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Improved metabolic control by depletion of Liver X Receptors in mice

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Abstract

Liver X Receptors (LXRs) coordinate the regulation of lipid and carbohydrate metabolism and insulin signaling. LXR-ligands lower plasma glucose in hyperglycemic rodents and have consequently been proposed as anti-diabetic agents. We investigated the metabolic effects induced by high carbohydrate diet in $LXR\alpha^{-/-}\beta^{-/-}$ mice. Irrespective of diets, $LXR\alpha^{-/-}\beta^{-/-}$ mice had reduced fatty acid, insulin, and C-peptide plasma levels than wild-type controls, suggesting a lower insulin production. High carbohydrate diet decreased the plasma glucose levels and the homeostasis model assessment (HOMA)-index in $LXR\alpha^{-/-}\beta^{-/-}$ mice and increased hepatic triglyceride content and mRNA levels of lipogenic genes in wild-type and $LXR\alpha^{-/-}\beta^{-/-}$ mice, proportionally. In wild-type mice high carbohydrate diet was associated with induced expression of LXR (1.5-fold), despite unchanged SREBP-1c expression. $LXR\alpha^{-/-}\beta^{-/-}$ mice responded to this diet by induction of SREBP-1c. Our study suggests that in $LXR\alpha^{-/-}\beta^{-/-}$ mice, glucose utilization seems to be privileged possibly due to reduced circulating free fatty acid levels.

Keywords: Liver X Receptor; Serum glucose levels; Insulin receptor substrate 2

Previous studies have suggested a role for nuclear Liver X Receptor (LXR) in the coordinate regulation of carbohydrate and lipid metabolism and as mediator of insulin signaling [1]. The two paralogs LXRα and LXRβ share high amino acid identity and seem to have similar, but not identical, functions [2–4]. Nevertheless, they can compensate for each other to a certain degree, since a pronounced phenotype is primarily observed in mice lacking both receptors [5]. Whereas LXRα is mainly expressed in metabolically active organs, like liver, kidney, or adipose tissue, LXRβ is found in essentially all tissues [6]. The natural ligands of both LXR isoforms seem to be oxygenated forms of cholesterol and certain bile acids [7]. Today, potent synthetic LXR-ligands, like T0901317 or GW3965, are available and the use of these compounds in different animal models demonstrates an anti-atherogenic effect following LXR stimulation [8,9]. Furthermore, previous *in vitro* and *in vivo* studies have led to the hypothesis that LXR agonists could be beneficial in the treatment of non-insulin-dependent diabetes (NIDDM) [10–13]. Synthetic LXR agonists lower plasma glucose levels in rodent models for NIDDM [12,13] and improve glucose tolerance in another rodent model with predisposition for developing obesity and insulin resistance [11]. All these effects seem to result from inhibition of hepatic glucose output follow-

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ing suppression of gluconeogenesis and increased hepatic glucose utilization. In parallel with the effects in liver, LXR activation increases peripheral glucose uptake by direct upregulation of the glucose transporter GLUT4 [11,14]. In addition, LXR agonists were shown to enhance insulin secretion by pancreatic β-cells [15]. However, LXR activation only slightly improves insulin sensitivity in diabetic mice despite considerable reduction in blood glucose, indicating that mechanisms other than direct effects on glucose metabolism could underlie the anti-diabetic effect of LXR agonists [13]. Since the majority of data on the LXR role for the coordinated regulation of carbohydrate and lipid metabolism generate from pharmacologic studies, the need for a better understanding of LXRs physiological relevance has prompted us to also investigate the metabolic effects induced by high carbohydrate challenge in LXR deficient mice.

Materials and methods

Animals. $LXR\alpha^{-/-}\beta^{-/-}$ mice were obtained as previously described [2,5]. All mice used in our study ($LXR\alpha^{-/-}\beta^{-/-}$ and wild-type control mice) had a similar mixed genetic background based on 129/Sv and C57Bl/6 strains, and were backcrossed three times into C57Bl/6 strain. Animals were housed with a regular 12-h light/12-h dark cycle. In the first experiment, 10 months old female mice ($n = 3$–5) had free access to plain water and to a low-fat standard rodent chow (R36 Lactamin AB, Vadstena, Sweden) or to water, containing 100 g/L fructose, and to low-fat standard rodent chow supplemented with 600 g/kg sucrose for one week. Animals were fasted 4 h prior to sacrifice. In the second experiment, 10 months old male mice ($n = 3$–5) were fed *ad libitum* either a low-fat standard rodent chow diet or supplemented with 250 mg/kg of the synthetic LXR agonist T0901317 for one week as previously described [10]. All the experiments were approved by the local Ethical Committee for animal experiments.

