Perturbation of developmental gene expression in rat liver by fibric acid derivatives: lipoprotein lipase and α-fetoprotein as models

BART STAELS 1 and JOHAN AUWERX 1,2,*

1Laboratorium voor Experimentele Geneeskunde en Endocrinologie, Department of Developmental Biology, Gasthuisberg, Katholieke Universiteit Leuven, Belgium
2Laboratoire de Biologie des Régulations chez les Eucaryotes, Centre de Biochimie, UMR 134 du CNRS, Parc Valrose, Nice, France
*Author for correspondence at the French address

Summary

Liver lipoprotein lipase (LPL) and α-fetoprotein (AFP) gene expression show similar developmental patterns. Both mRNAs are abundantly expressed in neonatal rat liver and gradually disappear upon ageing. Treatment with fibric acid derivatives, such as fenofibrate, not only delays the developmental extinction of the LPL gene, but also increases LPL mRNA levels in neonatal rat liver. Similarly, the developmental extinction of the AFP gene in the liver is clearly delayed after fenofibrate. In adult rat liver, fibric acid derivatives transcriptionally reinduce a mRNA with similar size as LPL, but no effect on AFP mRNA was detected. Sequence comparison of clones isolated from a fenofibrate-induced cDNA library demonstrates that the fenofibrate-(re)induced mRNA in adult rat liver is encoding for LPL. The induction of LPL after fenofibrate is tissue-specific, since heart and adipose tissue LPL mRNA levels remain unchanged. In conclusion, fibric acid derivatives modulate developmental expression patterns in rat liver, and may selectively reinduce the expression of extinct genes in adult rat liver.

Key words: gene regulation, transcription factors, steroid hormone receptors, PPAR, fibrates, HNF.

Abbreviations: LPL, lipoprotein lipase; AFP, α-fetoprotein; apo, apolipoprotein.

Introduction

Fibric acid derivatives, such as the drugs fenofibrate and clofibrate, are presently widely used in the treatment of diet-resistant hyperlipidemia (Sirtori and Francheschini, 1988). These drugs are extremely effective in lowering plasma triglyceride concentrations. Although very little is known about the action mechanism of fibrates, not only delays the developmental extinction of the LPL gene, but also increases LPL mRNA levels in neonatal rat liver. Similarly, the developmental extinction of the AFP gene in the liver is clearly delayed after fenofibrate. In adult rat liver, fibric acid derivatives transcriptionally reinduce a mRNA with similar size as LPL, but no effect on AFP mRNA was detected. Sequence comparison of clones isolated from a fenofibrate-induced cDNA library demonstrates that the fenofibrate-(re)induced mRNA in adult rat liver is encoding for LPL. The induction of LPL after fenofibrate is tissue-specific, since heart and adipose tissue LPL mRNA levels remain unchanged. In conclusion, fibric acid derivatives modulate developmental expression patterns in rat liver, and may selectively reinduce the expression of extinct genes in adult rat liver.

speculate that fibric acid derivatives not only regulate physiological processes, such as lipid and energy metabolism, but also mediate alterations in developmental patterns of gene expression, as has been demonstrated for other ligands belonging to the same superfamily (Guertin et al., 1983; Turcotte et al., 1985).

LPL is an enzyme that binds after secretion to glycosaminoglycans on the luminal surface of capillary endothelial cells (Olivecrona and Bengtsson-Olivecrona, 1987), where it hydrolyzes triglycerides from exogenous and endogenous origin, providing free fatty acids which are utilized as a source of energy by muscle and other tissues or which are stored in adipose tissue. Consequently, LPL plays a pivotal role in energy utilization and storage (Eckel, 1987). LPL is synthesized in several tissues, such as skeletal and heart muscle, adipose tissue and the lactating mammary gland, but not in adult liver (Garfinkel and Schotz, 1987). Recently, however, the synthesis of LPL in liver of newborn rats was reported (Burgaya et al., 1989; Llobera et al., 1979). Therefore the developmental pattern of LPL gene expression in liver was studied and compared to the expression of the α-fetoprotein (AFP) gene, which encodes for a well-known fetal trait protein. The hepatic expression of the AFP gene reaches low levels shortly after birth under

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the control of the transacting locus raf (Vogt et al., 1987) as a consequence of dominant repression (Vacher and Tilghman, 1990).

