Dietary lipids regulate \( \beta \)-oxidation enzyme gene expression in the developing rat kidney

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The aim of this study was to evaluate the effectiveness of dietary lipid to exert long-term or short-term control on \( \beta \)-oxidation enzyme mRNA abundance in the immature kidney cortex and ISOM. We focused on the long-chain acyl-CoA dehydrogenase (LCAD) and MCAD, which catalyze the first step of mitochondrial fatty acid \( \beta \)-oxidation, with distinct carbon chain length specificities. Gene expression of acyl-CoA oxidase (ACO), which catalyzes the initial step of peroxisomal \( \beta \)-oxidation, was studied in parallel.

The mechanism(s) underlying the effects of dietary fat on enzymes and protein of fatty acid metabolism remain hypothetical. Recent data suggest that these effects might involve a control of peroxisomal and mitochondrial \( \beta \)-oxidation enzymes in the kidney cortex and medulla of 3-wk-old rats and evaluates the role of glucagon or of the \( \alpha \)-isoform of peroxisome proliferator-activated receptor (PPAR\( \alpha \)) in mediating \( \beta \)-oxidation enzyme gene regulation in the immature kidney.

The long-chain (LCAD) and medium-chain acyl-CoA dehydrogenases (MCAD) and acyl-CoA oxidase (ACO) mRNA levels were found coordinately upregulated in renal cortex, but not in medulla, of pups weaned on a high-fat diet from day 16 to 21. Further results establish that switching pups from a low- to a high-fat diet for only 1 day was sufficient to induce large increases in cortical LCAD, MCAD, and ACO mRNA levels, and gavage experiments show that this upregulation of \( \beta \)-oxidation gene expression is initiated within 6 h following lipid ingestion. Treatment of pups with clofibrate, a PPAR\( \alpha \) agonist, demonstrated that PPAR\( \alpha \) can mediate regulation of cortical \( \beta \)-oxidation enzyme gene expression, whereas glucagon was found ineffective. Thus dietary lipids physiologically regulate gene expression of mitochondrial and peroxisomal \( \beta \)-oxidation enzymes in the renal cortex of suckling pups, and this might involve PPAR\( \alpha \)-mediated mechanisms.

Energy metabolism; postnatal period; mitochondria; peroxisome; gene regulation; peroxisome proliferator-activated receptor

**FATTY ACIDS HAVE BEEN identified for a long time as one of the main energy substrates used by the kidney of rat and other species (36).** Mitochondrial fatty acid \( \beta \)-oxidation, which allows high yields of ATP production, plays an essential role in supporting kidney reabsorptive functions, as evidenced by the effects of mitochondrial fatty acid utilization blockers, which induce marked impairments in proximal tubule reabsorption (36).

Mitochondrial energy metabolism is not mature in the newborn rat kidney (3) and undergoes profound changes during the first weeks after birth (14, 35). In particular, the postnatal development of energy metabolism involves an enhanced expression of nuclear genes encoding mitochondrial malate dehydrogenase, a tricarboxylic acid cycle enzyme, and medium-chain acyl-CoA dehydrogenase (MCAD), a mitochondrial fatty acid \( \beta \)-oxidation enzyme, in the renal cortex and inner stripe of the outer medulla (ISOM) (12). Gene expression of these enzymes is controlled, during the suckling period, by physiological factors, such as changes in glucocorticoid (12) or thyroid hormone plasma levels (13). During this period, lipids supplied by maternal milk provide 60% of total energy, compared with only 15% in the standard adult diet (17). The present work addresses the role of dietary lipids in regulating \( \beta \)-oxidation enzyme genes in the immature kidney.

The kidney is the only other organ in addition to the liver in which fatty acid \( \beta \)-oxidation can occur both in the mitochondria and in the peroxisomes (37). The renal peroxisomes, which are found exclusively in the proximal tubule of the nephron, rank among the largest peroxisomes known in different cell types (37). The presence of peroxisomes in the fetal kidney is ascertained by morphological studies in rat and mouse and in the human (37). After birth, there is a dramatic increase in the number of peroxisomes in the proximal tubule of rat and mouse kidney (37).