Chemical analysis of serum and tissue. Blood was drawn by cardiac puncture under light methoxyfluorane anesthesia before tissues were collected for further analyses. Total cholesterol, triglycerides, and glucose were determined by a Monarch automated analyser (ILS Laboratories Scandinavia AB, Sollentuna, Sweden). Serum triglyceride value for each animal was corrected with regard to the respective glycerol content. Free fatty acids (FFA) were determined manually by a commercially available kit (Wako Chemicals). Insulin and C-peptide were determined by RIA on pooled samples following the manufacturer's instructions. Lipids in livers were extracted according to Folch *et al.* [16] and total cholesterol and triglycerides analyzed using commercially available kits (Roche Molecular Biochemicals, Indianapolis, IN).

Quantitative real-time PCR (RTQ-PCR). Total RNA from the individual livers was isolated using Trizol® reagent (Invitrogen) following the manufacturer's instructions. cDNA was prepared as previously described using 1 μg total RNA [10]. The sequences for primer pairs were obtained from previous publications [10,17,18]. Sequences for additional primers, designed using Primer Express TM software, version 2.0.01 (PE Applied Biosystems), are given in Table 1. Quantification of specific mRNAs was carried out by SYBR® Green real-time PCR using ABI PRISM 7700 Sequence Detection Systems instrument and software (PE Applied Biosystems). The expression of a specific gene was normalized by 18S rRNA levels.

Statistics. Data are presented as means ± SEM. The significance of differences between groups was tested by 2-way ANOVA, followed by post hoc comparisons according to LSD test. When variances were not homogeneous between groups, data were log-transformed prior to statistical analysis (Statistica software, Stat Soft, Tulsa OK). A value of 100 was arbitrarily assigned to the corresponding wild-type control group.

Results

In the first experiment, in which animals were challenged with high carbohydrate diet for one week, wild-type mice responded with a 1.8-fold increase in serum glucose levels. In contrast, no effect on serum glucose levels was observed in $LXR\alpha^{-/-}\beta^{-/-}$ mice (Table 2). Furthermore, lower FFA levels were observed in $LXR\alpha^{-/-}\beta^{-/-}$ mice and a proportionally similar reduction occurred in both genotypes during dietary challenge. Likewise, high carbohydrate diet led to decreased insulin levels irrespective of the genotype. Nevertheless, LXR deficiency was always associated with markedly lower plasma insulin levels compared to wild-type animals. The homeostasis model assessment (HOMA)-index, calculated as insulin × free fatty acids, which inversely correlates with insulin sensitivity, was 7- to 10-fold higher in wild-type controls, both when fed standard low-fat chow and after challenging with high carbohydrate diet (Table 2). C-peptide plasma levels reflected the difference observed for serum insulin levels between the genotypes. Furthermore, as for insulin, high carbohydrate challenge decreased plasma C-peptide levels in both wild-type and $LXR\alpha^{-/-}\beta^{-/-}$ mice.

In addition, we wanted to investigate whether high carbohydrate intake can induce hepatic lipogenesis in LXR deficient mice. Both $LXR\alpha^{-/-}\beta^{-/-}$ and wild-type control mice responded with a 2-fold increase of hepatic triglyceride content when challenged with high carbohydrate diet,

Table 1
Primer pairs used for quantitative real-time PCR using SYBR® Green labeling

Gene	Sequences of forward and reverse primers	Primer concentration (nmol/L)
LXRα	5′-TCG CAA ATG CCG CCA-3′	200
	5′-AGT TCG CCT AGA CAA GAA GAC T-3′	200
LXRβ	5′-CCC CAC AAG TTC TCT GGA CAC-3′	200
	5′-TGG CGG AGG TAC TGG GC-3′	200
GLUT-1	5′-GCA GGC TGT GCT GTG CTC AT-3′	100
	5′-GCT CAG ATA GGA CAT CCA AGG CA-3′	100
GLUT-2	5′-TCA GCA ACT GGG TCT GCA ATT-3′	100
	5′-ACA CGT AAG GCC CAA GGA AGT-3′	100
18 S	5′-CCT GCG GCT TAA TTT GAC TCA-3′	100
	5′-AGC TAT CAA TCT GTC AAT CCT GTC C-3′	100

