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SHORT TERM TREATMENT BY FENOFIBRATE ENHANCES OXIDATIVE ACTIVITIES TOWARDS LONG-CHAIN FATTY ACIDS IN THE LIVER OF LEAN ZUCKER RATS

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Abstract—Lean Zucker rats were dosed orally for 1 week with fenofibrate (100 mg/kg/day). Liver weights of treated rats, expressed as per cent of body weight, were increased, while protein, DNA and triacylglycerol contents were not changed to any great extent per gram of liver, but increased when expressed per whole liver. Compared with the control animals, activities of fatty acid oxidase, of the peroxisomal fatty acid-oxidizing system and of catalase were markedly enhanced by fenofibrate, both per gram of liver and per total liver, while urate oxidase activity was slightly depressed when expressed per gram of liver. The activity of cytochrome *c* oxidase used as a mitochondrial marker was only higher when expressed per total liver. Besides, fenofibrate treatment induced a pronounced increase in the mitochondrial activities of carnitine palmitoyl- and acetyltransferases, of palmitoyl-CoA dehydrogenase and of carnitine-dependent oleate oxidation. Fenofibrate also enhanced significantly the carnitine content in liver and hepatic mitochondria. Malonyl-CoA content per gram of liver was found to be twice as high as in control rats, while the sensitivity of carnitine acyltransferase I to malonyl-CoA inhibition was hardly altered. The drug enhanced the percentage of palmitic acid in lipids of liver, but not in adipose tissues. The present data show that fenofibrate induced greater oxidative activities towards fatty acids, even in the lean animal. This stimulation could be related to the energy used for building new cells. In turn, at the same time of treatment, an enhanced fatty acid synthesis would provide specific fatty acids for the formation of new membranes. This latter effect will eventually disappear and the maintenance of a higher fatty acid oxidation may explain part of the overall hypolipaemic effect of fenofibrate.

Fenofibrate is a hypolipidaemic compound which has been used in man since 1975 [1]. This clofibrate-related drug represses *in vivo* HMG-CoA reductase [2, 3], enhances post-heparine lipase activity [4] and inhibits very low density lipoprotein secretion [5]. Besides, it has been shown that chronic administration of clofibrate to normal rodents [6–8] and of fenofibrate to genetically obese Zucker rats [9] increases the weight of the liver and the hepatic content in peroxisomes and mitochondria. Peroxisomes are known to shorten fatty acids via β-oxidation [10]. Mitochondria isolated from liver of fenofibrate-treated obese Zucker rats display higher activities for fatty acid oxidation and transfer to carnitine [9]. It was then suggested that the hypolipidaemic effect of fenofibrate may also originate from an enhanced fatty acid oxidation.

In the liver of genetically obese Zucker rats, lipogenesis and fatty acid esterification are enhanced [11–14], whereas fatty acid oxidation is depressed [15–18]. In this phenotype, fenofibrate stimulated all the hepatic reactions leading to β-oxidation and enhanced the weight of liver without altering its fat content [9]. The increasing percentage of palmitic acid in phospholipids [19] could account for a higher fatty acid synthesis. However, in obese rats fat storage is considerable in liver and peripheral tissues. Consequently fatty acid composition in liver could be largely influenced by fatty acids stored before treatment and released during treatment. Besides non-esterified fatty acids taken up in higher amount from plasma by hepatocytes would stimulate fatty acid oxidation, as already shown [20]. This mechanism could account for part of the higher fatty acid oxidation in our previous observations [9].

The preceding scheme may be avoided by using the lean Zucker rat because its adipose tissues are far less developed than in the obese. Moreover, the triacylglycerol content per gram of liver is even below that reported in the normal Wistar rat [21]. In this case, fatty acid composition of liver cannot be altered to a great extent by previously accumulated fatty acids which are liable to stimulate liver fatty acid oxidation.

The aim of this work was to investigate the effect of fenofibrate on mitochondrial fatty acid oxidation in the liver of lean Zucker rats, by focusing on the enzymatic steps regulating entry of long-chain fatty acids into mitochondria. Results are discussed by reference to malonyl-CoA which is known to affect the transfer of acyl groups into mitochondria [22]. Fatty acid synthesis is directly stimulated by malonyl-CoA content [23] and its importance can be assessed by the percentage of newly synthesized palmitic acid in lipids of liver and adipose tissues.