Peroxisomal \( \beta \)-oxidation, which involves a set of specific enzymes (24), differs from its mitochondrial counterpart in many aspects. In particular, peroxisomal fatty acid \( \beta \)-oxidation is not directly coupled to the mitochondrial respiratory chain, does not perform complete oxidation of fatty acids, and exhibits a different substrate specificity, compared with the mitochondrial pathway (33). Biochemical studies showed that liver peroxisomes can shorten very-long-chain fatty acids and other fatty acids that are poor substrates for the mitochondrial \( \beta \)-oxidation machinery, allowing their further use as energy substrates by mitochondria (33).

Feeding adult rats a high-fat diet leads to a stimulation of peroxisomal \( \beta \)-oxidation in the liver (32). Nevertheless, the effects of fat supply on kidney peroxisomal or mitochondrial \( \beta \)-oxidation have not, so far, been investigated. Peroxisomal metabolism is insufficiently documented in the developing kidney (37). There are, in particular, no data on peroxisomal fatty acid \( \beta \)-oxidation in the kidney of suckling pups.

The aim of this study was to evaluate the effectiveness of dietary lipid to exert long-term or short-term control on \( \beta \)-oxidation enzyme mRNA abundance in the immature kidney cortex and ISOM. We focused on the long-chain acyl-CoA dehydrogenase (LCAD) and MCAD, which catalyze the first step of mitochondrial fatty acid \( \beta \)-oxidation, with distinct carbon chain length specificities. Gene expression of acyl-CoA oxidase (ACO), which catalyzes the initial step of peroxisomal \( \beta \)-oxidation, was studied in parallel.
mitochondrial β-oxidation gene expression mediated through binding of fatty acids to a nuclear receptor, the α-isof orm of peroxisome proliferator-activated receptor (PPARα) (27). Other data suggest that glucagon, the plasma level of which increases with a high-fat diet, could trigger gene expression of liver β-oxidation enzymes (34). This led us to study PPARα mRNA levels in the kidney of pups fed high- and low-fat diets, and to determine whether clofibrate, a PPARα agonist, can stimulate gene expression of the β-oxidation enzymes studied in the immature kidney. The effects of glucagon in regulating gene expression of these enzymes were investigated in parallel.

Our data indicate that changes in the dietary fat supply can induce large changes in gene expression of mitochondrial and peroxisomal β-oxidation enzymes in the kidney cortex, but not in the ISOM. These changes in β-oxidation enzyme mRNA levels appear unrelated to the plasma levels of glucagon. In contrast, PPARα-dependent gene regulation of mitochondrial and peroxisomal β-oxidation enzymes can clearly operate in the developing kidney during the suckling period.

MATERIALS AND METHODS

Animals and diets. Pregnant Wistar rats were bred and mated in our laboratory and had free access to water and standard food (UAR 113, containing, per 100 g food, 51 g carbohydrate, 22 g protein, and 5 g lipid; Usine d’Alimentation Rationnelle, Valmois-sain-sur-Orge, France). Each litter was reduced to 10 animals at birth. Pups were kept with their mother until day 21 after birth, or precociously weaned on postnatal day 16 and then put on a low- or a high-fat solid food diet.

The low-fat diet was obtained commercially from Usine d’Alimentation Rationnelle and provided, per 100 g, 58 g carbohydrate, 19 g protein, and less than 1 g residual lipids; under this diet, lipids account for less than 3% of the total caloric supply. The high-fat diet, prepared by adding 25% coconut oil (Sigma, St. Louis, MO) to the low-fat food, provided, per 100 g, 41 g carbohydrate, 14 g protein, and 25 g lipid, corresponding, lipids accounted for 55% of the caloric supply in the high-fat diet. By comparison, milk lipids provide 60% of the total caloric intake in suckling rats (17). Coconut oil was chosen because it contains 86% saturated long-chain and medium-chain fatty acids (25), which are physiological substrates of LCAD, MCAD, and ACO and which represent ~65% of total fatty acids supplied by maternal milk (2, 19).

In a first set of experiments, litters were divided in two groups on day 16, and from day 16 to 21, one-half of the litter was kept on the low-fat diet, while the other half was put on the high-fat regimen. Food intake in the various groups of animals was determined daily by weighing the amount of food consumed. Body weight measurements were performed daily in parallel.