Table 2
Metabolic parameters in serum and liver in mice following high carbohydrate intake

	Wild-type	Wild-type	$LXR\alpha^{-/-}\beta^{-/-}$	$LXR\alpha^{-/-}\beta^{-/-}$
Sucrose (600 g/kg) fructose (100 g/L)	−	+	−	+
Hepatic triglycerides (mg/g tissue)*,¶	53.9 ± 11.9	94.9 ± 7.63†	11.5 ± 1.59	27.7 ± 15.2
Glucose (mmol/L)*	6.8 ± 1.0	10.4 ± 0.7†	5.4 ± 0.7	5.0 ± 1.3‡
FFA (mmol/L)§	2.1	1.62	1.26	0.67
Insulin (ng/ml)§	3.44	1.52	0.85	0.36
HOMA (FFA × insulin)§	7.23	2.46	1.07	0.24
C-peptide (nmol/L)§	0.63	0.47	0.44	0.19

*: Means ± SEM ($n = 3$–5 animals group); §: pooled serum sample. †$p < 0.05$, untreated wild-type mice vs. treated wild-type mice; ‡$p < 0.05$, treated wild-type mice vs. treated $LXR\alpha^{-/-}\beta^{-/-}$ mice; ¶$p < 0.001$ all $LXR\alpha^{-/-}\beta^{-/-}$ mice vs. all wild-type mice.

although a statistical significance was only reached in wild-type animals ($p < 0.05$; Table 2). However, hepatic triglyceride content was 5-fold lower in $LXR\alpha^{-/-}\beta^{-/-}$ mice compared to their controls regardless of the diet (2-way ANOVA: $LXR\alpha^{-/-}\beta^{-/-}$ vs. wild-type; $p < 0.001$).

The hepatic mRNA levels of various genes encoding proteins involved in lipid and glucose homeostasis following feeding of high carbohydrate diet were determined by real-time PCR (Table 3). In wild-type mice, a slight but not significant decrease of sterol regulatory element binding protein 1c (SREBP-1c) expression was observed, despite a 1.5-fold increase in both LXRα and LXRβ expression. However, in wild-type mice the mRNA levels of the lipogenic enzymes acetyl CoA carboxylase (ACC) and fatty acid synthetase (FAS), and stearoyl CoA desaturase-1 (SCD-1) were significantly increased (5- to 10-fold) upon dietary carbohydrate. In LXR deficient mice, carbohydrate feeding significantly induced the expression of ACC and FAS. The increase was however much smaller than in wild-type mice and it was paralleled by a minor but significant increase in SREBP-1c mRNA levels. Feeding high carbohydrate diet significantly induced the expression of glycerol-3-phosphate-acyltransferase (GPAT), acetyl CoA synthetase, malic enzyme, ATP citrate lyase (ATP-CL), and glucose-6-dehydrogenase 3- to 6-fold in wild-type mice. A similar trend was observed in $LXR\alpha^{-/-}\beta^{-/-}$ mice for malic enzyme, ATP-CL, and glucose-6-dehydrogenase, whereas on the contrary acetyl CoA synthetase was conversely significantly reduced upon high carbohydrate

Table 3
Hepatic expression of genes involved in lipogenesis, utilization of glucose, and insulin signaling