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MATERIALS AND METHODS

Chemicals. Fenofibrate was supplied by Laboratoires Fournier (Dijon, France). The chemicals were purchased from Prolabo (France) and from Merck (Darmstadt, F.R.G.). The biochemicals were obtained from Sigma the Chemical Co. (St Louis, MO, U.S.A.). L- and D-carnitine forms were a gift from Dr C. Cavazza of Sigma-Tau (Pomezia, Italy). [1-^{14}C]Oleic acid was provided by CEA (Saclay, France); it was diluted with the unlabelled fatty acid to a specific activity of 2 Ci/mol and used as potassium salt. Oleoyl- and palmitoyl-CoA were prepared by using the method of Goldman and Vagelos [24]. Highly purified fatty acid synthetase from rat liver was obtained from Dr M. Lavau (INSERM U177, Institut Biomédical des Cordeliers, Paris, France).

Animals. Lean (Fa/?) male Zucker rats were bred in the Centre de Sélection et d'Elevage d'Animaux de Laboratoire, C.N.R.S., Orléans-la-Source, France. They were 11 weeks old on arrival and were given a standard laboratory chow (AO3, UAR, 91360 Epinay-sur-Orge, France) *ad lib.* They received by gastric intubation a daily dose of 100 mg fenofibrate emulsified in 5 mL of 3% arabic gum per kg body wt for 7 days. In each experiment, control rats received 5 mL of arabic gum mixture per kg by the same route for the same period. During the treatment period, no difference in feed intakes could be observed between both groups. Animals were fasted overnight and received the last dose 20 hr before being killed at 8:00 a.m.

Lipid determinations. Livers and pieces of adipose tissues removed from behind the kidneys were quickly blotted with paper, weighed and cut into small pieces. Lipid extractions were made on 2 g samples of tissue as described by Folch *et al.* [25]. Tripentadecanoin was added to the extracts as an internal standard. Triacylglycerols were separated on thin layers of silica gel using the solvent system heptane/diethyl ether/glacial acetic acid (60/40/2, by vol.). The spots containing triacylglycerols and samples of total lipid extracts were saponified in 5% KOH/methanol (w/v) at 100° for 1 hr. Free fatty acids were extracted with pentane from the acidified mixtures and treated by methanol/H_2SO_4 (95:5, v/v) at 100° for 3 hr. Methyl esters were extracted by hexane and estimated by gas–liquid chromatography at 190° with nitrogen as the carrier gas. The used model 419 Becker-Packard apparatus was equipped with a 30 m × 0.3 mm i.d. glass capillary column coated with carbowax 20M. Fatty acid estimation was done by reference to the known amount of pentadecanoic acid.

Mitochondrial fraction. The remaining liver of each animal was immediately cooled to 4° in a mixture of 0.25 M sucrose, 10 mM triethanolamine and 1 mM EDTA, at pH 7.4. It was then cut, rinsed several times, blotted, weighed and homogenized in 15 volumes of the same mixture with two strokes of the Teflon pestle in a Potter–Elvehjem homogenizer. In order to prepare a highly purified mitochondrial fraction poor in peroxisomes, mitochondria were isolated from a postnuclear supernatant as previously described [26]. This procedure almost completely discarded peroxisomes and left a very small amount of nuclei in the mitochondrial fraction [27], without modifying the specific activity of cytochrome *c* oxidase.

Enzyme assays. The liver mitochondrial content was assessed by the activities of monoamine oxidase for the external membrane [28] and of cytochrome *c* oxidase for the internal membrane [29]. The activity of total carnitine palmitoyltransferase (CPT-I + CPT-II) was measured as in Ref. 30, with some modifications [9]. The activity of the outer carnitine palmitoyl transferase I (CPT-I) alone and the sensitivity of this enzyme to malonyl-CoA were estimated at 25° according to Bremer [31] with slight modifications [26].

Peroxisomal activities of liver were measured in homogenate by using catalase [32] and urate oxidase [33]; the fatty acyl-CoA oxidase activity which is the first oxidative reaction in peroxisomes, was assessed by the palmitoyl-CoA dependent H_2O_2 generation as described in Ref. 34; the peroxisomal fatty acid-oxidizing system (PFAOS), reported by Lazarow and De Duve [10], was determined by CN^--insensitive palmitoyl-CoA-dependent NAD^+ reduction [35] in the presence of 75 μM palmitoyl-CoA.

Total and free carnitine contents in homogenates and mitochondria were measured in the presence of carnitine acetyltransferase by spectrophotometry [36].

