Pharmacological activation of LXR in utero directly influences ABC transporter expression and function in mice but does not affect adult cholesterol metabolism

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van Straten EM, Huijkm NC, Baller JF, Kuipers F, Plösch T. Pharmacological activation of LXR in utero directly influences ABC transporter expression and function in mice but does not affect adult cholesterol metabolism. Am J Physiol Endocrinol Metab 295: E1341–E1348, 2008. First published October 7, 2008; doi:10.1152/ajpendo.90597.2008.—Cholesterol is critical for several cellular functions and essential for normal fetal development. Therefore, its metabolism is tightly controlled during all life stages. The liver X receptors-α (LXRA; NR1H3) and -β (LXRB; NR1H2) are nuclear receptors that are of key relevance in coordinating cholesterol and fatty acid metabolism. The aim of this study was to elucidate whether fetal cholesterol metabolism can be influenced in utero via pharmacological activation of LXR and whether this would have long-term effects on cholesterol homeostasis. Administration of the LXR agonist T0901317 to pregnant mice via their diet (0.015% wt/wt) led to induced fetal hepatic expression levels of the cholesterol transporter genes Abcg5/g8 and Abca1, higher plasma cholesterol levels, and lower hepatic cholesterol levels compared with controls. These profound changes during fetal development did not affect cholesterol metabolism in adulthood nor did they influence coping with a high-fat/high-cholesterol diet. This study shows that the LXR system is functional in fetal mice and susceptible to pharmacological activation. Despite massive changes in fetal cholesterol metabolism, regulatory mechanisms involved in cholesterol metabolism return to a “normal” state in offspring and allow coping with a high-fat/high-cholesterol diet.

The biosynthesis of cholesterol and its conversion into bioactive steroids are regulated by a complex network of enzymes that are tightly controlled by several hormones, by cholesterol itself and by oxysterols. Several oxysterols, in particular 22(R)-, 24(S)-, 27-, and 24(S), 25-hydroxycholesterol, are natural ligands of the liver X receptor-α (LXRα; NR1H3) and -β (LXRβ; NR1H2), two members of the nuclear receptor superfamily of ligand-activated receptors (12). LXRα and -β are key players in coordinating cholesterol and fatty acid metabolism in mammals. LXRα is mainly expressed in the liver, adrenal, intestine, adipose tissue, and macrophages, while LXRβ is ubiquitously expressed (19). Both LXR isoforms are activated by oxysterols with no specificity documented. Several synthetic LXR ligands have been generated during the past years (6). Activated LXRs heterodimerize with ligand-activated retinoid X receptor (RXR) at LXR response elements present in the promoters of target genes to induce their transcription. General activation of LXRs by synthetic agonists such as T0901317 induces transcription of multiple genes involved in cellular sterol efflux (ATP-binding cassette family members ABCA1, ABCG5, and ABCG8), bile acid synthesis (cholesterol 7α-hydroxylase CYP7a1), and de novo lipogenesis (sterol regulatory element-binding protein-1c SREBP1c and fatty acid synthase FASN) in a variety of cell types (29). Treatment of C57BL/6 mice with T0901317 increases HDL cholesterol concentrations in plasma and induces feline sterol excretion, while at the same time hepatic steatosis develops (8, 15, 21). In addition, LXRs repress inflammatory genes like NOS2 (nitric oxide synthase), PTGS2 (cytochrome c oxidase II), IL6 (interleukin 6), and IL1b (interleukin 1β) in macrophages (11).

Since the LXRs are fundamental regulators of cholesterol fluxes in the adult, it is tempting to speculate that they may have important roles in the development of fetal cholesterol metabolism as well. Expression of Lxrα and Lxrβ has been demonstrated in mouse fetuses from day 11.5 post coitum onwards (2); however, the functional role of LXRs in fetal development in the newborn has not yet been defined. It has been stated that LXR is important but not essential for normal fetal development, as is also evident from studies with Lxrα-, Lxrβ-, and Lxrαβ-null mice (1, 17, 22). Specifically, activating LXR during fetal development might alter lipid and cholesterol metabolism in the developing fetus and have long-term effects into adulthood, especially when the animal receives a cholesterol-rich diet.

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The aim of this study was to elucidate whether LXR is functionally active in the regulation of cholesterol metabolism in utero and whether activating LXR during fetal development influences the coping with a high-fat/high-cholesterol (HFHC) diet in the offspring at a later age. We show that when the LXR functionally active in the regulation of cholesterol metabolism in utero and whether activating LXR during fetal development from 8 wk. impact on the response to a HFHC diet in the offspring at an age of 8 wk.

