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EFFECT OF DIABETES AND STARVATION ON THE ACTIVITY OF RAT LIVER EPOXIDE HYDROLASES, GLUTATHIONE *S*-TRANSFERASES AND PEROXISOMAL β-OXIDATION

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Abstract—The activities of peroxisomal β-oxidation, cytosolic and microsomal epoxide hydrolase as well as soluble glutathione *S*-transferases have been determined in the livers of alloxan- and streptozotocin-diabetic male Fischer-344 rats. Five, seven and ten days after initiation of diabetes serum glucose levels were elevated 3.6-, 5.7- to 6.2- and 6-fold, while the activities of peroxisomal β-oxidation and cytosolic epoxide hydrolase were elevated 1.5- and 2.5-fold, 1.4- and 2.7-fold and 1.3- and 2.0-fold, respectively. The activities of microsomal epoxide hydrolase and glutathione *S*-transferases were reduced to about 71% and 80% of controls. Application of 10 I.U./kg depot insulin twice a day for 10 consecutive days to alloxan-diabetic individuals approximately restored the initial glucose levels and enzyme activities except for peroxisomal β-oxidation. Starvation of Fischer-344 rats for 48 hours and 5 days similarly resulted in a 1.3-fold to 2.1-fold and 1.2- to 1.6-fold increase in peroxisomal β-oxidation and cytosolic epoxide hydrolase activity, respectively. Microsomal epoxide hydrolase was significantly decreased to 57% and 61% of control activity whereas glutathione *S*-transferase was only marginally reduced to 91% and 92%. Except for glutathione *S*-transferases initial enzyme activities were restored upon refeeding within 10 days. These results are similar to those obtained upon feeding of hypolipidemic compounds with peroxisome proliferating activity, and may indicate that high levels of free fatty acids or their metabolites which are known to accumulate in liver in both metabolic states may act as endogenous peroxisome proliferators.

Epoxides can be formed from xenobiotic and endogenous compounds by the action of cytochrome P-450-dependent monooxygenases. One way to protect the cells against toxic effects of these reactive metabolites is the enzyme-catalysed addition of water by epoxide hydrolases. Up to now several forms of epoxide hydrolase have been described. One form of epoxide hydrolase is present in the endoplasmic reticulum. This enzyme catalyses the hydrolysis of a wide variety of epoxides. In routine assays benzo[*a*]pyrene 4,5-oxide and styrene oxide are the most commonly used substrates.

Another form of epoxide hydrolase is a predominantly cytosolic enzyme, which is routinely assayed with *trans*-stilbene oxide as substrate. Peroxisomes contain an enzyme, which is very similar if not identical with cytosolic epoxide hydrolase. Microsomal and cytosolic epoxide hydrolases differ in most properties investigated e.g. subcellular localization, substrate specificity, isoelectric points, inhibition, activation, molecular mass, peptide maps, amino acid composition and other biochemical characteristics (for reviews see Refs. 1–5).

Both enzymes differ also in their inducibility. Whereas treatment of rats with classical inducers of xenobiotic metabolizing enzymes e.g. *trans*-stilbene oxide, methylcholanthrene, phenobarbitone or Aroclor 1254 led to an increase in specific activity of liver microsomal epoxide hydrolase, cytosolic epoxide hydrolase activity was not affected [6, 7]. It was first demonstrated by Hammock and Ota [8] and Waechter *et al.* [9] that mouse liver cytosolic epoxide hydrolase is inducible by clofibrate and nafenopin, respectively. Both compounds exert peroxisome proliferating activity. In the meantime several studies have shown that administration of various peroxisome proliferators causes induction of cytosolic epoxide hydrolase in mice, rats and guinea-pigs [6, 7, 10–13].

These compounds also induce cyanide-insensitive β-oxidation, which has been shown to be localized in peroxisomes. The peroxisomal β-oxidation system contributes, in addition to mitochondria, to the oxidation of fatty acids, but differs in several properties from mitochondrial β-oxidation [14]. Previously it was reported that treatment of rats with the diabetogenic compound alloxan as well as starvation led to an increase in peroxisomal β-oxidation [15], which was less pronounced than that caused by xenobiotic peroxisome proliferators [7, 14]. As with various hypolipidemic compounds a concomitant induction of peroxisomal β-oxidation and cytosolic epoxide hydrolase had been observed. We have now investigated the effect of starvation and diabetes on these enzyme activities. In addition the activities of microsomal epoxide hydrolase and cytosolic glutathione *S*-transferases were estimated.

