Fibrates, PPAR-α agonists, are often used in the treatment of dyslipidaemia characterized by high TG and low HDL cholesterol levels. Until now, the effects of PPAR-α agonists on the improvement of lipid profiles were essentially attributed to their action on the liver and the arterial wall. However, PPAR-α is also expressed in the intestine. In a genome wide analysis of intestinal RNA isolated from PPAR-α ligand-treated mice, intestinal PPAR-α was found to regulate fatty acid metabolism. Moreover, PPAR-α activation decreased the secretion of apoB by enterocytes. Therefore, we studied whether

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**Figure 6** Peroxisome proliferator-activated receptor-α activation increases fatty acid oxidation genes in Caco-2/TC7 and in human jejunal biopsies. Q-PCR analysis of CPT-1 (A and D), acyl coenzymeA oxidase-1 (B and E), and long-chain acyl-CoA synthetase family member 5 (C) was performed on RNA isolated from Caco-2/TC7 (A–C) or human jejunal biopsies (D and E) treated with GW7647 (600 nM) or GFT505 (1 μM) for 24 or 18 h, respectively. Values are expressed as means ± SD (t-test; *p < 0.05; **p < 0.01; ***p < 0.001 vehicle vs. treatment).
intestinal PPAR-α activation could contribute to the control of HDL metabolism. Using a humanized mouse model of mixed dyslipidaemia, the apoE2-KI mouse, we show in line with previous studies that FF and GFT505 treatments improve the lipid profile by decreasing TG, total cholesterol, and by increasing HDL cholesterol. In our study, the HDL increasing effect of GFT505 was more pronounced than FF at concentrations (10 vs. 100 mpk) inducing similar expression levels of ACOX1 in the liver. Although FF did induce intestinal fatty acid oxidation-related genes, suggesting that FF can activate intestinal PPAR-α, only GFT505 induced the expression of intestinal HDL production-related genes such as apoAI and ABCA1. Thus, GFT505 and FF differ in the spectrum of regulated target genes, giving the rational to design new selective PPAR modulators. Furthermore, the different activity of FF vs. GFT505 on intestinal gene expression is due to the extensive enterohepatic recycling and faecal excretion of GFT505, whereas FF is excreted in the urine (Rubenstrunk A et al., manuscript in preparation).

Using the Caco-2/TC7 model, we confirmed that PPAR-α ligands decrease apoB secretion, suggesting a decrease in TG-rich lipoprotein secretion. Moreover, we showed that PPAR-α activation increased ABCA1 gene expression and apoAI secretion. Although the previously reported absence of apoAI mRNA regulation demonstrates the limits of the Caco-2/TC7 model (apoAI mRNA was increased in PPAR-α agonist-treated human jejunal biopsies), PPAR-α activation increased the number of HDL secreted, which in turn enhanced cholesterol efflux from human monocyte-derived macrophages.

As we did not observe any difference in the levels of apical cholesterol uptake nor in the levels of cholesterol secreted at the basal side of treated Caco-2/TC7, we hypothesized that PPAR-α activation induces a shift of the absorbed cholesterol from the chylomicron to the HDL production pathway. This hypothesis is strengthened by the fact that less cholesterol was esterified in treated cells. The decrease in esterification may be explained by a decrease in ACAT-2 gene expression which results, as shown in human hepatic cells and macrophages, in a decrease in ACAT-2 activity which is also under the control of substrate availability at its site of action, the endoplasmic reticulum. By investigating cholesterol trafficking using a fluorescent cholesterol derivative, we observed cholesterol retention in the subapical compartment of GW7647-treated Caco-2/TC7 and an increase in the lipid droplet size concomitantly with an increase in PLIN2 expression, which is necessary for lipid droplet stabilization, and ABHD5, sequensted by PLIN2 at the lipid surface. We did not observe any regulation of Rab proteins that are required for vesicular trafficking, nor NPC1 and NPC2 (not shown) which contrasts to macrophages. Thus, the mechanism responsible for the effects of PPAR-α activation on intracellular cholesterol trafficking remains to be clarified. However, the decrease in ACAT-2 gene expression was concomitant to an increase in CPT-1A expression, which could decrease the availability of fatty acid for cholesterol esterification, as shown in macrophages. In line, PPAR-α activation increased the esterase arylacetamide deacylase (not shown) and ACSL5 gene expression, both associated with a reduction in TG accumulation and an increase in fatty acid oxidation in rodent hepatocytes. Different mechanisms could thus act in concert to divert cholesterol from esterification: decrease in ACAT-2 gene expression, reduction in fatty acid availability through an increase in CPT-1A expression and fatty acid oxidation enzymes and/or retention in cholesterol in lipid droplets.

It has been recently shown that a mutation of CREB3L3 in humans is associated with hypertriglyceridaemia. cAMP responsive element-binding protein-3-like-3-deficient mice are hypertriglyceridaemic and display defective TG clearance. Interestingly, we observed a PPAR-α-dependent up-regulation of CREB3L3 expression in GW7647-treated Caco-2/TC7 and in GFT505-treated mice. The importance of the regulation of this gene expression and its implication in the modulation of lipid homeostasis upon PPAR-α activation still remain to be established.

The results of our study collectively show that the increase in ABCA1 expression, the modification in cholesterol trafficking and the decreased cholesterol esterification capacity induced by PPAR-α activation potentially contribute to the overall effects on intestinal secretion of apoAI-containing HDL by Caco-2/TC7. The transcriptional regulation of HDL-related genes was observed in mice and in human jejunal biopsies. Therefore, the decrease in TG and the increase in HDL levels observed in PPAR-α agonist-treated patients could be due, in addition to hepatic actions, to effects in the intestine. Our work strengthens the idea that the intestine is an important target organ for strategies to increase HDL production via the activation of intestinal PPAR-α. Moreover, our data demonstrate the relevance of designing new specific PPAR-α modulators with appropriate tissue and gene selective profiles.

Supplementary material
Supplementary material is available at European Heart Journal online.

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Conflict of interest: none declared.

References
Activation of intestinal peroxisome proliferator