Further experiments were designed to evaluate short-term regulation of gene expression by dietary lipids. In contrast to adult rats, young rats aged less than 1 mo eat at any time of the day (17), and cannot be conditioned to consume their food within a few hours. We found that the shortest period of time during which reproducible food intake values can be obtained from 3-wk-old pups is 24 h (data not shown). To investigate the effects of a high-fat diet over 24 h, litters of 16-day-old rats were first weaned on the low-fat diet from day 16 to 21, to avoid background effects due to milk feeding. Then, from day 21 to 22, one-half of the litter was switched on the high-fat diet, whereas the other half was maintained on low-fat food. A similar protocol was used to study the effects of a 1-day-long supplementation by clofibrate, a PPARα ligand (15). Accordingly, pups weaned on low-fat diet from day 16 to 21 were switched on low-fat food supplemented with 0.5% clofibrate (Sigma) from day 21 to 22. Control pups were kept on low-fat food during the same period.

Finally, the very short-term regulation of MCAD gene expression was investigated in 21-day-old rats kept on a low-fat diet from day 16 to 21. A first group of animals were given 1 ml of coconut oil or vehicle (sterile water) by gavage; another group received 1 ml of 50 mg/ml clofibrate solution or vehicle (NaCl 0.9%, ethanol 7%, and a last group received a single subcutaneous injection of glucagon (150 µg/100 g body wt; Sigma); all these animals were killed 6 h later.

The kidneys and liver were removed on day 21 or 22, under ketamine anesthesia (100 mg/kg body wt, Imalgéne; Rhône-Mérieux, Lyon, France). The tissues were immediately frozen in liquid nitrogen and stored at −80°C. Cortex and ISOM were dissected by hand at −20°C. Blood samples were collected at 9:30 AM, from axillary artery, in heparinized glass tubes and immediately centrifuged. Plasma samples were kept at −80°C until analysis. Nonesterified fatty acids (NEFA) plasma levels were determined using the NEFA C WAKO kit (Dardilly, France).

The values of growth, food, energy intake, lipid consumption, and NEFA plasma levels in high- and low-fat fed pups are presented in Table 1. Body growth was slightly lower in high-fat than in low-fat fed pups, but growth rates in both groups remained in the physiological range for 3-wk-old rats (26, 29). Pups exhibited lower appetence for high-fat than for low-fat food, as reflected by the food intake values. However, since the caloric content per gram of high-fat food (4 kcal/g) was higher than that of low-fat food (2.2 kcal/g), the daily dietary energy intakes were similar regardless of whether rats were kept on a low- or a high-fat diet. Altogether, the protocols and diets used in this study allowed us to induce a marked increase in the dietary intake of saturated fat and in circulating fatty acids in high-fat fed animals compared with low-fat fed littersmates (Table 1).

Northern blot analysis. Isolation of total RNA from frozen liver and kidney cortex and ISOM, electrophoresis through a formaldehyde-containing agarose gel (15 µg of RNA/lane), and transfer to nylon membrane followed by ultraviolet cross-linking were carried out as described elsewhere (12, 13). The membranes were probed with cDNAs labeled [α-32P]dCTP using the random primer technique. The mitochondrial enzyme cDNA probes used in this study were rat MCAD EcoRI fragment of 871 bp (21) and rat LCAD EcoRI fragment of 1,200 bp (20). A 559-bp ACO cDNA was synthesized from total liver RNA by RT-PCR for 25 cycles using primers 5'-CAATCAGCGCATTGTCTGCTC-3' (upstream) and 5'-AAGCTCAGGAGTTCACGAGG-3' (downstream) chosen from the

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Values are means ± SE of 4–10 animals. *P < 0.05 and †P < 0.001 compared with the low-fat group value.
The rat ACO cDNA sequence published by Miyazawa et al. (30). The ACO cDNA was then directly cloned into pCR II TA cloning vector according to the manufacturer’s protocol (Invitrogen). A cDNA comprising part of the D and E domains of the rat PPARα (28) was obtained by RT-PCR (30 cycles). The primers used were 5'-CCCGGGTCACTCAGCAGG-3' (upstream) and 5'-TCAGTACATGTCTCTGTAG-3' (downstream). The resulting cDNA (717 nucleotides long) was purified on agarose gel and directly used for labeling. Prehybridization and hybridization were performed in an hybridization oven at 68°C, using the QuickHyb solution from Stratagene following the manufacturer’s instructions. The membranes were washed twice with 2× SSC (1× SSC is 0.15 M NaCl/0.015 M sodium citrate) for 15 min at room temperature, once with 1× SSC and 1% SDS for 10 min at room temperature, and with 1× SSC and 1% SDS for 30 min at 60°C. Signal densities for each mRNA were quantified by computerized densitometric analysis of the autoradiograms. The blots were also hybridized with an 18S cDNA probe to correct variations in the amount of RNA loaded.