	Wild-type	Wild-type	$LXR\alpha^{-/-}\beta^{-/-}$	$LXR\alpha^{-/-}\beta^{-/-}$
Sucrose (600 g/kg) fructose (100 g/L)	−	+	−	+
LXR-α	100 ± 18	146 ± 59*	n.d.	n.d.
LXR-β	100 ± 45	141 ± 146	n.d.	n.d.
Fatty acid and triglyceride synthesis				
SREBP-1c	100 ± 17	76 ± 16	62 ± 12*	101 ± 16†
ACC¶	100 ± 12	953 ± 364*	100 ± 23	243 ± 71*,†,#
Fatty acid synthase¶	100 ± 4	1016 ± 610*	61 ± 11	171 ± 28†,#
SCD-1	100 ± 49	464 ± 277*	37 ± 19	18 ± 15*,#
Glycerol-3-P-acyltransferase¶	100 ± 24	296 ± 171*	55 ± 18*	63 ± 14#
Utilization of glucose				
GLUT-1	100 ± 26	32 ± 15*	74 ± 28	116 ± 70#
GLUT-2	100 ± 34	85 ± 24	75 ± 31	167 ± 128
Glucokinase	100 ± 46	88 ± 17	42 ± 8*	41 ± 17*,#
PEPCK¶	100 ± 45	37 ± 50*	177 ± 62	77 ± 37
Acetyl CoA synthetase	100 ± 44	298 ± 147*	109 ± 47	41 ± 5*,†,#
Malic enzyme	100 ± 25	430 ± 235*	40 ± 14*	77 ± 18†,#
ATP citrate lyase	100 ± 25	574 ± 248*	73 ± 22	115 ± 41#
Glucose-6-dehydrogenase	100 ± 10	635 ± 680*	81 ± 41	170 ± 84
Insulin signaling				
Insulin receptor	100 ± 13	76 ± 16	85 ± 29	82 ± 13
IRS1	100 ± 17	80 ± 53	83 ± 46	96 ± 66
IRS2	100 ± 39	79 ± 70	58 ± 14	164 ± 35†,#
IGFBP-1	100 ± 83	223 ± 230	116 ± 56	394 ± 271*

The mRNA expression levels are presented as a percentage of the untreated wild-type mice. Each value symbolizes mean values ± SEM ($n = 3$–5). * denotes the level of statistical significance $p < 0.05$ vs. untreated wild-type mice; †$p < 0.05$ vs. untreated $LXR\alpha^{-/-}\beta^{-/-}$ mice; #$p < 0.05$ treated wild-type mice vs. treated $LXR\alpha^{-/-}\beta^{-/-}$ mice; ¶$p < 0.05$ all $LXR\alpha^{-/-}\beta^{-/-}$ mice vs. all wild-type mice; n.d.: not determined.

diet. Moreover, the expression of ACC, FAS, and PEPCK was significantly reduced in $LXR\alpha^{-/-}\beta^{-/-}$ mice, regardless of their diet, compared to wild-type mice. Whereas in control mice hepatic mRNA levels of GLUT-1 were significantly reduced, the initially lower levels of GLUT-2 and GLUT-1 were induced by 2-fold in $LXR\alpha^{-/-}\beta^{-/-}$ mice in response to dietary carbohydrates.

Finally, the mRNA levels of insulin receptor substrate 2 (IRS 2) and insulin-like growth factor binding protein-1 (IGFBP-1) were induced (3-fold) in $LXR\alpha^{-/-}\beta^{-/-}$ mice following feeding of carbohydrate enriched diet, although the statistical significance was not attained for the IGFBP-1. A similar trend for IGFBP-1 was also seen in wild-type controls.

In the second experiment, in which T0901317 (250 mg/kg) was administered to mice for one week, LXR stimulation did not affect plasma glucose levels in either wild-type or $LXR\alpha^{-/-}\beta^{-/-}$ mice (Table 4). Again, the relative amounts of hepatic mRNAs from various genes involved in utilization of glucose or in insulin signaling were determined by real-time PCR (Table 4). LXR stimulation induced the hepatic expression of GLUT-1, acetyl CoA synthetase, ATP-CL, glycerol-3-phosphate-acyltransferase, and malic enzyme (2- to 6-fold) in wild-type mice. No changes were observed for GLUT-2.

The expression of these genes, with the exception of GLUT-1 and GLUT-2, were significantly less induced in $LXR\alpha^{-/-}\beta^{-/-}$ mice compared to the wild-type controls following the administration of T0901317.

In wild-type mice and in $LXR\alpha^{-/-}\beta^{-/-}$, administration of T0901317 did not change the expression of genes encoding insulin receptor, IRS1 and IRS2. An increased expression for IGFBP-1 was only observed in wild-type controls.