In our studies, it was demonstrated that the expression of liver LPL diminished during development in a similar fashion as AFP expression. Furthermore, it was shown that fibric acid derivatives (or their potential natural analogues) play a role in developmental processes by perturbing the developmental pattern of both LPL and AFP gene expression. In addition, these compounds are able to reactivate the expression of the LPL, but not the AFP gene in adult rat liver.

Materials and methods

Animals and treatments

Male Wistar rats were killed at 5, 10, 15, 20, 30, 40, 60 and 80 days of age. Since fibric acid derivatives have been shown to be active in fetal tissues after maternal administration (Wilson et al., 1991), treatment of timed pregnant rats with fenofibrate (Laboratoires Fournier, Dax, France; 0.5%, w/w, mixed in rat chow) was started on day 15 after conception. Control mothers received normal rat chow. Pups born between the morning of 1 day and the morning of the next were considered 0 days old. On day 5 post-natally, each litter was reduced to 9 pups per mother. One third (n=3) of control and fenofibrate-treated pups were killed on days 13, 20 and 30 after birth, respectively. Adult male Wistar rats received fenofibrate or clofibrate for the indicated periods of time mixed at the indicated concentrations (w/w) with standard rat chow.

At the end of the experiments animals were killed by exsanguination under ether anesthesia. Liver, heart and adipose tissue were removed immediately, rinsed with 0.9% NaCl and frozen in liquid nitrogen.

RNA analysis

RNA was prepared by the guanidine isothiocyanate/cesium chloride procedure from pooled (developmental expression) or individual (studies with fibric acid derivatives) liver, adipose or heart muscle tissues (Chirgwin et al., 1979). Northern and dot blot hybridizations of total cellular RNA were performed as described previously (Auwerx et al., 1988; Staels et al., 1989). The following probes were labeled by random priming (Boehringer Mannheim): rat apo E (Staels et al., 1989), AFP (Jagodzinski et al., 1981), a 1.36 kb Eco RI fragment of the human LPL cDNA clone hLPL-26 (Auwerx et al., 1988), and a chicken β-actin cDNA clone (Cleveland et al., 1980). After hybridization, filters were washed in 0.5×SSC and 0.1% SDS for 10 minutes at room temperature and twice for 30 minutes at 65°C and subsequently exposed to X-ray film (X-OMAT-AR, Kodak). Transcripts were quantitated by laser densitometric scanning of dot blot autoradiographs (Staels et al., 1989).

Isolation of nuclei and transcriptional rate assay

Nuclei were prepared from livers of untreated rats and from livers of rats treated for 14 days with fenofibrate (0.5%, w/w, in rat chow) exactly as described by Gorski et al., 1986. Transcription run-on assays were performed as described by Nevins (1987). Equivalent amounts of labeled nuclear RNA were hybridized for 36 hours at 42°C to 5 µg of purified cDNAs immobilized on Hybond-C Extra filters (Amersham). The following cDNA probes were spotted: the human LPL cDNA clone hLPL-26 (Auwerx et al., 1988) and a rat apo E cDNA probe (Staels et al., 1989). As a control, 5 µg of vector DNA also was applied to the filter. After hybridization, filters were washed at room temperature for 10 minutes in 0.5 × SSC and 0.1% SDS and twice for 30 minutes at 65°C and subsequently exposed to X-ray film (X-OMAT-AR, Kodak).

