Physiological Differences between Human and Rat Primary Hepatocytes in Response to Liver X Receptor Activation by 3-[3-[N-(2-Chloro-3-trifluoromethylbenzyl)-(2,2-diphenylethyl)amino]propyloxy]phenylacetic Acid Hydrochloride (GW3965)

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ABSTRACT

The liver is central to the maintenance of glucose and lipid homeostasis, and liver X receptors (LXRs) are key regulators of expression of the genes involved. So far, effects of activation of LXR in human hepatocytes have not been well characterized. Here we show that treatment of primary human hepatocytes with the synthetic LXR ligand 3-[3-[N-(2-chloro-3-trifluoromethylbenzyl)-(2,2-diphenylethyl)amino]propyloxy]phenylacetic acid hydrochloride (GW3965) results in reduced output of bile acids and very low density lipoprotein triglycerides and induced expression of adipose differentiation-related protein accompanied by increased lipogenesis. Genome-wide expression profiling identified novel human LXR target genes in the glycolytic and lipogenic pathways and indicated that LXR activation reduced hepatic insulin sensitivity. Comparative experiments showed significant differences in the response to GW3965 between human and rat hepatocytes, raising the question as to how well rodent models reflect the human situation. In summary, the risk of hepatic steatosis upon pharmaceutical targeting of LXR may be a particularly serious consequence in humans.

When adaptive physiological strategies to cope with surplus energy become exceeded, associated pathogeneses such as glucose intolerance, insulin resistance, and dyslipidemia develop. Members of the nuclear receptor family have emerged as key metabolic sensors regulating the expression of genes involved in intermediary metabolism (Francis et al., 2003; Shulman and Mangelsdorf, 2005) and LXRα and LXRβ, acting as cholesterol sensors, are considered to be potential drug targets for the alleviation of symptoms of metabolic diseases (Zelcer and Tontonoz, 2006).

In rodents but not in humans, LXR activation enhances hepatic cholesterol catabolism partly through increased expression of cytochrome P450 7A1, the rate-limiting enzyme in the classic conversion of cholesterol to bile acids (Chiang et al., 2001). Moreover, it has been shown that LXR agonists

ABBREVIATIONS: LXR, liver X receptor (gene symbols: LXRα, NR1H3 and LXRβ, NR1H2); GO, Gene Ontology; SLR, signal log ratio; ADFP, adipose differentiation-related protein; ChREBP, carbohydrate response element binding protein (gene symbol MLXIPL); qPCR, quantitative polymerase chain reaction; VLDL, very low density lipoprotein; TG, triglyceride; GCK, glucokinase; PKLR, liver pyruvate kinase; PEPCK, phosphoenolpyruvate carboxy kinase (gene symbol PCK1); GLUT2, glucose transporter 2 (gene symbol SLC2A2); SREBP, sterol response element binding protein; FASN, fatty acid synthase; SCD, stearoyl CoA desaturase; DGAT, diacylglycerol transferase; ABC, ATP-binding cassette; LDLR, low density lipoprotein receptor; CPT, carnityl palmitoyl transferase; GW3965, 3-[3-[N-(2-chloro-3-trifluoromethylbenzyl)-(2,2-diphenylethyl)amino]propyloxy]phenylacetic acid hydrochloride; T0901317, N-[2,2,2-trifluoroethyl]-N-[4-[[2,2,2,-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide.
Materials and Methods

Primary Hepatocyte Cultures. Primary human hepatocytes were isolated from resected liver tissue or unused donor liver tissue essentially as described by Strom et al. (1996). The Institutional Review Board at the University of Pittsburgh and the Regional Ethical Review Board in Stockholm approved the study. Primary rat hepatocytes were isolated from 7-week-old female Sprague-Dawley rats (Scanbur, Stockholm, Sweden) as described previously (He­lander et al., 2003). The Stockholm South Ethical Committee of the Swedish National Animal Welfare Agency approved all animal procedures. Hepatocytes were seeded onto Biomatrix-coated dishes at a density of 3.5 × 10^5 per 60-mm dish or 10 × 10^5 per 100-mm dish. Biomatrix was prepared from Engelbreth-Holm-Swarm sarcoma propagated in C57BL/6 female mice as described previously (Schuetz et al., 1988). Human hepatocytes were maintained in hepatocyte maintenance medium (Lonza Walkersville, Walkersville, MD) supplemented with penicillin (100 U/ml), streptomycin (100 μg/ml), and gentamicin (100 μg/ml), and rat hepatocytes were maintained in Williams’ E medium (Invitrogen, Paisley, Scotland, UK) supplemented with penicillin (100 U/ml) and streptomycin (100 μg/ml). Insulin (Actrapid; NovoNordisk A/S, Denmark) was added to the culture media at 0.3, 3, or 30 nM as indicated. These concentrations represent physiologically relevant levels of insulin in the hepatic portal circulation in normal human subjects and/or in insulin-resistant individuals. The media have a glucose concentration of 11 mM, gentamicin (100 μg/ml), and the 0.3 nM insulin culture condition as calibrators as indicated in the figures. The concentrations in the VDLF fraction were calculated by integration of the individual chromatograms using the EZChrom Elite software (Scientific Software; Agilent Technologies).