Malonyl-CoA was extracted from liver powdered in liquid nitrogen by chilled 6% $HClO_4$ and its content was estimated from the rate of fatty acid synthesis, with [^{3}H]acetyl-CoA, in the presence of fatty acid synthetase as described by McGarry *et al.* [23].

Protein determination. The protein content of various preparations was determined by the biuret method [37], slightly modified for the liver homogenates which contain high triacylglycerol amounts [27].

Oxidative activities. The incubation medium for oleate oxidation was a mixture of 20 mM potassium phosphate pH 7.4, 50 mM KCl, 4 mM $MgCl_2$, 1 mM ATP, 50 μM CoA, 1 mM L-carnitine, 0.2 mM L-malate, 50 μM [1-^{14}C]potassium oleate bound to bovine albumin (fraction V, fatty acid-free) in molar ratios from 1 to 3; controls were performed omitting carnitine to assess strictly carnitine-dependent oxidation. The reaction was started with 1 mg of mitochondrial protein in 2 mL of medium kept at 35° with gentle shaking. After 8 min, the reaction was stopped at 0° by adding 0.1 mL 10 N HCl and then 8 mL 10% $HClO_4$ which precipitates proteins, acyl-CoA, acylcarnitines and long-chain fatty acids remaining intact. Thereafter the medium was filtered on a Millipore filter (pore 0.45 μm). The radioactivity of the filtrate, which corresponds to labelled ketone bodies, acetyl-CoA, acetyl-carnitine and to intermediary products of the Krebs cycle, was measured in picofluor 15 (Packard Instrument Co.) in a Packard 300C scintillation counter. The carbon dioxide production was found to be negligible. The palmitoyl-CoA dehydrogenase activity was measured according to Korsrud *et al.* [38] in a medium containing 35 μM palmitoyl-CoA with 2 mM KCN,

Table 1. Effects of fenofibrate treatment on body and liver weights, protein, DNA and lipid contents of liver from lean Zucker rats

	Control	Fenofibrate-treated
Body weight (g)	289 ± 5	283 ± 6 NS
Liver weight		
(g)	8.28 ± 0.29	10.90 ± 0.29*
(g/100 g body wt)	2.85 ± 0.07	3.84 ± 0.08†
Protein		
(mg/g liver)	218 ± 2	227 ± 4 NS
DNA		
(mg/g liver)	6.89 ± 0.08	6.06 ± 0.10*
Liver lipids		
Total fatty acids (mg/g liver)	23.37 ± 0.97	27.87 ± 0.33†
Triacylglycerols (mg fatty acids/g liver)	2.97 ± 0.18	2.87 ± 0.14 NS
Other lipids (mainly phospholipids)	19.93 ± 0.85	24.48 ± 0.23‡

Five 12-week-old lean Zucker rats were given a daily dose of 100 mg fenofibrate per kg for 7 days by gastric intubation. Five control rats were given the excipient only. Results are means ± SE. NS, not significant; * $P < 0.02$; † $P < 0.01$; ‡ $P < 0.001$ (Student's *t*-test).

Table 2. Enzymic activities in liver homogenates of lean Zucker rats after treatment by fenofibrate

	Control	Fenofibrate-treated
Monoamine oxidase (μmol/min/g liver)	0.820 ± 0.021	0.587 ± 0.027†
Cytochrome *c* oxidase (μmol/min/g liver)	66.8 ± 3.6	70.1 ± 8.4 NS
Urate oxidase (μmol/min/g liver)	3.90 ± 0.15	2.98 ± 0.16*
Catalase (10^{-3}μmol/min/g liver)	53.9 ± 2.7	84.0 ± 4.9†
Fatty acid oxidase (μmol/min/g liver)	1.17 ± 0.07	5.30 ± 0.42‡
Peroxisomal fatty acid-oxidizing system (μmol/min/g liver)	1.21 ± 0.05	6.06 ± 0.30‡

Five 12-week-old lean Zucker rats were given a daily dose of 100 mg fenofibrate per kg for 7 days by gastric intubation. Five controls received only the gum water excipient. Results are means ± SE.

NS, not significant; * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ (Student's *t*-test).

15 μM rotenone, 10 μM antimycin to block the respiratory chain and 0.05% Triton X-100 to obtain maximal enzymatic activity. The difference due to fenofibrate-treatment was assessed by the Student's *t*-test.