Isolation and sequencing of fenofibrate-induced cDNA clones from rat liver

Poly(A)+ mRNA was isolated from total liver RNA from fenofibrate-treated rats (0.5%, w/w, mixed in rat chow during 14 days) (Aviv and Leder, 1972). A lambda cDNA library was constructed in the Uni-ZAP XR vector (Stratagene, La Jolla, CA, USA) and screened with a 32P-labeled 1.36 kb EcoRI fragment of the human LPL cDNA clone hLPL-26 (Auwerx et al., 1988) at high stringency (two final washes of 30 minutes at 65°C). Several clones were obtained and two of them were characterized in detail. These two clones were subcloned in pBluescript SK- by in vivo excision rescue according to the manufacturer’s instructions. Parts of each strand of both clones were sequenced by the dideoxy chain termination DNA sequencing method (Sanger et al., 1977). Homology searches were performed with the GENEPRO program (Riverside Scientific, Seattle, WA, USA).

Results

LPL is expressed in neonatal rat liver and its developmental extinction pattern resembles that of AFP

No or little LPL mRNA can be detected in adult rat liver (Fig.1B). However, in neonatal animals substantial amounts of LPL mRNA can be detected in the liver. The expression of the LPL gene in rat liver is highest during the first days after birth and decreases gradually thereafter, becoming undetectable around day 30 of life (Fig.1A). This developmental extinction of liver LPL is confirmed by northern blot analysis. In addition, it can be seen that this developmental pattern is very similar to that of AFP (Fig.1A,B). Consistent with our previous data (Staels et al., 1989), hybridization of the same blots with apo E demonstrates that apo E mRNA steady-state levels remain constant in rat liver throughout the postnatal development period (Fig.1A,B).

Fibric acid derivatives modulate the developmental pattern of liver LPL and AFP gene expression

Recently a group of receptors, activated by peroxisomal proliferators (such as fibric acid derivatives), belonging to the large erb-A/steroid receptor gene superfamily has been identified (Issemann and Green, 1990; Dreyer et al., 1992). After activation by their ligands, receptors belonging to this family activate the transcription of ligand-inducible genes and mediate thereby profound physiological and developmental changes in higher eukaryotes (Evans, 1988). In view of these observations and since fibric acid derivatives can alter LPL activity levels (Nikkilä et al., 1976, 1977; Goldberg et al., 1979; Vessby et al., 1980), we next addressed the question of whether fibric acid derivatives might influence liver developmental processes. Both the LPL and AFP genes were considered suitable as models to test this hypothesis. Consequently, treatment with fenofibrate was started in utero and continued until animals were killed. LPL and AFP mRNA levels were determined in livers of...
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Fig. 1. The developmental expression pattern of the LPL and AFP genes in rat liver is identical. (A) Quantitative analysis of LPL and AFP mRNA disappearance from the neonatal rat liver by dot blot hybridization. RNA was prepared from the livers of male rats of the indicated age and LPL, AFP and apo E mRNA levels were measured and expressed as described in Materials and methods. (B) Northern blot analysis of the developmental expression of the LPL, AFP and apo E genes in rat liver. 30 µg of total RNA were subjected to electrophoresis, transferred to a nylon membrane and hybridized as described in Materials and methods. The position of the 18S and 28S rRNA bands are indicated on the upper panel. Lane 1: 5 days; Lane 2: 10 days; Lane 3: 15 days; Lane 4: 20 days; Lane 5: 30 days; Lane 6: 40 days; Lane 7: 60 days; Lane 8: 80 days after birth.

treated rats at day 13 of life, when both LPL and AFP mRNAs are abundantly present, at day 20, when both mRNAs are declining, and at day 30, when both mRNAs are completely extinguished, and were compared to the levels in livers of control rat of the same age. Administration of fenofibrate increased hepatic LPL mRNA levels at all ages (Fig.2 left panel), with the effect being most pronounced at day 30 when LPL is no longer present in untreated rat liver. In contrast to LPL, hepatic AFP mRNA levels did not change significantly at 13 and 20 days of age, but AFP mRNA remained clearly detectable in fenofibrate treated rat liver at day 30 (Fig.2 middle panel). As a control, hepatic apo E mRNA levels were measured. Consistent with the developmental pattern of liver apo E gene expression (Fig.1), apo E mRNA levels remained constant at any age and are not affected by fenofibrate treatment (Fig.2 right panel).