Triglyceride, Cholesterol, and Bile Acid Analysis of Cell Culture Medium. Lipoproteins were separated essentially as described previously (Parini et al., 2006) using a Superose-6 PC 3.2/30 column (GE Healthcare, Chalfont St. Giles, Buckinghamshire, UK). Cholesterol and triglycerides were assayed online using the Chol Roche/Hitachi and the TG Roche/Hitachi colorimetric enzymatic kits, respectively (Roche Diagnostic GmbH, Mannheim, Germany). The concentrations in the VDLF fraction were calculated by integration of the individual chromatograms using the EZChrom Elite software (Scientific Software; Agilent Technologies).

Bile acids from cell culture media were measured as described previously (Elli et al., 1998). Trimethylsilyl ether derivatives were analyzed by gas chromatography/mass spectrometry (Column HP-1, 6890N GC System, 5973 Mass Selective Detector; Agilent Technologies).

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peroxidase-linked anti-rabbit IgG (1:5000) (GE Healthcare). Anti-body signals were visualized on X-ray film using the enhanced chemiluminescence blotting analysis system (Amersham Biosciences).

**Cellular Triglyceride Analysis.** In brief, cellular lipids from $10 \times 10^6$ cells were extracted in CHCl$_3$/MeOH (2:1 v/v) and dried under N$_2$ at 40°C. Lipids were resolubilized in 3 ml of CHCl$_3$/MeOH (2:1 v/v), and 0.6 ml of 0.1 M H$_2$SO$_4$ was added. After transferring the lower phase to a new glass tube, triglycerides (TG) were determined in 200-μl aliquots by a colorimetric enzymatic kit (Roche Diagnostics GmbH).

**Results**

**Gene Expression Profiling of Insulin and LXR Signaling in Cultured Primary Human Hepatocytes.** The microarray experiment was performed on primary human hepatocytes cultured at 0.3, 3, or 30 nM insulin ± 2 μM GW3965 for the last 18 h of the 96-h culture time. Correlation coefficients ($r^2$) of pair-wise comparisons were ≥0.94 between any samples and ≥0.99 for replicate samples comparing the complete 55,000 array probe sets, indicating a very homogeneous material (Fig. 1A). Further data analysis was focused on genes annotated for a role in lipid and/or carbohydrate metabolism and/or in the generation of precursor metabolites and energy (available at http://www.geneontology.org) (see Supplemental Table S1). Using pair-wise comparisons (Fig. 1, B and E), we observed that the expression of more than twice as many genes was suppressed, 84, than induced, 38, by insulin (Fig. 1, C and D). A similar trend was observed with GW3965 treatment in which expression of 105 genes was suppressed whereas the expression of 85 genes was induced by the LXR agonist (in 0.3, 3, and 30 nM insulin combined) (Fig. 1, F and G). It is noteworthy that the number of genes regulated by insulin was markedly reduced in the presence of GW3965. Furthermore, LXR regulation of a number of genes was affected by the insulin concentration, particularly among the down-regulated genes (Supplemental Fig. 1. Gene regulatory effects of insulin (Ins) and GW3965 (GW) in cultured primary human hepatocytes. Cells were cultured for 96 h in 0.3, 3, or 30 nM insulin ± 2 μM GW for the last 18 h. RNA samples from duplicate dishes were subjected to microarray analysis. A, $r^2$ values in pair-wise comparisons for all 55,000 probe sets. B and E, experimental design and pair-wise comparisons were used (details provided in under Materials and Methods). C, D, F, and G, annotated genes with a function in lipid metabolism, carbohydrate metabolism, and generation of precursor metabolites and energy were clustered and presented in Venn diagrams. Genes with increased (C) or decreased (D) expression with increased concentration of insulin. Genes in each main group (A–D; comparisons shown at top) were subgrouped (e–s) according to their regulation by the different concentrations of insulin in the absence or presence of GW. Genes with increased (F) or decreased (G) expression by GW at 0.3 (E), 3 (F), and 30 nM (G) insulin (comparisons shown at top). Genes in each main group (E, F, and G) were subgrouped (e–k) according to their regulation by GW at different concentrations of insulin. The subgroups e–s or e–k are defined in detail in Supplemental Table S1.
Table S1). No selected regulation proved erroneous when relative expression levels were verified by qPCR, demonstrating high reliability of the microarray data analysis approach.