Discussion

The present study shows that LXR deficiency leads to lower plasma levels of FFA, insulin, and C-peptide, and that this is associated with an improved metabolic control following high dietary carbohydrate load. These findings are of great interest, since it has been reported that LXR agonists may act as anti-diabetic agents in rodent models for NIDDM. Administration of synthetic LXR agonists reduced serum glucose in diabetic db/db mice and Zucker diabetic (ZDF) rats [11–13], but not in normal C57Bl/6 mice [12,19]. Obese insulin-resistant Zucker (fa/fa) rats showed significantly improved glucose tolerance after LXR stimulation [12]. LXR activation resulted in lower blood glucose levels strictly by increasing glucose uptake by peripheral tissue in ob/ob mice [13]. However, this cited report revealed the striking observation that LXR-induced hepatic steatosis lacks the association with insulin resistance, with regard to the insulin-mediated suppression of hepatic glucose production [13]. This is most likely due to the counteracting anti-diabetic effects of the LXR agonist. Results from this previous study are in line with other reports revealing that the anti-diabetic effects of LXR agonists on carbohydrate metabolism are only seen in diabetic animal models [11,12,20].

Our paradoxical observation that LXR depletion has similar effects as LXR stimulation illustrates the complex mechanisms behind control of glucose homeostasis. LXR deficiency is associated with significantly lower plasma insulin and C-peptide levels than normal, indicating that $LXR\alpha^{-/-}\beta^{-/-}$ mice have a reduced production of insulin, despite serum glucose levels comparable to those of wild-type animals. As a consequence, it seems that $LXR\alpha^{-/-}\beta^{-/-}$ mice need less insulin to control their

Table 4
Serum glucose levels and hepatic mRNA amounts of genes regulating glucose utilization and insulin signaling following treatment with T0901317

	Wild-type	Wild-type	$LXR\alpha^{-/-}\beta^{-/-}$	$LXR\alpha^{-/-}\beta^{-/-}$
T0901317 (250 mg/kg)	−	+	−	+
Glucose (mM)	9.4 ± 0.4	9.3 ± 0.5	9.5 ± 0.3	10.4 ± 0.4
Utilization of glucose				
GLUT-1	100 ± 51	294 ± 81*	141 ± 139	247 ± 124
GLUT-2	100 ± 44	192 ± 143	107 ± 100	172 ± 52
Glucokinase¶	100 ± 31	188 ± 77	79 ± 58	42 ± 20*,†,#
Acetyl CoA synthetase	100 ± 49	615 ± 195*	135 ± 113	248 ± 81*,#
Malic enzyme¶	100 ± 54	411 ± 30*	70 ± 55	116 ± 31#
ATP citrate lyase	100 ± 35	307 ± 84*	84 ± 46	144 ± 54*,#
Glycerol-3-P-acyltransferase¶	100 ± 48	337 ± 59*	65 ± 33	121 ± 47#
Insulin signaling				
Insulin receptor	100 ± 75	171 ± 135	97 ± 100	150 ± 143
IRS1	100 ± 112	92 ± 96	66 ± 82	82 ± 47
IRS2	100 ± 25	171 ± 112	65 ± 55	71 ± 48
IGFBP-1	100 ± 15	246 ± 132*	137 ± 36*	180 ± 63

The mRNA expression levels are presented as a percentage of the untreated wild-type mice. Each value symbolizes mean values ± SEM ($n = 3$–5). * denotes the level of statistical significance $p < 0.05$ vs. untreated wild-type mice; $^{\dagger}p < 0.05$ vs. untreated $LXR\alpha^{-/-}\beta^{-/-}$ mice; $^{\#}p < 0.05$ treated wild-type mice vs. treated $LXR\alpha^{-/-}\beta^{-/-}$ mice; $^{\P}p < 0.05$ all $LXR\alpha^{-/-}\beta^{-/-}$ mice vs. all wild-type mice.

metabolic status. In line with this interpretation, a lower HOMA-index—that inversely correlates with insulin sensitivity—was observed in $LXR\alpha^{-/-}\beta^{-/-}$ mice. The lower HOMA-index in these animals was not only due to lower plasma insulin levels but also to lower levels of FFA. Studies on perfused pancreas have suggested that for a given level of glucose, insulin secretion will be positively influenced by the combined concentration of circulating FFA [21]. Thus, the lower plasma levels of FFA in $LXR\alpha^{-/-}\beta^{-/-}$ mice could in turn cause the observed lower insulin production.