**MATERIALS AND METHODS**

**Animals.** Pregnant C57BL/6J Sv129/OlaHsd mice were obtained from Harlan (Horst, The Netherlands) at day 2 post coitum. Lxra−/− female mice (26) on a C57BL/6J Sv129/OlaHsd background were crossed with Lxra+/− male mice on the same background in our laboratory to obtain offspring with genotypes. Animals were housed in temperature-controlled rooms (23°C) with 12-h light cycling and received standard RMH-B mouse chow (Arie Blok BV, Woerden, The Netherlands) and water ad libitum. Experimental procedures were approved by the local Ethical Committee for Animal Experiments of the University of Groningen.

**Experimental procedures.** From day 10 post coitum until day 1 after delivery, C57BL/6J Sv129/OlaHsd wild-type females received standard chow only or chow supplemented with 0.015% w/w T0901317 (Cayman Chemicals, Ann Arbor, MI). At days 13.5, 15.5, 17.5, and 19.5 post coitum, pregnant C57BL/6J mice were anaesthetized with isoflurane and terminated by heart puncture. Lxra−/− females received the T0901317 diet from day 10 post coitum till day 19.5 post partum. Blood was collected in EDTA containing tubes. Liver samples of the dams were snap-frozen in liquid nitrogen. Fetuses were removed from uteri, their weight and length were measured, and they were terminated by decapitation and dissected. Pups were killed at day 1 post partum. Blood samples were taken by exsanguination. Livers and intestines of fetuses and pups were collected, immediately snap-frozen in liquid nitrogen, and stored at −80°C until mRNA isolation or biochemical analysis. Experimental procedures were approved by the local Ethical Committee for Animal Experiments of the University of Groningen.

**Figure 1.** Hepatic (A) and plasma cholesterol (B) levels in pregnant mice. Filled bars, control mice; open bars, mice receiving 0.015% T0901317 in the diet from day 10 post coitum on. Values are means ± SD; n = 6. *P < 0.05, for treated vs. control. dpc, Days post coitum; dpp, days post partum.

**Figure 2.** Hepatic (A) and plasma cholesterol (B) levels in offspring of mice treated with a control diet (black bars) or a diet containing 0.015% T0901317 (open bars) from day 10.5 of gestation. Values are means ± SD; n = 6. *P < 0.05, for treated vs. control.
In another group of pups from chow-fed dams, the pups were taken away from the dam immediately after delivery, i.e., before the first suckling, and hand fed for 14 h with either Orisel-Junior (composition: glucose 0.2 mmol/l, 14 mg/l Na, 10 mg/l K, and 20 mg/l Cl; and osmolarity: 216 mosM; Nutricia, Zoetermeer, The Netherlands) or Collate First Life Puppy Colostrum [composition: see Supplemental Table 1 (Nettex, Kent, UK); supplemental data for this article is available online at the Am J Physiol Endocrinol Metab website] using a 1-ml syringe with a disposable feeding needle attached to it. Groups of four to five pups were placed in glass petri dishes filled with nesting material. The petri dishes were placed on a heating pad, and the temperature inside the petri dishes was kept ~30°C. After 14 h of hand feeding, the pups were terminated by decapitation, and the livers and blood were collected.

To investigate the influence of receiving T0901317 during fetal development on coping with a HFHC diet, pregnant C57BL/6J females received chow only or chow supplemented with 0.015% wt/wt T0901317 from day 10 of gestation until day 1 after delivery. All dams received chow till the pups were weaned. Offspring received chow until 6 wk of age and received either chow or a semi-synthetic Western-type diet (HFHC) containing 15% (wt/wt) cacao butter and 0.25% (wt/wt) cholesterol (Diet W; Special Diet Services, Witham, UK) for 2 wk. Offspring was terminated at 8 wk of age.

Analytical procedures. Liver homogenates were made by homogenization of the complete fetal liver (~20–80 mg, depending on age) in 200 μl of ice-cold water. Hepatic lipids were extracted using the Bligh and Dyer method (7). Commercially available kits were used for the determination of total cholesterol (Roche, Mannheim, Germany) in liver lipid extracts as well as in plasma. Pooled plasma samples from all animals of one group were used for the preparation of the samples.