**LXR Suppresses Bile Acid Synthesis in Primary Human Hepatocytes.** LXR activation suppressed expression of the rate-limiting enzyme CYP7A1 in the classic pathway of bile acid biosynthesis in primary human hepatocytes (Fig. 2A) and enhanced the expression of the rat ortholog in rat hepatocytes (data not shown), in accordance with previous reports (Goodwin et al., 2003). Both cholic acid and chenodeoxycholic acid levels in the culture medium were reduced by GW3965 treatment (Fig. 2B).

**LXR Suppresses Key Glycolytic Genes.** Anticipated dose-dependent insulin regulation of key genes in the glycolytic and gluconeogenetic pathways was observed; at 30 nM insulin compared with 0.3 nM, glucokinase (GCK) was induced more than 50-fold, liver pyruvate kinase (PKLR) was induced 2- to 5-fold, and phosphoenolpyruvate carboxy kinase (PEPCK) was reduced 2- to 10-fold (Fig. 3, A–C). Similar effects were observed in rat hepatocytes (Fig. 3, F–H), and in both human and rat hepatocytes, GW3965 further reduced PEPCK expression (Fig. 3, C and H). We were surprised to find that in human hepatocytes, GW3965 markedly suppressed the expression of GCK, glucose transporter 2 (GLUT2), and PKLR, and in most experiments ChREBP as well, conveying transcriptional regulation by glucose (Uyeda and Repa, 2006). (Fig. 3, A B, D, and E). These genes in rat hepatocytes were marginally affected by GW3965 or tended to be enhanced (Fig. 3, F G, I, and J). The effect of LXR activation on genes in the glucose metabolic pathway in hepatocytes from five individual donors cultured in 3 nM insulin is presented in Table 1; with the exception of ChREBP, the effects were highly significant. Induced expression of ChREBP in rat hepatocytes would be in line with the recent demonstration that the LXR agonist T0901317 induces ChREBP in mouse liver (Cha and Repa, 2007). Moreover, in human hepatocytes, GW3965 induced the expression of glucokinase regulatory protein (Supplemental Table S1), encoding a protein that retains GCK in the nucleus and thereby reducing GCK activity (Shiota et al., 1999).

**LXR-Induced Fatty Acid Synthesis Does Not Lead to Increased VLDL-TG Secretion.** The expression of genes in the fatty acid biosynthesis pathway, including sterol response element binding protein-1c (SREBP-1c), fatty acid synthase (FASN), stearoyl CoA desaturase 1 (SCD1), and thyroid-responsive SPOT14 homolog, was induced by GW3965 in cells from both human and rat livers (Fig. 4 and Supplemental Table S1). The fold-induction by LXR agonist was in general decreased with an increase of insulin concentration, which might be caused by the induction of these genes by increased insulin concentration alone. The insulin induction seemed more pronounced in cells from rat livers than from human livers. GW3965 induced genes involved in the formation of phosphatidic acid and diacylglycerol from glycerol such as glycerol kinase, mitochondrial glycerol-3-phosphate acyltransferase, and 1-acylglycerol-3-phosphate O-acyltransferase 2 (Supplemental Table S1). This, together with the increased increase in fatty acid synthesis, points to increased de novo lipogenesis. The final step in mammalian TG synthesis is catalyzed by diacylglycerol transferases (DGATs), and in human but not in rat hepatocytes, DGAT2 mRNA was reduced 2- to 4-fold by GW3965 (Fig. 5, A and B, and Table 1), demonstrating yet another intriguing difference in human versus rat hepatocytes.