RESULTS

Table 1 shows that after 1 week of treatment with the chosen dose of 100 mg of fenofibrate/kg, the body weight of rats was not changed. However the liver weight, expressed in g/100 g body weight, was significantly increased (+35%). Hepatic protein and DNA contents were hardly affected when expressed as mg/g tissue, but increased in the whole organ owing to liver hypertrophy. Fenofibrate did not alter the triacylglycerol content per gram of liver, but slightly enhanced other lipids, mainly represented by phospholipids.

The content in organelles involved in fatty acid oxidation was assessed by the activities of specific enzymes in liver homogenates (Table 2). After treatment, the activity of monoamine oxidase, only present in mitochondria, was significantly diminished per gram of tissue, while total activity calculated in whole organ was not modified. No alteration of cytochrome *c* oxidase activity was observed when expressed per gram of tissue; however calculating its activity for total liver indicates a 35% increase due to hypertrophy. For peroxisomal markers, the activity of urate oxidase was lowered when expressed per gram of liver, but the total activity in whole liver did not differ from that in controls; catalase activity was found to be enhanced by the treatment per gram of tissue and to a greater extent in whole organ. Table 2 also shows that the activities of the peroxisomal fatty acid oxidase and of the CN^--insensitive palmitoyl-CoA-dependent NAD^+ reduction were increased by fenofibrate when expressed per gram of liver, as well as in whole liver attributable to the gain in weight.

As shown in Table 3, the enzymes involved in the transfer of fatty acids through the mitochondrial inner membrane were all stimulated by fenofibrate treatment. The enzymes involved in the transfer of long-chain and medium-chain fatty acids were found to be about twice as active, whereas the transfer of acetyl-CoA was elevated 11-fold after treatment. Moreover Table 3 indicates that the carnitine content increased dramatically in liver tissue and in

Table 3. Effects of fenofibrate treatment on the mitochondrial carnitine transferase activities and on carnitine and malonyl-CoA contents in the liver of lean Zucker rats

	Control	Fenofibrate-treated
Carnitine transferase activities (nmol/min/mg mitochondrial protein)		
Total carnitine palmitoyltransferase (CPTI + II)	9.20 ± 0.23	21.0 ± 0.6‡
Carnitine palmitoyltransferase I (CPT I)	2.55 ± 0.05	2.93 ± 0.09*
Carnitine octanoyltransferase	17.9 ± 1.1	41.6 ± 2.7‡
Carnitine acetyltransferase	1.83 ± 0.38	21.4 ± 2.9‡
Carnitine content in		
Liver mitochondria (nmol/g protein)	75 ± 8	274 ± 8‡
Liver (nmol/g wet tissue)		
Free form	214 ± 10	494 ± 22‡
Total	397 ± 19	899 ± 41‡
Malonyl-CoA in liver (nmol/g wet tissue)	4.02 ± 0.53	10.76 ± 1.92†

Five 12-week-old Zucker rats were given 100 mg fenofibrate emulsified in gum water per kg for 7 days by gastric intubation. Five controls received an equivalent volume of gum water only. Values are means ± SE.

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ (Student's t-test).

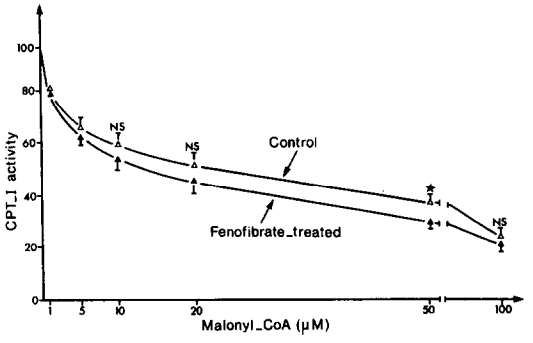

Fig. 1. Effect of increasing malonyl-CoA concentrations on the activity of CPT-I in mitochondria isolated from livers of obese Zucker rats treated by fenofibrate (▲) or vehicle only (△). Results are expressed as per cent of CPT-I activity, estimated in the absence of malonyl-CoA. Each point represents the mean of five duplicated determinations; each determination corresponds to one mitochondrial preparation from one rat. T-bars show SE.
NS, not significant; ★ $P < 0.05$ (Student's t-test).

mitochondria after fenofibrate treatment. Malonyl-CoA content per gram of liver was found to be 2.5-fold higher after treatment, while isolated mitochondria showed a CPT-I activity slightly more sensitive to malonyl-CoA inhibition, 50% of the inhibition being obtained with 20 ± 6 and 13.3 ± 1.1 μM malonyl-CoA for control and treated rats, respectively (Fig. 1).