The concept that FFA interfere with glucose utilization was initially proposed by P.J. Randle [22]. Today, a large amount of data support the view that fatty acid oxidation inhibits glucose catabolism both in humans and in animal models (for review, see [23]). Thus, the reduced levels of FFA present in $LXR\alpha^{-/-}\beta^{-/-}$ mice would also explain the improved metabolic control in LXR depleted mice when fed high carbohydrate diet. In this vein, McGarry has proposed that insulin resistance results from dysregulation of fat metabolism, including presence of high FFA levels [24].

Administration of T0901317 did not lead to any significant change in plasma glucose levels, either in $LXR\alpha^{-/-}\beta^{-/-}$ mice or in wild-type mice. This is in line with previously published data [11,12], confirming that LXR activation affects serum glucose levels only in hyperglycemic states.

High carbohydrate diet increased hepatic triglyceride content and enhanced transcription of genes controlling *de novo* biosynthesis of triglycerides, regardless of genotype. However, in wild-type mice the hepatic mRNA level of LXRα was increased 1.5-fold and those of the major lipogenic enzymes 3- to 10-fold upon carbohydrate challenge, despite unchanged mRNA levels of SREBP-1c. In contrast, in $LXR\alpha^{-/}\beta^{-/-}$ mice, a minor and significant elevation of SREBP-1c expression was observed, which was paralleled by elevated mRNA levels of ACC and FAS. All these findings are somewhat contrasting with the concept that both LXRs, by inducing the hepatic expression of SREBP-1c, can increase lipogenesis [18,19,25,26]. Nevertheless, as already mentioned above, the study performed by our group in LXR deficient mice suggests that, *in vivo*, LXRβ might be the more relevant LXR paralog involved in regulation of triglyceride metabolism [5].

In rodents, refeeding is a strong inducer of insulin secretion, which in turn leads to an overshoot of hepatic SREBP-1c expression [27,28]. Transcriptional upregulation of SREBP-1c expression may also be observed following insulin injection [26–28]. Interestingly, the rapid induction of SREBP-1c expression following insulin treatment is paralleled by increased hepatic mRNA levels of LXRα [26]. The observations that, in $LXR\alpha^{-/-}\beta^{-/-}$ mice, neither a single insulin injection nor refeeding could induce hepatic expression of SREBP-1c, indicate that LXRs, at least in part, mediate the insulin-stimulated transcription of SREBP-1c [26,29]. However, the fact that $LXR\alpha^{-/-}\beta^{-/-}$ mice have increased hepatic SREBP-1c mRNA levels, despite lowered plasma insulin levels when challenged with high carbohydrate diet, suggests that under certain metabolic conditions, hepatic SREBP-1c expression may be regulated independently of plasma insulin levels as well as of LXRs. In support of this hypothesis, insulin was found not to be required for the induction of hepatic SREBP expression, in a late phase response of mice fed a high carbohydrate diet [30].

Our results also show that IRS-2 expression was significantly stimulated only in $LXR\alpha^{-/-}\beta^{-/-}$ mice, following feeding of a high carbohydrate diet and that treatment with T0901317 induced hepatic expression of IRS-2 only in wild-type. Thus, whereas a pharmacologic stimulation of the gene encoding IRS-2 seems to occur by LXR agonist, the presence of LXR conversely seems to preclude the effects of carbohydrate diet on IRS-2. Previous studies with transgenic mice have suggested that many insulin responses, in particular those that are associated with carbohydrate metabolism, are mainly mediated through the IRS-2 branch of the insulin/IGF—signaling pathway [31,32]. Deletion of IRS-2 profoundly impaired hepatic carbohydrate metabolism *in vivo* and peripheral insulin sensitivity in humans and mice [33–38]. Thus, the finding of a negative correlation between the mRNA levels of IRS-2 and plasma insulin levels in $LXR\alpha^{-/-}\beta^{-/-}$ mice supports the concept of better glucose utilization in $LXR\alpha^{-/-}\beta^{-/-}$ mice due to low plasma levels of FFA.

In conclusion, our study shows that $LXR\alpha^{-/-}\beta^{-/-}$ mice have lower plasma insulin levels and an improved metabolic control than wild-type mice following ingestion of a high carbohydrate diet. This finding suggests that LXR deficiency, by leading to lower FFA levels in blood, enhances glucose utilization. Although activation of LXR has been proposed as a strategy to improve insulin sensitivity, our observations underscore the complexity of the role played by LXRs in the regulation of glucose metabolism and raise the question whether chronic stimulation of LXR is necessarily associated with an improved metabolic control.

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