Measurement of MCAD activity. MCAD activity was determined spectrophotometrically at 37°C by following the decrease in ferricenium ion absorbance at 300 nm as previously described (12). Briefly, kidney cortex or ISOM were weighed and homogenized (1:5 wt/vol) in ice-cold 100 mM HEPES (pH 7.6)/0.1 mM EDTA, using a motor-driven Teflon/glass homogenizer. The homogenates were centrifuged at 7,200 g for 1 min. For enzyme assay, 5 µl of supernatant was added to 500 µl of reaction mixture containing 100 mM HEPES, pH 7.6, 0.1 mM EDTA, 200 µM ferricenium hexafluorophosphate (FcPF₆), 0.5 mM sodium tetrathionate, and 100 µM octanoyl-CoA. MCAD activity was calculated from the decrease in FcPF₆ absorbance observed during the first minute of reaction. The results were corrected for absorbance decrease measured in the absence of octanoyl-CoA.

Expression of results and statistical analysis. The β-oxidation enzyme mRNA abundance was expressed on a relative percentage basis; the results were obtained from at least two different Northern blots. MCAD enzyme activity is expressed as micromoles of octanoyl-CoA oxidized per minute per gram wet weight. All the data are expressed as means ± SE. The means from 4–10 rats in each experimental group were subjected to ANOVA and Fishers test.

RESULTS
Mitochondrial and peroxisomal β-oxidation enzyme gene expression in immature kidney cortex and ISOM: Effects of dietary lipid content. In the renal cortex, the mRNA levels of LCAD, MCAD, and ACO were marked higher (+175%, +50%, and +71%, respectively) in rats fed a high-fat diet from day 16 to 21, than in littersmates kept on a low-fat diet during the same period (Fig. 1A). Upregulation of MCAD gene expression in response to a high-fat diet went together with...
parallel increase in MCAD enzyme activity (in \( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{g wet wt}^{-1} \)) in the cortex (6.37 ± 0.25 in the low-fat vs. 8.29 ± 0.28 in the high-fat group; \( n = 6 \), \( P < 0.001 \)). This was in contrast to the data obtained from the renal ISOM, since similar \( \beta \)-oxidation enzyme mRNA levels (Fig. 1B) and MCAD enzyme activities (low fat, 2.54 ± 0.15; high fat, 2.21 ± 0.22 \( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{g wet wt}^{-1} \); \( n = 6 \)) were found in this part of the kidney, in both groups of animals.

Further experiments were performed to determine whether upregulation of \( \beta \)-oxidation enzyme gene expression can occur in the immature cortex in response to a shorter exposure to a high-fat diet. Rats were fed a low-fat diet from day 16 to 21 and then switched onto a high-fat diet (HF), or kept on low-fat food (LF), until day 22. Total RNA extracted from kidney cortex was analyzed by Northern blot. Bars are means ± SE of 4–6 animals. Values found in the low-fat group were taken as reference. **\( P < 0.01 \). ***\( P < 0.001 \). Absence of error bars indicates that the SE is smaller than the symbol.

can be seen in Fig. 2, the animals put on a high-fat diet for 1 day exhibited a large and coordinated increase in LCAD (+100%), MCAD (+84%), and ACO (+350%) gene expression in the kidney cortex, compared with those kept on a low-fat diet.

PPAR\( \alpha \) gene expression in 3-wk-old rat kidney: Effects of clofibrate on \( \beta \)-oxidation enzyme gene expression. In Northern blots run from cortex and ISOM of 3-wk-old rats, the PPAR\( \alpha \) cDNA probe generated a single band of \( \sim 8.5 \) kb, similar to that reported in studies of adult rat kidney or liver (22). PPAR\( \alpha \) mRNA signals were fourfold higher in the cortex than in the ISOM (Fig. 3). Comparable amounts of PPAR\( \alpha \) transcripts were found in the immature cortex of 22-day-old rats fed low- or high-fat diet for 24 h (Fig. 4). Addition of 0.5% clofibrate to low-fat food for 1 day did not lead to significant change in PPAR\( \alpha \) mRNA, compared with the levels found in littermates on the low-fat diet only (Fig. 4). Switching pups onto a clofibrate-containing diet resulted in a marked and coordinated increase of LCAD (+56%), MCAD (+110%), and ACO (+700%) mRNA steady-state levels (Fig. 5). In contrast, no changes in MCAD gene expression occurred in response to clofibrate in the ISOM of the same animals (data not shown).