Elevated insulin concentrations increased the secretion of VLDL-TG from both human and rat hepatocytes. GW3965 markedly reduced the VLDL-TG secretion from human hepatocytes at all insulin concentrations but had no or possibly a slight stimulatory effect on VLDL-TG output from rat hepatocytes (Fig. 5, C and D). Secretion of cholesterol from human hepatocytes was affected similarly to VLDL-TG by insulin and GW3965; however, the reductive effect of GW3965 was prominent only at 30 nM insulin (data not shown).

**LXR Induces Genes Encoding Lipid Transfer Proteins.** GW3965 induced the expression of key genes in lipid transfer, including the ATP-binding cassette (ABC) transporters ABCA1, 6-fold, and ABCG1, 17-fold, and the cholesteryl ester transfer protein, 8-fold. Although ABCG5 and ABCG8 did not pass the selection criteria used in the microarray analysis, qPCR analyses showed a 2-fold induction by GW3965 (Supplemental Table S1 and data not shown). Central to cholesterol metabolism is low-density lipoprotein receptor (LDLR), whose expression was induced 2.5-fold by...
GW3965. This was concomitant with induced expression of proprotein convertase subtilisin/kexin, which is shown to accelerate the turnover of the LDLR protein (Benjannet et al., 2004), thus indicating opposing effects on LDLR protein. It is noteworthy that GW3965 induced the expression of VLDL receptor 6-fold. VLDL receptor is usually not associated with hepatic expression, but its forced over-expression in liver in a mouse atherosclerosis model has been shown to reduce atherosclerosis (MacDougall et al., 2006).

**LXR Activation Increases ADFP and Lipid Storage.** Storage of neutral lipids has been shown to be directly proportional to the abundance of ADFP, a protein residing at the surface of lipid droplets and indicated to be involved in the regulation of metabolism of stored lipids (Londos et al., 1999). Indeed, GW3965 clearly induced ADFP in human but not in rat hepatocytes (Figs. 4F and 5E; Table 1). Increased ADFP mRNA correlated to increased ADFP protein (Fig. 5G). The determination of intracellular TG indicated that in-

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![Graphs showing gene expression](image-url)
increased insulin concentration and GW3965 treatment for 18 h increased TG content (data not shown) and showed that 48 h of GW3965 treatment significantly increased TG accumulation at all insulin concentrations (Fig. 5H).

**Discussion**

Primary hepatocytes, cultured under conditions when the adult liver phenotype is maintained (Schuetz et al., 1988), constitute an invaluable in vitro system to investigate the aspects of liver physiology. This study provides novel information regarding the effects of pharmacological activation of LXR, putative therapeutic targets for various human metabolic disorders, in primary human hepatocytes. It is noteworthy that gene regulatory effects correlated strongly to corresponding endpoints of metabolic pathways.

A wide-ranging cross-talk between LXR and insulin signaling was apparent in the human hepatocytes; most markedly, pharmacological LXR activation attenuated the magnitude of the insulin response for many genes. This suggests that pharmacological LXR activation would render human liver less sensitive to insulin, which is a serious concern in the context of LXR as a drug target. It is also in consonance with free fatty acids, increased by LXR activation, interfering with glucose utilization and with the observation that LXR-deficient mice have improved metabolic control (Randle, 1998; Schuster et al., 2006). The physiological dose range of insulin used had little effect on the magnitude of the LXR response; however, lipogenic genes were in general more induced at the lowest insulin concentration. This implies that the hepatic effects of pharmaceutical LXR activation in vivo could have different effects in normoinsulinemic versus hyperinsulinemic subjects, which is in line with observations in human muscle (Kase et al., 2005). The suggestion that glucose is a physiological LXR ligand (Mitro et al., 2007) further implicates that glucose and insulin levels could have an impact on pharmaceutical targeting of LXR and vice versa.

The primary hepatic glucose transporter GLUT2 is a facilitating and bidirectional transporter, whereas GCK, the first enzyme in the glycolytic pathway, is acting as a hepatic glucose sensor and is crucial for the subsequent expression of glycolytic and lipogenic genes (Dentin et al., 2004). The finding that the LXR agonist markedly reduced the expression of GLUT2 and of the glycolytic key genes GCK and PKLR in human but not in rat hepatocytes was completely unprecedented. There is evidence that glucose metabolism mediated by GCK is necessary for the appropriate expression of ChREBP in rodent hepatocytes (Dentin et al., 2004), which independently of insulin serves as a transcriptional regulator of PKLR and lipogenic genes (Uyeda and Repa, 2006). However, the effect of GW3965 on ChREBP expression in human cells was not significant (Table 1). The potential of LXR