Fig. 3. FPLC analysis of pooled plasma (n = 10 per group) of 19 dpc control fetuses (■) or 19 dpc fetuses from dams receiving T0901317 (○). Analysis was performed as described in MATERIALS AND METHODS. IDL, intermediate density lipoprotein; VLDL, very low-density lipoprotein.

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Fig. 4. Changes in relative hepatic gene expression in C57BL/6 fetuses on several days of gestation upon treatment of the dam with T0901317. Hepatic expression levels of Lxra (A), Lxrb (B), Abcg5 (C), Abcg8 (D), Abca1 (E), and Hmgcr (F) are displayed. Results were normalized to 18s mRNA levels. Adult expression levels are arbitrarily defined as 1. Filled bars, control fetuses; open bars, fetuses from dams receiving 0.015% T0901317. Values are means ± SD; n = 6. *P < 0.05, for treated vs. control.
RESULTS

T0901317 administration influences cholesterol levels in pregnant mice and their offspring. Dams receiving T0901317 from days 10.5 to 19.5 post coitum had slightly lower body weights on day 19.5 of gestation compared with control dams (Table 1). Liver weights of the treated animals, expressed as a percentage of total body weight, were increased by ~50% during the entire treatment period (Table 1). T0901317 treatment had no influence on the number of offspring per dam (Table 1). T0901317 administration significantly reduced hepatic cholesterol levels to 75% of control values after 3 days of treatment and to 70 and 67% of control levels, respectively, after 9 and 11 days of treatment (Fig. 1A). Plasma cholesterol concentrations were increased by ~50% in treated dams compared with controls from 5 days of treatment onwards (Fig. 1B). FPLC analysis revealed that the increase in cholesterol reflected elevated HDL levels (data not shown).

Fetuses of treated dams weighed 15% less and were 10% shorter in length at day 19.5 post coitum, while at the other days of gestation no differences in weight or length between the groups were observed (Table 1). Fetal hepatic cholesterol levels were decreased at days 13.5 and 17.5 of gestation compared with controls, while no differences were seen at other days of gestation (Fig. 2A). Hematoxylin-eosin staining of fetal livers showed no morphological differences between control and treated fetuses (data not shown). Plasma cholesterol in the offspring was measured at day 19.5 of gestation and at day 1 after delivery only and found to be doubled in the treated fetuses/newborns (Fig. 2B). FPLC analysis showed a profile typical for fetal murine plasma and revealed that the increase in cholesterol on day 19 of gestation reflects elevated intermediate density lipoprotein/LDL levels (Fig. 3).

Administration of T0901317 to dams induces Lxr target genes in fetal tissue. Fetal hepatic Lxra expression levels were around half the values of adult expression levels throughout gestation and rose to approximately adult levels at day 1 after delivery (Fig. 4A). Surprisingly, fetal hepatic expression levels of Lxrb were two to three times higher on all days of gestation compared with adult hepatic expression levels and remained at this level at day 1 after delivery (Fig. 4B). Administration of T0901317 to the diet of the dam did not influence expression levels of either Lxra or Lxrb (Fig. 4, A and B).

In fetal control liver, cholesterol transporters and LXR target genes Abcg5/g8, encoding the canalicular cholesterol transporter, were expressed a 100 times lower than adult levels at day 13.5 and remained very low during the gestation. At day 1 after delivery, Abcg5/g8 expression levels acutely increased and were comparable with adult expression levels (Fig. 4, C and D). Hepatic Abcg5/g8 expression was induced 20- and 5-fold, respectively, at day 13.5 post coitum in fetuses from T0901317-receiving dams compared with control fetuses. The induction was most pronounced on day 17.5 of the gestation, when hepatic expression levels of Abcg5 in treated fetuses were 50 times higher and Abcg8 levels were 25 times higher than in control fetuses. On day 1 after delivery, Abcg5 expression levels were induced four times and Abcg8 levels were induced 2.5 times in livers of mice exposed to T0901317 before birth.

Expression levels of the cholesterol transporter Abca1 were similar to adult levels at days 13.5 and 15.5 of gestation in the
fetal liver and were two to three times higher than adult levels at days 17.5 and 19.5 of gestation and at day 1 after delivery (Fig. 4E). Administration of T0901317 to the diet of the dam induced fetal hepatic expression levels of Abca1 significantly at days 15.5 and 19.5 of gestation to 2- and 1.3-fold of control levels, respectively. Fetal hepatic expression levels of the rate-controlling enzyme in of the cholesterol synthesis pathway Hmgcr were around adult levels throughout the gestation and did not change upon treatment of the dam with T0901317 (Fig. 4F).