MATERIALS AND METHODS

Chemicals. [2,3-^{3}H]2-phenyloxirane ([^{3}H]styrene

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oxide, 11.7 GBq/mmol) and [2,3-^{3}H]*trans*-2,3-diphenyloxirane ([^{3}H]*trans*-stilbene oxide, 0.41 GBq/mmol) were synthesized as described in Refs 16 and 17, respectively. 1-Chloro-2,4-dinitrobenzene, alloxan, streptozotocin and porcine insulin (24 I.U./mg; 0.5% Zn) were obtained from Sigma Chemical Co. (Deisenhofen, F.R.G.) and bovine depot insulin (40 I.U./ml) was a product of Hoechst AG (Frankfurt/M., F.R.G.). The kit for measurement of serum glucose was purchased from Merck (Darmstadt, F.R.G.). All other chemicals were of analytical grade or the purest grade commercially available.

Animal experiments. Male Fischer-344 rats weighing 180–220 g or 220–260 g and 300–330 g were obtained from Charles River Wiga GmbH (Sulzfeld, F.R.G.) and Zentrale Versuchstieranstalt (Hannover, F.R.G.), respectively. Animals had free access to water and a defined diet (Altromin) and were kept at constant temperature under a constant light–dark cycle.

Diabetes was induced in groups of animals weighing 180–220 g and 220–260 g by a single s.c. injection of alloxan (120 mg/kg in 0.9% saline) or streptozotocin (50 mg/kg in 0.1 M citrate buffer, pH 4.5). Both diabetogenic compounds were dissolved immediately prior to injection. Control animals received an equivalent amount of carrier.

Urine was collected 3 and 5 days after treatment, and diabetes was assessed qualitatively by analysis of urinary glucose with the Combur®-Test (Boehringer, Mannheim, F.R.G.).

One group of alloxan-diabetic animals was divided and two animals each were injected 3 I.U./kg and 6 I.U./kg porcine insulin, respectively, once a day on 5 consecutive days in the tail vein starting on the seventh day after induction of diabetes. A second group received 10 I.U./kg s.c. of bovine depot insulin twice a day for 10 consecutive days starting on the sixth day after induction of diabetes. Control animals were given an appropriate amount of saline at the same time.

Short term starvation was performed with rats weighing 180–220 g for 48 hr while long term starvation was extended to 5 days using animals initially weighing 300–330 g. During fasting, all animals had free access to water. Refeeding was allowed to proceed for 10 days on a standard diet following starvation for 5 days.

Preparation of subcellular fractions. Rats were killed by decapitation at a constant time of day. The livers were perfused with ice-cold homogenization buffer (10 mM Tris/HCl, pH 7.4, containing 0.25 M sucrose), minced and homogenized using an Ultra-Turrax to give a 25% (w/v) homogenate. After centrifugation for 10 min at 600 *g* an aliquot of the supernatant was used for determination of peroxisomal β-oxidation activity. Then centrifugation was continued for 20 min at 12,000 *g*. The resultant supernatant was centrifuged for 60 min at 100,000 *g* to give the cytosol. The pellet was washed in 20 mM Tris/HCl, pH 8.0, containing 0.5 M KCl. After centrifugation at 100,000 *g* for 60 min the microsomal pellet was resuspended in a volume of homogenization buffer, which was equivalent to the original liver weight.

Enzyme assays. Activity of peroxisomal β-oxidation was determined in the 600 *g* supernatant [18] and activity of microsomal epoxide hydrolase in the microsomal fraction using styrene oxide as substrate [16]. Activity of cytosolic epoxide hydrolase [6] was measured with *trans*-stilbene oxide and that of glutathione *S*-transferase with 1-chloro-2,4-dinitrobenzene as substrate [19], respectively.

Determination of serum glucose. Rats were killed by decapitation and blood was collected. After coagulation for 20 min at room temperature the serum was obtained by centrifugation for 5 min at 3000 *g*. Serum glucose levels were determined using a commercial kit based on the glucose dehydrogenase reaction as recommended by the manufacturers.

RESULTS

The effects of diabetes and starvation on the activity of peroxisomal β-oxidation and foreign compound metabolizing enzymes were investigated in two sets of independent experiments, and experimental conditions were varied to exclude experimental errors possibly connected with these unstable metabolic states. Long term starvation was performed with older animals to guarantee their survival during the experimental period.