Short-term regulation of MCAD gene expression: Effects of lipids, clofibrate, and glucagon. To determine whether upregulation of \( \beta \)-oxidation enzyme gene can
occur within hours, MCAD mRNA levels were studied in kidney cortex 6 h after gavage with coconut oil or clofibrate. Figure 6A shows that a 30% increase in MCAD mRNA occurred in both groups of animals, compared with vehicle-treated pups.

To test a possible effect of glucagon in mediating short-term regulation of MCAD gene expression, 21-day-old rats kept on a low-fat diet from day 16 to 21 received a bolus dose of glucagon, and the liver and kidneys were removed 6 h later. Liver was used as a control, since glucagon was previously reported to increase MCAD gene expression in this tissue (31). Accordingly, Northern blot analysis revealed a 38% (P < 0.05) increase in hepatic levels of MCAD mRNA (Fig. 6B). In contrast, MCAD mRNA abundance was unchanged in the kidney cortex of pups receiving glucagon (Fig. 6B).

DISCUSSION

The present data clearly indicate that changes in the dietary fat supply can induce marked changes in fatty acid oxidation enzyme gene expression in the immature rat kidney cortex. Upregulation of mitochondrial and peroxisomal β-oxidation enzyme mRNA, together with a parallel increase in MCAD enzyme activity, was first shown to occur in the kidney cortex of pups fed a high-fat diet over the period from day 16 to 21. In contrast, in the renal medulla gene, expression of these enzymes was unaffected by changes in lipid supply. This cortex-specific response is consistent with previous data showing that, after 5 days on a high-fat diet, the activity of β-hydroxyacyl-CoA dehydrogenase, a mitochondrial β-oxidation enzyme, is upregulated in the proximal convoluted tubule, but not in the medullary thick ascending limb, of 21-day-old rat kidney (4).

The present results also show that lipid supply can exert short-term regulatory effects on β-oxidation enzyme gene expression. Thus increasing lipid supply for only 24 h was sufficient to induce large and coordinated increases in the mRNA levels of LCAD, MCAD, and ACO in the immature kidney cortex. In addition, experiments run in 21-day-old rats receiving coconut oil by gavage showed that upregulation of MCAD gene expression was already initiated within 6 h after lipid ingestion.

Regulation by lipid supply of enzymes and proteins of fatty acid metabolism has been very little studied in the rat kidney (4, 6) and is documented more thoroughly in...
other organs (10, 18, 33). ACO activity increases markedly in the liver of adult rats chronically fed a high-fat diet (32, 33). In weanling rats, the activity of liver carnitine-palmitoyl-transferase 1, which catalyzes the import of long-chain fatty acid into the mitochondria, is stimulated after 10 days on a high-fat diet (34). In the long-term range, these changes in enzyme activities or gene expression are probably mediated by multiple regulatory pathways. Indeed, chronic changes in fat supply modify pancreatic hormone plasma levels (17) but also induce progressive changes in cell membrane phospholipid composition, and these latter changes might in turn result in changes in a number of signal transduction pathways (10).

The hypothesis of short-term regulatory effects of dietary fat on gene expression has only been proposed recently, based on studies run in rat liver or intestine (1, 11). Fatty acids might directly mediate these short-term regulatory effects by interacting with the α isoform of PPAR, a nuclear receptor of the steroid-thyroid hormone receptor superfamily. In fact, cotransfection experiments indicate that, after activation by fatty acids, PPARα mediates transcriptional stimulation of MCAD, ACO, and other genes involved in fatty acid catabolism (27). Fatty acids, clofibrate, and other agonists were recently shown to act as ligands of PPARα (15, 23).