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**Fig. 4.** Regulation of fatty acid synthesis by insulin and GW3965. Primary hepatocytes were cultured for 96 (human) or 72 (rat) h in 0.3, 3, or 30 nM insulin + GW3965 for the last 18 h. Gene expression was analyzed by qPCR. Data represent the average of duplicate cell culture dishes with cells from each of three donors or rats and are given as relative expression. Expression of SREBP-1c in human (A) and rat (B) hepatocytes. Expression of FASN in human (C) and rat (D) hepatocytes. Expression of SCD1 in human (E) and rat (F) hepatocytes.
agonists as drugs has been questioned because of their lipogenic effect in rodent models. If, as indicated by our results, the glycolytic pathway is compromised by pharmacological LXR activation in human hepatocytes, an additional concern of therapeutic aspects of LXR agonists could be hyperglycemia. It might be speculated that reduced GCK expression and simultaneously induced expression of hexokinase 2 and phosphoglucone dehydrogenase direct glucose metabolism to the hexose monophosphate shunt pathway, providing the NADPH necessary for fatty acid synthesis.

The role of insulin in the regulation of hepatic VLDL assembly and output is complex and associated with controversies (Gibbons et al., 2002). However, continuous exposure of hepatocytes to increased concentrations of insulin in vitro is coupled to increased VLDL-TG output (Aarsland et al., 1996), which was observed with both human and rat hepatocytes. The different effect of LXR agonist treatment on VLDL-TG output from human and rat hepatocytes was striking; the reduced output of VLDL-TG from human hepatocytes is in line with observations in monkeys, in which pharmacological LXR activation showed no evidence of hypertriglyceridemia (Groot et al., 2005). This could imply that results in rodents have exaggerated the risk of hypertriglyceridemia as a side effect of pharmacological targeting of LXR. The mechanism(s) by which LXR activation suppresses VLDL-TG output can rely on various liver specific processes; it has been shown that increased uptake and processing of glucose, dependent on glucose phosphorylation by GCK, in rat hepatocytes is associated with enhanced VLDL-TG output (Durrington et al., 1982; Brown et al., 1999).

Fig. 5. Regulation of the lipogenic pathway by insulin and GW3965. Primary hepatocytes were cultured for 96 (human) or 72 (rat) h in 0.3, 3, or 30 nM insulin ± GW3965 for the last 18 h (A–G) or 48 h (H). Gene expression was analyzed by qPCR, and data are given as relative expression; DGAT2 expression in human (A) and rat (B) hepatocytes. Output of VLDL-TG was analyzed in cell culture medium from human (C) and rat (D) hepatocytes. qPCR analysis of ADFP expression in human (E) and rat (F) hepatocytes. qPCR data represent the average of duplicate cell culture dishes with cells from each of three donors or rats. G, ADFP protein, analyzed by Western blot, in human hepatocytes exposed to increasing concentration of GW3965 at 3 nM insulin, and fold induction of the mRNA level is indicated. H, intracellular content of TG was analyzed in human hepatocytes; data shown are the mean ± S.D. of results from quadruplicate dishes with cells from one donor; one-way analysis of variance followed by Newman-Keuls multiple comparison test was used to determine p values. *, p < 0.05; **, p < 0.01; ***, p < 0.001.
tocytes, it is possible that the reduced expression of GCK, GLUT2, and PKLR contributes to reduced VLDL-TG output; it is also possible that the reduced expression of DGAT2 plays a role. In animal models, antisense oligonucleotide-mediated reduction of DGAT2 mRNA levels is associated with inhibition of TG synthesis (Yu et al., 2005), and it is suggested that DGAT2 plays important roles in the assembly of de novo synthesized fatty acids into VLDL-TG particles (Meegalla et al., 2002). It is worth mentioning that the expression profiling data indicated no effect of GW3965 on arylacetamide deacetylase involved in the lipolysis of cytosolic TG (Gibbons et al., 2000) or on apolipoprotein B, microsomal triglyceride transfer protein, ADP-ribosylation factor 1, or apolipoprotein E necessary for synthesis, maturation, and secretion of VLDL particles (Shelness and Sellers, 2001).