Fibric acid derivatives reinduce LPL, but not AFP gene expression in adult rat liver

To investigate whether fibric acid derivatives are able to reverse the developmental extinction of the LPL and AFP genes, liver LPL and AFP gene expression were determined in adult rats after treatment with fenofibrate. A mRNA species similar in size to LPL mRNA already became detectable in adult rat liver after 3 days of fenofibrate treatment and increased further to levels comparable to those observed in neonatal rat liver after 14 days of treatment (Fig.3A). In contrast, AFP mRNA remained undetectable in adult rat liver treated with fenofibrate, whereas hepatic apo E mRNA steady-state levels did not change during the period of treatment with fenofibrate (Fig.3A). Northern blot analysis confirmed the results obtained by dot blot analysis and showed that fenofibrate caused the appearance of a hybridization pattern comparable to neonatal liver LPL mRNA (Fig.3B).

The influence of the dose of fenofibrate on the induction of the LPL gene was investigated next. LPL mRNA was undetectable at a dose of 0.005% fenofibrate, but became detectable at the intermediate dose of 0.05% and increased 10-fold at the highest dose of fenofibrate tested (Fig.4A). Northern blot analysis confirmed the dose-dependence of LPL induction by fenofibrate (Fig.4B). Again AFP mRNA could not be detected at any dose tested, even after prolonged exposure of the filters (Fig.4A,B). As expected, apo E mRNA did not change markedly after treatment with different doses of fenofibrate (Fig.4A,B).

To ascertain that the mRNA detected after fenofibrate treatment indeed corresponded to LPL and not to another mRNA with similar size, a fenofibrate-induced liver cDNA library was constructed and screened at high stringency with the human LPL clone, hLPL26 (Auwerx et al., 1988). In contrast to the absence of LPL clones in an adult rat liver cDNA library, several clones were isolated from a library prepared with liver mRNA obtained from fenofibrate-treated animals. Two different clones were isolated, sequenced and the cDNA as well as the deduced amino acid sequence were compared to the amino acid sequence of
mouse, human, bovine and guinea pig LPL (Table 1). Clone 1, which was found to code for the middle part of the LPL protein, showed a high degree of homology, both at the DNA and amino acid level, with all other species. The sequence of this clone differed in only one amino acid with the sequence of the mouse, the species that is most closely related to the rat (Table 1). Clone 1 contains the interfacial lipid-binding domain with the enzymatically essential serine (Table 1). The high degree of homology between all species within this region is remarkable and points to the importance of this region for LPL function. Clone 2 contains the carboxy-terminal part of the protein (Table 1). Our data confirm and extend previous observations that most of the divergence between different species occurs near the end of the molecule, with the middle showing higher conservation (compare clone 1 and 2, Table 1) (Kirchgessner et al., 1987). However, even in this part of the molecule rat and mouse sequences show an extremely high degree of homology (91% at the amino acid and 93% at the DNA level). More divergence between the rat and human, bovine and guinea pig LPL was, however, detected in this clone. Both rat and mouse LPL have lost one amino acid near the end of the molecule, and contain therefore only 447 instead of 448 amino acids in the mature protein (Kirchgessner et al., 1987).

Finally, to investigate whether the induction of liver LPL was a general effect of fibric acid derivatives, or confined to fenofibrate only, adult male rats were treated with another fibric acid derivative, clofibrate. Administration of clofibrate mixed at a dose of 0.5% in rat chow caused the reappearance of LPL in adult rat liver to a level comparable to the induction observed after 0.05% fenofibrate (data not shown).