PPARα is highly expressed in the proximal tubule of rat kidney (7, 22), in which its function(s) remains unclear. The expression of PPARα gene during development had not yet been studied in the rat kidney. A faint PPARα signal was found by in situ hybridization in the proximal convoluted tubule of 8-day-old mouse kidney, which increased during the postnatal period up to adulthood (5). The present data establish that PPARα gene is expressed in the cortex, and to a lower level in the ISOM, of 3-wk-old rat kidney. Clofibrate supplementation for 24 h resulted in marked increases in cortex mRNA levels of LCAD, MCAD, and ACO. Pups receiving clofibrate by gavage also exhibited, within 6 h, significant increases in cortex MCAD gene expression. PPARα mRNA steady-state levels in the kidney cortex of clofibrate-treated rats were similar to those found in control or high-fat fed animals. Thus PPARα can effectively control gene expression of β-oxidation enzymes in kidney cortex of 3-wk-old rats and could mediate short-term changes in gene expression of these enzymes, and this does not require upregulation of PPARα gene expression. This contrasts with the data obtained from the ISOM in which mRNA levels of mitochondrial and peroxisomal β-oxidation enzymes were found unchanged in response to clofibrate, despite the presence of detectable levels of PPARα mRNA. Studies of MCAD gene 5′-flanking regions indicate that the PPARα response element lies within a pleiotropic regulatory DNA sequence that can bind various combinations of nuclear receptors (8). The expression of specific transcription factors, competing with PPARα for binding on DNA regulatory sequence, might possibly account for the lack of changes in MCAD gene expression in response to clofibrate in the ISOM.

Data obtained from rat liver suggest that glucagon could represent an important factor in the regulation of β-oxidation enzyme gene expression during the postnatal period, as well as in the adult (9, 17, 31). Since the transition from a low- to a high-fat diet is accompanied by an increase in glucagon plasma level, we studied MCAD gene expression levels in the liver and kidney of pups receiving glucagon. In agreement with data obtained in the adult liver, MCAD mRNA levels were found increased in response to a single injection of glucagon. However, expression of MCAD gene in the cortex of the same animals was found unchanged. This strongly suggests that glucagon is not involved in mediating changes in β-oxidation enzyme gene expres-

Fig. 6. Effects of coconut oil, clofibrate, or glucagon on renal and hepatic MCAD gene expression over a 6-h period. Data were obtained from 21-day-old rats fed a low-fat diet from day 16 to 21. A: animals received by gavage 1 ml of coconut oil or 1 ml sterile water (left columns), or 1 ml of 50 mg/ml clofibrate solution or 1 ml of clofibrate vehicle (right columns). B: animals received a single injection of glucagon (150 µg/100 g body wt) or vehicle. Tissues were always removed 6 h later. MCAD mRNA abundance was analyzed by Northern blots (top). Results are means ± SE of 4–6 animals. * P < 0.05, compared with vehicle-treated animals, taken as 100%.
sion in response to variations in lipid supply in the immature kidney cortex.

Taken together, these data allow one to conclude that gene expression of mitochondrial and peroxisomal \( \beta \)-oxidation enzyme in the immature kidney cortex can be physiologically coregulated according to variations in the lipid supply to the rat pups. This supports the recent hypothesis suggesting that both peroxisomes and mitochondria might represent a major target for a nutritional control of lipid metabolism (16). The signaling pathway(s) involved in regulating \( \beta \)-oxidation enzyme gene expression as a function of dietary lipid supply cannot be inferred from the present data. However, since activation of PPAR\(\alpha\) led to a marked stimulation of both peroxisomal and mitochondrial \( \beta \)-oxidation genes in the kidney cortex of rat pups, it is tempting to speculate that fat supply-dependent gene regulation might operate via PPAR\(\alpha\). It was recently demonstrated that PPAR\(\alpha\) can recognize a broad array of fatty acids and lipid-derived metabolites and can regulate gene expression in all fatty acid catabolism pathways (27). Nevertheless, the physiological relevance of these functions, unique among the nuclear receptors, remains far from being completely elucidated. Further studies will help to delineate whether, as suggested by the present data, PPAR\(\alpha\) might play a major role in triggering the postnatal development of fatty acid utilization in organs like kidney, which closely depend upon these mechanisms to ensure their energy homeostasis.

We thank Drs. A. Strauss and D. P. Kelly for providing us with the rat LCAD and MCAD cDNAs, respectively, and Dr. T. Gilbert for careful reading of the manuscript.

This work was presented in abstract form at the Annual Meeting of the American Society of Nephrology in San Antonio, TX, November 1997.

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Received 11 February 1998; accepted in final form 27 July 1998.

REFERENCES