As shown in Table 4, the complete oxidation of oleic acid was higher (+40%) and the activity of palmitoyl-CoA dehydrogenase was more than doubled after treatment. It has to be noticed that the specific activity of cytochrome c oxidase was not diminished by the drug to any great extent.

In Table 5, the fatty acid composition of triacylglycerols in adipose tissue, which was not modified by fenofibrate, did not influence the triacylglycerol composition of liver. By contrast, fenofibrate altered the composition of hepatic triacylglycerols by enhancing the amount of palmitic (16:0) and oleic (18:1) acids and decreasing linoleic acid (18:2). In other lipids mainly represented by phospholipids, a similar increase in palmitic acid after treatment should be noted (Table 6).

DISCUSSION

It is well-documented that the endocrine status of liver influences the partition of fatty acids taken up from the bloodstream between esterification and oxidation [39]. Hyperinsulinemia in the obese Zucker rat directs fatty acids towards esterification [40]. On the contrary in the lean Zucker rat, the β-oxidative pathway is more active, at the expense of esterification, as the triacylglycerol content is extremely low in liver (Table 1). Fenofibrate treatment significantly increased the active mass of liver in lean Zucker rat as also shown in normal Wistar rat [41], but hardly altered the contents in protein, DNA and lipids per gram of liver (Table 1). The fact that hepatomegaly was not accompanied by a concomitant increase in triacylglycerol content per gram liver, provides evidence that a close control of esterification still occurs in the hepatocyte of treated lean rats. Besides, mitochondrial and peroxisomal activities involved in fatty acid oxidation were found to be enhanced by fenofibrate (Tables 2–4). Qualitatively peroxisomal activities are quite similar to those found in obese Zucker rats [9] and in normal Wistar rats after fenofibrate [41–43] or clofibrate [10] treatment.

In lean rats, the drug enhanced mitochondrial carnitine acyltransferase activities and the carnitine content of liver and mitochondria, as already observed in the obese [9] and in clofibrate-treated Wistar rats [44–47]. After treatment, evidence of the efficiency of the higher acylcarnitine transport through the mitochondrial inner membrane and of the higher activity at the first step of the β-oxidative way (palmitoyl-CoA dehydrogenase) was provided by greater carnitine-dependent oleate oxidation (Table 4). These activities could account for an

Table 4. Effects of fenofibrate treatment on several oxidative activities in liver mitochondria of lean Zucker rats

	Control	Fenofibrate-treated
Carnitine-dependent oleate oxidation (nmol/min/mg protein)		
Molar ratio oleate/albumin: 1	1.73 ± 0.06	2.34 ± 0.12*
2	2.09 ± 0.09	3.28 ± 0.28*
3	1.87 ± 0.13	2.55 ± 0.28*
Palmitoyl-CoA dehydrogenase activity (nmol/min/mg protein)	10.40 ± 0.35	24.21 ± 0.85†
Cytochrome *c* oxidase (μmol/min/mg protein)	0.680 ± 0.023	0.560 ± 0.028*

Five 12-week-old lean Zucker rats were given a daily dose of 100 mg fenofibrate per kg for 7 days by gastric intubation. Five controls were given the excipient only. Results are means ± SE.

* $P < 0.01$; † $P < 0.001$ (Student's *t*-test).

Table 5. Effects of fenofibrate treatment on fatty acid composition of triacylglycerols in liver and adipose tissue of lean Zucker rats

	Liver		Adipose tissue	
	Control	Fenofibrate-treated	Control	Fenofibrate-treated
14: 0	1.65 ± 0.14	1.65 ± 0.08 NS	1.73 ± 0.07	1.82 ± 0.06 NS
16: 0	25.05 ± 0.57	31.08 ± 0.59†	26.84 ± 0.53	27.62 ± 0.68 NS
16: 1	2.22 ± 0.25	3.21 ± 0.79 NS	4.54 ± 0.28	5.19 ± 0.41 NS
18: 0	4.04 ± 0.48	3.39 ± 0.29 NS	3.37 ± 0.06	3.17 ± 0.07 NS
18: 1	20.26 ± 0.65	26.55 ± 0.86†	27.18 ± 0.12	26.76 ± 0.35 NS
18: 2	34.73 ± 0.79	26.76 ± 0.41†	32.08 ± 0.67	31.30 ± 0.95 NS
20: 4	7.00 ± 0.62	3.84 ± 0.17*	0.64 ± 0.01	0.61 ± 0.03 NS

Results are expressed in per cent of total fatty acids. Six 12-week-old Zucker rats were given a daily dose of 100 mg fenofibrate emulsified in gum water per kg for 7 days by gastric intubation. Six controls only received an equivalent volume of gum water.