In the fetal intestine, Abcg5/g8 expression levels were very low before day 17.5 of gestation and rose to around adult levels on day 1 after delivery (Fig. 5, A and B). Administration of T0901317 to the diet of the dam led to a significant increase of Abcg5 expression levels on day 19.5 of gestation in fetal intestine. On all other days examined the increase seen in Abcg5 and Abcg8 expression levels upon T0901317 administration was not significantly different from controls. Abca1 expression levels in fetal intestine ranged between 0.5 times adult expression to around adult expression levels throughout gestation. Addition of T0901317 to the diet of dams led to a three to five times induction of fetal intestinal Abca1 levels throughout gestation (Fig. 4F).

Gene expression levels in pups on day 1 after delivery are independent of dietary cholesterol. Since we found fetal hepatic Abcg5/g8 levels to be extremely low during gestation and suddenly increased to adult levels after delivery, we investigated whether this increase was caused by the change from a low-cholesterol environment in the uterus to a high-cholesterol diet after delivery. C57BL6/6J pups were taken away from the dam immediately after delivery, not allowing them to suckle, and were hand fed for 14 h. The pups received either an oral rehydration salts solution or puppy colostrum to mimic mother’s milk. No differences in hepatic (Fig. 6A) or intestinal (Fig. 6B) Abcg5/g8 expression levels between the two groups were seen.

T0901317 directly induces Lxr in the fetus. To investigate to what extent T0901317-induced effects were directly mediated by fetal Lxra, Lxra+/- females were crossed with Lxra+/-/+ males. In this way, fetuses of all Lxra genotypes were obtained, i.e., Lxra+/-+/-, Lxra+/-/-, and Lxra-/--. Only results of Lxra+/-+/- fetuses are shown (Fig. 7). For the wild-type (Lxra+/-+) and Lxra-knockout (Lxra-/-) fetuses on day 19.5 of gestation upon treatment of the heterozygote dam with T0901317. Results were normalized to 18s mRNA levels. Hepatic expression levels of fetal Lxra (A), Abca1 (B), Abcg5 (C), and Abcg8 (D) are displayed. Filled bars, control fetuses; open bars, fetuses from dams receiving 0.015% T0901317. Values are means ± SD; n = 6. *P < 0.05, for treated vs. control; #P < 0.05, for knockout vs. wild type.
Hepatic expression levels of Abca1 were not different in knockout fetuses from T0901317-treated dams compared with wild-type fetuses from T0901317-treated dams (Fig. 7B). Expression of Abcg5/8 in Lxra−/− fetuses from dams receiving T0901317 was increased ~15 times compared with Lxra+/+ fetuses from control dams while T0901317 treatment in Lxra−/− fetuses led to a 2.5 increase of Abcg5/8 compared with untreated knockout fetuses, but relative expression levels in the T0901317-treated knockout fetuses were still very low with an average of 0.18, compared with an average of 0.08 in untreated knockout fetuses for Abcg5 (Fig. 7, C and D). T0901317 administration did not change hepatic cholesterol levels in wild-type or knockout fetuses (data not shown).

Perinatal Lxr activation does not influence adult cholesterol metabolism. Offspring of T0901317 and chow-fed mice were fed either a HFHC or standard low-cholesterol chow from 6 until 8 wk of age, after which the animals were killed. There were no differences in body weight or body weight to liver weight ratio between the four treatment groups within one gender (Table 2). Hepatic gene expression levels of the representative LXR target genes Abcg8 and Abca1 were higher in all offspring fed HFHC except Abca1 in females (Fig. 8, A and B), regardless of receiving T0901317 during gestation. Hepatic and plasma cholesterol levels were induced in all offspring that received HFHC compared with controls except plasma levels in females (Table 2). Hepatic cholesterol levels were two times higher in the control females than in the control males, and females showed a three times increase of hepatic cholesterol levels upon receiving HFHC, while the HFHC-fed males showed a two times increase compared with chow-fed males. In all offspring, increases in hepatic cholesterol upon the HFHC diet were independent from the treatment in utero.

**DISCUSSION**

The LXR are of great significance in regulating cholesterol metabolism in the adult. So far, the influence of LXR on cholesterol metabolism during fetal development is unknown. In this study, we show for the first time that cholesterol metabolism in the fetal mouse can be activated by addition of the LXR agonist T0901317 to the diet of the dam. The LXR-specific effects on cholesterol metabolism in the fetus are comparable to the effects seen in adult mice (15, 21).