**The induction of adult liver LPL by fenofibrate is transcriptional**

To determine whether the induction of liver LPL mRNA was associated with an increased transcription of the LPL gene, nuclear run-on experiments were performed on nuclei isolated from livers of fenofibrate treated as well as control rats. The transcription of the LPL gene was clearly induced in nuclei from fenofibrate-treated livers than from control livers, whereas the transcription rate of the β-actin gene remains fairly constant (Fig. 5).

**The induction of adult liver LPL by fenofibrate is reversible**

To investigate whether the effects of fibric acid derivatives on the induction of LPL gene expression is reversible or not, adult rats were treated for 14 days with fenofibrate (0.5%, w/w, mixed in rat chow) and liver LPL mRNA levels were determined on day 0, 1, 3, 7, 14 and 28 after cessation of fenofibrate therapy. LPL mRNA already decreased after 1 day and became undetectable 14 days after cessation of fenofibrate administration (Fig. 6). In contrast, liver apo E
mRNA levels remained constant throughout the treatment and wash-out period.

The effects of fenofibrate are tissue-selective
Since LPL is abundantly present in heart and adipose tissue and is also present in other tissues (Kirchgessner et al., 1987; Enerback et al., 1987), the influence of different doses of fenofibrate on extrahepatic LPL gene expression was determined. In contrast to the liver, LPL mRNA was abundantly present in heart muscle and adipose tissue of untreated rats (Table 2). However, administration of fenofibrate did not cause any significant change in LPL mRNA levels in both tissues (Table 2). Thus, fibric acid derivatives regulate LPL gene expression in a tissue-selective manner.

Discussion
The results in this study show for the first time that LPL mRNA is present in neonatal, but not adult rat liver. The developmental pattern of LPL gene expression in liver is reminiscent of the expression pattern of the AFP gene (Liao et al., 1980). Both genes are abundantly expressed in neonatal rat liver and their expression is turned off within a few weeks after birth. Furthermore, the developmental extinc-

tion of these genes is strongly influenced by transcription factors of the steroid/erb A receptor family (Evans, 1988). This latter action is exemplified by the involvement of glucocorticoid hormones in the suppression of AFP gene transcription in developing rat liver (Guertin et al., 1983; Turcotte et al., 1985). The neonatal extinction of LPL gene expression is accelerated in a similar fashion by hydrocortisone (Peinado-Onsurbe et al., 1992). Thus, both LPL and AFP belong to a class of hepatic proteins that are expressed during fetal and neonatal hepatic tissue differentiation and are repressed once full tissue maturation is reached (Abelev, 1971; Liao et al., 1980; Tilghman and Belayew, 1982; Turcotte et al., 1985).

The developmental expression pattern of both the AFP and LPL genes is markedly influenced by fibric acid derivatives. In contrast to glucocorticoids, fibric acid derivatives delay the neonatal extinction of both genes, thereby retarding the developmental alterations in hepatic gene expression. However, some interesting differences in response to fibric acid derivatives are noted between the AFP and LPL gene. First, in contrast to AFP, LPL gene expression actually increases in neonatal rat liver during fenofibrate treatment. Second, only LPL, but not AFP, gene expression can be reinduced by a 14 day treatment period with fibric acid derivatives in adult rat liver. It can, however, not be excluded at present that more prolonged treat-

