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

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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.

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

Abbreviations: LPL, lipoprotein lipase; AFP, α-fetoprotein; apo, apolipoprotein.
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 postnatally, 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 developmental extinction. In addition, these compounds are able to reactivate the expression of the LPL, but not the AFP gene in adult rat liver.

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., 1980), a 1.36 kb EcoRI 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 cdNA 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
Gene regulation by fibric acid derivatives

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.

Fig. 2. Treatment with fenofibrate reinduces 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 extinction 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. 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

<table>
<thead>
<tr>
<th>Amino acid sequence</th>
<th>% Homology Protein</th>
<th>% Homology DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLONE 1 (75-186)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>REPDNSVIVVDWLRYRAQQHYPVSAGYTKLGVNDVARFINWLEEFNYPLDNVHLLCGSLGAHAAGVAGS</td>
<td>99</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>S...E...............Q.........M.......I...</td>
<td>96</td>
</tr>
<tr>
<td>87</td>
<td>S...S.......Q...K.M...MAD....G............I...</td>
<td>92</td>
</tr>
<tr>
<td>Bovine</td>
<td>S...S........G.A.Q..S........AP...........N....</td>
<td>87</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>R..T..S................T.........Q........</td>
<td>87</td>
</tr>
<tr>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CLONE 2 (380-448)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>LTKKVNNRTGLDPAGPNFEYAEAPSRLSPDDADFDVDSLHFT</td>
<td>91</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>S...S.......G.A.Q..S........AP...........N....</td>
<td>87</td>
</tr>
<tr>
<td>82</td>
<td>S...S.N........G.D.G..S...M.Y......SPVI........NR...</td>
<td>77</td>
</tr>
<tr>
<td>Bovine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>I...S...S..GR.T.T...IV..S...K....E.P........N....</td>
<td>77</td>
</tr>
<tr>
<td>78</td>
<td></td>
<td></td>
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<tr>
<td>78</td>
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ment of adult rats with fibric acid derivatives could reinduce AFP mRNA levels. In fact AFP has been shown to be present in liver tumours (Bélanger et al., 1979; Petropoulos 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) suggests that they might affect the expression of several developmentally important liver-specific genes, although definite proof of this awaits further study. Most likely these compounds may induce or activate specific transcription factors, which may in turn regulate the expression of these genes. For instance, fibric acid derivatives and other peroxisomal proliferators can activate a subgroup of receptors termed PPAR or peroxisomal proliferator activated receptor (Issemann and Green, 1990; Dreyer et al., 1992). PPAR belongs to the erb-A/steroid hormone receptor gene superfamily. 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 derivatives, 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 receptor, 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 concentration of liver-specific transcription factors, thereby explaining the tissue-selective effects of these drugs on LPL gene expression. Possible candidates are proteins belonging to a group of liver-specific nuclear DNA-binding proteins, such as HNF-1 (Courtois et al., 1987)/ HP-1 (Schorpp et al., 1988)/LF-B1 (Monaci et al., 1988)/ APF (Cereghini et al., 1988), which has been shown to bind specific regions of the AFP and albumin genes and regulate their transcription (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). The C/EBP protein is not only detected in liver cells, but also in adipocytes (Birkenmeier et al., 1989; Christy et al., 1989) and has been shown to activate liver- and adipocyte-specific genes (Friedman et al., 1989). A differential effect of fibric acid derivatives on liver and adipose tissue C/EBP activity would then be required to explain the tissue-selective effects of these compounds. In

![Fig. 5](image-url) The induction of liver LPL mRNA is transcriptional. Nuclei were isolated from livers of adult control rats (C) and rats treated 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](image-url) 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 extrahepatic LPL gene expression

<table>
<thead>
<tr>
<th>Dose (%)</th>
<th>Heart muscle (R.A.U.)</th>
<th>Adipose tissue (R.A.U.)</th>
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<tbody>
<tr>
<td>0</td>
<td>100 ± 14</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>0.005</td>
<td>120 ± 40</td>
<td>106 ± 18</td>
</tr>
<tr>
<td>0.05</td>
<td>117 ± 6</td>
<td>109 ± 16</td>
</tr>
<tr>
<td>0.5</td>
<td>134 ± 19</td>
<td>99 ± 2</td>
</tr>
</tbody>
</table>

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, representing the mean ± s.d., are expressed relative to the levels of β-actin mRNA.
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 transcription 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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