Annicotte et al. (2) investigated expression patterns of Lxr in various fetal mouse tissues using in situ hybridization experiments and showed that both Lxra and Lxrb are expressed in fetal liver from day 10.5 post coitum onwards. They suggest that Lxr is important but not essential for normal fetal development, as is evident from the phenotypes of the various Lxr-null mice (1, 14, 25). Balasubramaniyan et al. (5) reported low RNA expression levels of Lxrα during fetal rat development, comparable to our results, and Sakamoto et al. (20) showed that Lxra is mainly expressed in fetal rat macrophages from gestational day 12 onwards, while expression in the hepatocyte is only present from gestational day 18 onwards. So far, however, the metabolic functions of Lxr in the fetus have not been determined. In the current study, we focused on the regulatory functions of Lxr in fetal cholesterol metabolism in the mouse.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>T09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Offspring, g</td>
<td>M control 22.9±1.2, M HFHC 22.7±0.8, F control 17.6±0.8, F HFHC 17.2±1.9</td>
<td></td>
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Table 2. Parameters of adult offspring

<table>
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<tr>
<th>Weight</th>
<th>Liver Weight Dams to Body Weight, %</th>
<th>Hepatic Total Cholesterol, umol/g</th>
<th>Plasma Cholesterol, mM</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>T09</td>
<td>Control</td>
<td>T09</td>
</tr>
<tr>
<td>M control</td>
<td>22.9±1.2, 20.7±4.6</td>
<td>5.7±0.5, 5.5±0.6</td>
<td>1.6±0.2, 1.8±0.4</td>
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<tr>
<td>M HFHC</td>
<td>22.7±0.8, 23.8±0.9</td>
<td>5.2±0.7, 5.4±0.4</td>
<td>3.4±0.7*, 3.8±0.4*</td>
</tr>
<tr>
<td>F control</td>
<td>17.6±0.8, 19.6±1.2</td>
<td>4.5±0.6, 4.0±1.5</td>
<td>3.2±0.5, 2.6±0.4</td>
</tr>
<tr>
<td>F HFHC</td>
<td>17.2±1.9, 18.5±1.2</td>
<td>5.1±0.5, 4.3±0.3</td>
<td>9.3±1.9*, 7.5±0.8*</td>
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Parameters of C57BL/6d OlaHsd offspring of dams that received either chow or chow with T0901317. M, male; F, female. Offspring received either chow or a high-fat/high-cholesterol diet from 6–8 wk of age. Data are means ± SD; n = 6. *P < 0.05, HFHC vs. control.

**Fig. 8. Changes in relative hepatic gene expression in offspring of mice fed chow containing 0.015% T0901317 or control chow during gestation. Offspring received either chow or a high-fat/high-cholesterol (HFHC) diet from 6 till 8 wk of age. A: gene expression in male offspring; B: gene expression in female offspring. Open bars, control offspring of control mice; light shaded bars, HFHC offspring of control mice; dark shaded bars, control offspring of T0901317-fed mice; filled bars, HFHC offspring of T0901317-fed mice. Values are means ± SD; n = 6. *P < 0.05, for control chow vs. control HF; **P < 0.05, for T0901317 chow vs. T0901317 HF. MCC and FCC, male and female control chow, respectively. MCHF and FCHF, male and female HF chow, respectively. MTC and FTC, male and female T0901317-treated chow, respectively. MTHF and FTHF, male and female T0901317-treated HF, respectively.**
The synthetic Lxr agonist T0901317 has frequently been used to delineate functions of Lxr in the adult mouse (8, 15, 21). We show that overall effects of this agonist in the developing fetus are in concordance with findings in adult mice. Activation of Lxr led to higher fetal plasma cholesterol concentrations. Fetal murine lipid profiles are distinctly different from adult lipid profiles, with only one predominant lipoprotein present in fetal plasma in the last stages of gestation (3, 10). In treated fetuses on day 19.5 of gestation, the increase in plasma cholesterol represents an increase in all lipoprotein fractions, putatively attributable to induction of hepatic and intestinal Abca1, which is crucial for lipoprotein formation. Contrarily, hepatic cholesterol concentrations were lowered. Since absence of effects on hepatic Hmger expression suggests unaffected cholesterol biosynthesis, this latter effect is assumed to be caused by induction of Abca1 and the heterodimeric cholesterol transporter Abcg5/Abcg8 (8). Abcg5/g8 in hepatocytes is crucially involved in transporting cholesterol into the bile. It has been shown that bile formation is an ontogenetically regulated process and that bile excretion function is still immature at birth in rodents (4, 9). Our results indicate that the rapid increase in hepatic Abcg5/g8 expression levels on day 1 after delivery is apparently not directly caused by the onset of dietary cholesterol intake of the pup. Molecular mechanisms behind this increase in hepatic cholesterol transporters remain undefined. Based on our data, it is tempting to speculate that both excretory pathways to HDL and to bile are already functional in the fetal mouse liver under conditions of Lxr activation.