Fig. 3. Fenofibrate administration reinduces LPL, but not AFP gene expression in adult rat liver. (A) Quantitative analysis of LPL, AFP and apo E mRNA levels in livers of fenofibrate-treated adult rats. RNA was prepared from the livers of adult, male rats treated during the indicated number of days with fenofibrate (0.5%, w/w, mixed in rat chow). LPL, AFP and apo E mRNA levels were measured as described in Materials and methods. Values are expressed relative to the level in rats treated during 14 days with fenofibrate. Each value represents the mean ± s.d. of 3 animals. (B) Northern blot analysis of the influence of fenofibrate on hepatic LPL (top panel), AFP (middle panel) and apo E (lower panel) gene expression. 30 µg of total RNA were subjected to agarose gel electrophoresis, transferred to a nylon membrane and hybridized as described in Materials and methods. The position of the 18S and 28S mRNA bands are indicated on the upper panel.
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Fig. 4. The induction of hepatic LPL gene expression by fenofibrate is dose-dependent. (A) Quantitative analysis of LPL, AFP and apo E mRNA levels in livers of adult rats treated with different doses of fenofibrate. RNA was prepared from the livers of adult, male rats treated for 14 days with the indicated doses (% w/w, mixed in rat chow). LPL, AFP and apo E mRNA levels were measured as described in Materials and methods. Values are expressed relative to the level in rats treated during 14 days with fenofibrate. Each value represents the mean ± s.d. of 3 animals. (B) Northern blot analysis of the influence of different doses of fenofibrate on hepatic LPL (top panel), AFP (middle panel) and apo E (lower panel) gene expression. RNA was prepared from livers of rats treated with different doses (1=Control, 2=0.005%, 3=0.05%, 4=0.5%, wt/wt, in rat chow) of fenofibrate for 14 days. 30 µg of total RNA were subjected to agarose gel electrophoresis, transferred to a nylon membrane and hybridized as described in Materials and methods. The position of the 18S and 28S rRNA bands are indicated on the upper panel.

Table 1. Partial amino acid sequence and homology comparison of fenofibrate-induced rat liver LPL

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<th>Amino acid sequence</th>
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**Table 1. Partial amino acid sequence and homology comparison of fenofibrate-induced rat liver LPL**
ment of adult rats with fibric acid derivatives could rein-
duce AFP mRNA levels. In fact AFP has been shown to
be present in liver tumours (Bélanger et al., 1979; Petropou-
los et al., 1983).

How fibric acid derivatives may exert their effects on the
expression of the LPL and AFP genes is unclear at present.
The fact that fibric acid derivatives influence hepatocyte
proliferation and longevity (Bars and Elcombe, 1991) sug-
gests that they might affect the expression of several develop-
mentally important liver-specific genes, although definite
proof of this awaits further study. Most likely these com-
pounds may induce or activate specific transcription fac-
tors, which may in turn regulate the expression of these
genes. For instance, fibric acid derivatives and other per-
oxosomal proliferators can activate a subgroup of receptors
termed PPAR or peroxisomal proliferator activated recep-
tor (Issemann and Green, 1990; Dreyer et al., 1992). PPAR
belongs to the erb-A/steroid hormone receptor gene super-
family. Other receptors belonging to this family have been
shown to modulate developmental changes in AFP gene
expression (Guertin et al., 1983; Turcotte et al., 1985). It
is hypothesized that PPAR might mediate the profound
effects of fibric acid derivatives on gene transcription, via
interactions with a specific PPAR-RE, such as recently
demonstrated for the rat acyl CoA oxidase gene (Tugwood
et al., 1992; Dreyer et al., 1992). Similarly, PPAR might
mediate the profound effects of fibric acid derivatives on
LPL and AFP gene transcription. Although, it seems
unlikely that chemical substances such as fibric acid deri-
vatives, are present during normal development, the results
of this study together with the distinct developmental
expression of different *Xenopus* PPARs (Dreyer et al.,
1992) suggests that these agents are capable of modulating
developmentally determined patterns of gene transcription.
Although PPAR can not be classified as an orphan recep-
tor, no natural ligand or activator is yet known. In view of
the data in this paper, an eventual natural ligand might play
an important role in developmental processes. Alternatively
fibric acid derivatives could modify the activity or concen-
tration of liver-specific transcription factors, thereby
explaining the tissue-selective effects of these drugs on LPL
gene expression. Possible candidates are proteins belong-
ing to a group of liver-specific nuclear DNA-binding pro-
teins, such as HNF-1 (Courtois et al., 1987)/ HP-1 (Schorpp
et al., 1988)/LF-B1 (Monaci et al., 1988)/ AFP (Cereghini
et al., 1988), which has been shown to bind specific regions
of the AFP and albumin genes and regulate their tran-
scription (Lichtsteiner et al., 1987; Courtois et al., 1988;
Cereghini et al., 1988; Hardon et al., 1988; Feuerman et al.,
1989; Kuo et al., 1990). Other candidates are HNF-3, which
also binds to the AFP gene, HNF-4 (Costa et al., 1989), or
the liver-enriched transcription factor, C/EBP (Friedman et
al., 1989). A differential effect of fibric acid derivatives on liver and adi-
pose tissue C/EBP activity would then be required to
explain the tissue-selective effects of these compounds. In