Values are means ± SE.

NS, not significant; * $P < 0.01$; † $P < 0.001$ (Student's *t*-test).

enhanced fatty acid oxidation in liver and beyond for reduced lipaemia. Carnitine is essential in shuttling long-chain fatty acids across the mitochondrial inner membrane [48, 49] and its higher synthesis in liver after treatment could balance the enhancement of carnitine acyltransferase activities, both proceeding from a same regulatory effect. Such alterations in liver have already been observed in rats receiving fat-enriched diets [50]. In the obese, the effect of fenofibrate could partially be ascribed to lipolysis in the large adipose tissues. Released fatty acids, taken up by liver, might stimulate their own oxidation, as in some other physiological conditions [21]. In the lean, the hepatic effects of the drug would be mainly due to its own properties.

Table 6. Effects of fenofibrate treatment on fatty acid composition of lipids other than triacylglycerols, mainly phospholipids in liver of lean Zucker rats

	Control	Fenofibrate-treated
16: 0	17.27 ± 0.09	24.53 ± 0.45†
16: 1	0.39 ± 0.08	0.49 ± 0.13 NS
18: 0	24.62 ± 0.51	19.55 ± 0.27†
18: 1	4.80 ± 0.20	5.41 ± 0.17 NS
18: 2	14.32 ± 0.14	14.29 ± 0.08 NS
20: 4	30.45 ± 0.49	28.03 ± 0.59*

Results are expressed in per cent of total fatty acids. Six 12-week-old Zucker rats were given a daily dose of 100 mg fenofibrate emulsified in gum water per kg for 7 days by gastric intubation. Six controls only received an equivalent volume of gum water.

Values are means ± SE.

NS, not significant; * $P < 0.02$; † $P < 0.001$ (Student's *t*-test).

After 1 week of fenofibrate treatment, malonyl-CoA content was doubled per gram of liver. This metabolite which is used for fatty acid synthesis, gives rise to palmitic acid (16:0) [23]. Indeed, it can be seen from Tables 5 and 6 that the content of 16:0 was higher in triacylglycerols and other lipids (mainly phospholipids) of liver after treatment. Nevertheless, such alterations did not occur in triacylglycerols of adipose tissues, in which 16:0 remained in low proportion, as in liver of untreated rats (Table 5).

Thus fenofibrate also induced specific fatty acid synthesis for building new cells, as stated by the greater content in DNA of whole liver and in phospholipids per gram of tissue (Table 1). Besides malonyl-CoA is known to inhibit carnitine palmitoyltransferase I (CPT-I) [22] and the treatment slightly enhanced the sensitivity of CPT-I to inhibitory effect of malonyl-CoA (Fig. 1). However Bird and Saggerson [51] reported that L-carnitine displaced malonyl-CoA from liver mitochondrial binding sites. Therefore the higher content in carnitine after treatment may efficiently counteract the inhibiting effect of malonyl-CoA.

On the whole, after 1 week of treatment, hepatomegaly is not completed and the new lipidic structures require a greater fatty acid synthesis, giving rise at first to higher malonyl-CoA synthesis. This result appears very close to that obtained with a hypolipidaemic plasticiser which increases lipogenic activities during only 2 weeks [52]. Similar data have also been reported after some days of thyroid hormone injection [53], although hyperthyroidism is known to stimulate fatty acid oxidation. Since the malonyl-CoA content was higher after a week of treatment, the energy required for building new membranes may arise more from the breaking down of carbohydrates than that of fatty acids. Nevertheless, energy can also originate from fatty acid oxidation on account of much greater peroxisomal and mitochondrial activities. The duration of treatment appears important to obtain such a metabolic state. Later, after stabilization of hepatomegaly, the maintenance of greater activities of fatty acid oxidation may partly explain the hypolipaemic effect of fenofibrate. Our results and explanations are incentive to studying the partition between lipogenesis and fatty acid oxidation in shorter and longer treatment periods.

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