Even though the impact of LXR agonist on VLDL-TG output in human hepatocyte cultures, extrapolated to human beings, would be beneficial, the pronounced induction of ADFP, which has a central role in the formation of lipid droplets (Imamura et al., 2002), suggests a detrimental effect (i.e., increased risk of hepatic steatosis). A recent study shows that ADFP enhances TG storage and reduces output of TG and VLDL in primary rat hepatocytes by preventing fatty acid transfer from cytosolic TG to VLDL-TG (Magnusson et al., 2006). Furthermore, ADFP-deficient mice show reduced hepatic TG content, and it is suggested that ADFP affects the balance of TG pools in the liver (Chang et al., 2006), and ADFP is induced in hepatocytes upon increased lipid load (Motomura et al., 2006). As expected, the experimental conditions in which the cells were cultured for several days in the presence of 11 mM glucose and insulin resulted in well-filled stores of lipids, observed with oil red O staining (data not shown) and is in line with glucose being an endogenous LXR ligand (Mitro et al., 2007). Despite this, TG storage was markedly increased after 48 h of GW3965 treatment, particularly at 30 nM insulin. This indicates that the risk of hepatic steatosis would be especially serious in insulin-resistant individuals upon pharmacological LXR targeting. It cannot be excluded, however, that an increased risk of steatosis could be compensated by simultaneously stimulated lipid β-oxidation; mitochondrial fatty acid oxidation is facilitated by carnityl palmitoyl transferases (CPTs), and GW3965-induced CPT1 and CPT2 2-fold in human cells (Supplemental Table S1 and data not shown).

A summary of gene regulatory effects of LXR stimulation in human hepatocytes is shown in Fig. 6 (also see Supplemental Table S1); extrapolated to the human situation in vivo, the following consequences can be perceived. Decreased cholesterol metabolism through reduced biliary acid formation may reduce the flux of cholesterol through the reverse cholesterol pathway in the hepatocyte and possibly contribute to atherosclerosis development. On the other hand, decreased cholesterol catabolism could lead to the channeling of free cholesterol to high-density lipoprotein synthesis through increased ABCA1 and ABCG1 expression (Vaughan and Oram, 2006), two genes markedly induced by GW3965. Perturbation of biliary acid formation might also have consequences for cholesterol gallstone disease (Portincasa et al., 2006). That LXR agonism causes hypertriglyceridemia might be of less concern in humans than in rodents. On the other hand, the risk of hepatic steatosis caused by increased expression of ADFP and possibly also by reduced expression of DGAT2 might be higher in humans than in rodents. It is plausible that suppression of glycosylation in human hepatocytes is coupled to the observed effects on cholesterol and lipid pathways.

### Table 1

Effects of GW3965 in human hepatocytes on genes in carbohydrate and lipid metabolic pathways

<table>
<thead>
<tr>
<th>Gene</th>
<th>Control, 3 nM Ins</th>
<th>GW3965, 3 nM Ins</th>
<th>p Value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT2</td>
<td>100 ± 9</td>
<td>48 ± 13</td>
<td>0.007</td>
<td>5</td>
</tr>
<tr>
<td>GCK</td>
<td>100 ± 7</td>
<td>37 ± 13</td>
<td>0.001</td>
<td>5</td>
</tr>
<tr>
<td>PKLR</td>
<td>100 ± 7</td>
<td>39 ± 10</td>
<td>0.006</td>
<td>5</td>
</tr>
<tr>
<td>PEPCK</td>
<td>100 ± 13</td>
<td>64 ± 24</td>
<td>0.040</td>
<td>5</td>
</tr>
<tr>
<td>ChREBP</td>
<td>100 ± 20</td>
<td>75 ± 27</td>
<td>0.409</td>
<td>5</td>
</tr>
<tr>
<td>ADP</td>
<td>100 ± 5</td>
<td>255 ± 28</td>
<td>0.010</td>
<td>4</td>
</tr>
<tr>
<td>DGAT2</td>
<td>100 ± 7</td>
<td>51 ± 9</td>
<td>0.001</td>
<td>5</td>
</tr>
</tbody>
</table>

*Note:* Gene expression is given as mean ± S.E.M. Student’s t-test was used to determine p values. Data from one donor was excluded in the analysis of ADFP because the induction was 27-fold (i.e., approximately 10-fold higher than in the other samples).
but may also pose a risk for hyperglycemia. Studies in mice suggest that specific targeting of LXRβ would alleviate the negative effects of TG synthesis in the liver, being exerted mainly by LXRs (Quinet et al., 2006). Whether this also applies to humans is a pertinent issue to address, particularly because human and rat hepatocytes respond differently to a pan LXR agonist.

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References


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