<table>
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<tr>
<td>0</td>
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Adult male rats (*n*=3) were treated with the indicated dose (% w/w, in
rat chow) fenofibrate for 14 days. RNA was prepared and LPL mRNA
levels were measured as described in Materials and methods. Values, rep-
resenting the mean ± s.d., are expressed relative to the levels of β-actin
mRNA.

Fig. 5. The induction of liver LPL mRNA is transcriptional.
Nuclei were isolated from livers of adult control rats (C) and rats
reated with fenofibrate (FF; 0.5%, w/w, mixed in rat chow) for 14
days and nuclear run-on assays were performed as described in
Materials and methods.

Fig. 6. The induction of liver LPL gene expression by fenofibrate
is reversible. Adult male rats were treated for 14 days with
fenofibrate (0.5%, w/w, mixed in rat chow). Administration of
fenofibrate was stopped on day 0. LPL, AFP and apo E mRNA
levels were measured as described in Materials and methods in
livers of untreated control rats (C) and in livers of rats 0,1,3,7,14
and 28 days after cessation of fenofibrate treatment. Each group
consisted of 3 animals.

Table 2. Dose-dependent influence of fenofibrate on extra-
hepatic LPL gene expression

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addition, the interaction of several different transcription factors may be required to explain the observed effects. Such an interaction between the proto-oncogenes c-Jun/c-Fos and the glucocorticoid receptor results in a complex, interactive regulation of the AFP gene (Zhang et al., 1991).

Finally, it is also possible that a repressor molecule could negatively influence trancription and is only present or active in non-expressing, differentiated tissues. This could be due to interaction of a negative regulator protein with cis-acting elements in the promoter region of these genes. Such a negative trans-acting factor has been implicated in the postnatal repression of the AFP gene (Campere and Tilghman, 1989). In addition, a negative cis-acting element involved in the developmental extinction of hepatic LPL expression has been delineated in the human LPL promoter (Auwerx et al., 1990). On the other hand repression could also be caused by regulatory proteins not directly interacting with DNA, such as the RI-α regulatory subunit of PKA (or Tse-1) which might be implicated in gene regulation (Boshart et al., 1991; Jones et al., 1991).

Fibric acid derivatives are potent inducers of the β-oxidation system of fatty acids in the liver (Reddy et al., 1982). Administration of these drugs to rodents results in a strong proliferation of peroxisomes, a hepatomegaly and may ultimately lead to the development of hepatocarcinomas in animals treated for a prolonged period (Svoboda & Azarnoff, 1966; Reddy et al., 1980). In this study, fibric acid derivatives reinduced LPL, but not AFP gene expression in adult livers. However, treatment periods were not sufficiently long to produce hepatocarcinomas and it is not impossible that prolonged administration of these drugs may induce AFP gene expression, as is the case in neoplastic liver cells (Bélanger et al., 1979; Petropoulos et al., 1983).

In conclusion, these studies on the LPL and AFP genes demonstrate that fibric acid derivatives have profound and tissue-selective effects on hepatic gene expression. Together with steroid and thyroid hormones and morphogens, such as retinoic acid, fibric acid derivatives or their natural analogues appear to be important in regulating developmental patterns of gene expression.

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