Gene expression levels of Abcg5/g8 were very low in the fetal liver and increased 10-fold at day 1 after delivery compared with expression levels during gestation. In the fetal intestine, gene expression levels of Abcg5/g8 were also very low before day 17.5 of gestation but increased gradually over the following gestational days to reach 80–100% of adult levels at day 1 after delivery. Abcg5/g8 is thought to transfer cholesterol and other sterols from the enterocytes back into the intestinal lumen, hence reducing cholesterol absorption efficiency (16). As stated previously, Abcg5/g8 are target genes of Lxr, which in turn is activated by oxysterols. We postulated that the increase in hepatic gene expression levels on day 1 after delivery was caused by the sudden change from exposure to low levels of cholesterol or oxysterols in the uterus to receiving high amounts of dietary cholesterol (derivatives) from mother’s milk after delivery. To test this hypothesis, we hand fed newborn pups that had not yet received mother’s milk for 14 h with either a colostrum replacer or with oral rehydration solution which does not contain any lipids. Hepatic and intestinal gene expression levels of Abcg5/g8 did not differ between the two groups and were comparable to gene expression levels of control pups on day 1 after delivery in our previous experiments.

Since administration of T0901317 to the diet of the dam led to induction of LXR target genes in fetal liver and intestine, we assume that T0901317 is transported across the placenta and directly activates fetal Lxr. However, there is a possibility that effects observed in the fetus were caused by higher plasma (chole)sterol levels in the treated dam. To determine whether induction of Lxr target genes in the fetuses was caused by direct actions of T0901317 or by the changed lipid profile of the dam, we crossed Lxra-heterozygous mice and provided T0901317 to the pregnant mice. In this way, the fetal environment was similar for all fetuses but potential direct effects of T0901317 in fetuses of the same dam were dependent on the different genotype of the fetuses. In Lxra−/− fetuses exposed to T0901317 via the dam, hepatic expression of the Lxr target genes Abcg5 and Abcg8 was ~15 times lower than in wild-type and heterozygote fetuses of the same dam. Our data indicate that T0901317 is indeed directly effective in fetuses, mainly via the activation of Lxra. However, there was a small but significant twofold increase in hepatic Abcg5/g8 expression levels even in the absence of Lxra. This could be due to activation of Lxrb in these fetuses. Fetal hepatic expression of Lxrb was about three times higher compared with adult expression levels, as was seen in the WT-experiments, and could compensate the loss of Lxra activity in the knockout mice.

To determine whether pharmacological activation of the Lxr system during fetal development, i.e., severe distortion of fetal lipid homeostasis, has detrimental or beneficial long-term effects, we fed a HFHC diet to 6-wk-old offspring obtained from control or T0901317-treated wild-type dams. As expected, based on previous studies (23, 27), plasma cholesterol levels, hepatic cholesterol levels, and hepatic gene expression of cholesterol transporters rose upon receiving the HFHC diet. T0901317 administration before birth, however, had no influence on any of the parameters. We can therefore assume that, although administration of T0901317 in utero has considerable direct and strong effects on the fetal cholesterol metabolism, these metabolic adaptations are diminished during (young) adulthood and do not influence general responses to a HFHC diet provided for a relatively short period of time. Obviously, this does not exclude the occurrence of (subtle) consequences on other aspects of cholesterol metabolism that have not been addressed in this study.

In conclusion, we present for the first time evidence that Lxr is functionally active in fetal liver when stimulated with the synthetic agonist T0901317. Moreover, the pathways controlled by Lxr in adult mouse liver related to maintenance of cholesterol homeostasis can be influenced by providing this synthetic agonist via the diet of the dam. However, effects appeared to be transient and activation of Lxr in utero did not evidently affect coping with a HFHC diet in adulthood.

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GRANTS

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