Diabetes

A single s.c. treatment of male Fischer-344 rats (180–220 g) with the diabetogenic compounds alloxan and streptozotocin resulted in about a 6-fold increase of serum glucose levels within 7 days from 75.9 ± 25.9 mg/dl in controls to 432.6 ± 77.9 and 470.8 ± 67.4 mg/dl respectively. During the same time a body weight loss of 26% for alloxan-diabetic and 16% for streptozotocin-diabetic animals was accompanied by a 29% and 22% decrease of the liver weight, which left the liver/body weight ratio of 3.7% basically unchanged compared with control animals.

Alterations in enzyme activities observed 7 days after induction of diabetes are presented in Table 1. Alloxan and streptozotocin increased significantly peroxisomal β-oxidation, 1.4- and 1.3-fold respectively. Activity of cytosolic epoxide hydrolase was 2.7 times the level of controls whereas microsomal epoxide hydrolase activity with styrene oxide as a substrate remained unchanged by the diabetic status in this experiment (data not shown). Glutathione *S*-transferase was decreased to about 80% of control. Even 10 days after initiation of diabetes by alloxan serum glucose level and activities of peroxisomal β-oxidation and cytosolic epoxide hydrolase were increased 6-fold, 1.3-fold and 2-fold respectively (Table 2).

Treatment of alloxan-diabetic animals on 5 consecutive days with a single i.v. dose of 3 I.U./kg or 6 I.U./kg of porcine insulin reduced the serum glucose levels to about 40 mg/dl, a moderately hypoglycemic state with somewhat less than 50% of the control level. However, activity of peroxisomal β-oxidation remained elevated while cytosolic epoxide hydrolase showed a slight, 25–19%, decrease compared with alloxan-diabetic controls (Table 2).

Induction of diabetes by 120 mg/kg alloxan in male

Table 1. Effect of alloxan- and streptozotocin-induced diabetes on the activities of peroxisomal β-oxidation, cytosolic epoxide hydrolase and glutathione *S*-transferase

Treatment	Peroxisomal β-oxidation*	Cytosolic epoxide hydrolase†	Glutathione *S*-transferase*
Control	4.7 ± 0.5	30.4 ± 5.6	1477 ± 62
Alloxan	6.7 ± 1.7**	80.7 ± 19.6*****	1157 ± 149****
Streptozotocin	6.0 ± 1.2****	81.5 ± 10.2*****	1228 ± 132****

Diabetes was induced in rats weighing 180–220 g by a single s.c. injection of alloxan (120 mg/kg body wt) or streptozotocin (50 mg/kg body wt). Enzyme activities were determined from 5 rats (alloxan: 4 rats) 7 days after treatment.

* Specific activity is given in nmol/min × mg protein.

† Specific activity is given in pmol/min × mg protein.

P values for results significantly different (Student's *t*-test) from control data at ** $P < 0.05$, **** $P < 0.01$, ***** $P < 0.001$.

Table 2. Effect of insulin treatment on alloxan-induced increases of peroxisomal β-oxidation, cytosolic epoxide hydrolase activity and blood glucose level

Treatment	Insulin	Serum glucose (mg/dl)	Peroxisomal β-oxidation*	Cytosolic epoxide hydrolase†
Control	—	89.3	4.1	44.0
Alloxan	—	536.0	5.2	87.7
Alloxan	3 I.U.	40.4	5.5	74.6
Alloxan	6 I.U.	38.7	5.3	70.6

Diabetes was induced in rats weighing 180–220 g by a single s.c. injection of 120 mg alloxan/kg body wt. Five days after alloxan treatment insulin was given i.v. on 5 consecutive days as a single dose in the morning. Data given are means from two animals (control: 3 animals) after an experimental period of 10 days.

* Specific activity is given in nmol/min × mg protein.

† Specific activity is given in pmol/min × mg protein.

Fischer-344 rats weighing 220–260 g resulted in a 3.6-fold elevated serum glucose level within 5 days of 383.3 ± 37.3 mg/dl from initially 107.5 ± 11.4 mg/dl. A 23% loss of body weight within this period of time was accompanied by a 44% reduction of the liver weight which led, in contrast to the 180–220 g animals, to a marked decrease of the calculated liver/body weight ratio from an average of 4.2% in non-diabetic controls to 3.4%.

Similar to the younger animals and more extended time points, alloxan treatment increased the activities of peroxisomal β-oxidation and cytosolic epoxide hydrolase significantly, 1.5-fold and 2.5-fold respectively, after 5 days. Microsomal epoxide hydrolase activity was reduced slightly, significant to about 70% of control values, while the activity of glutathione *S*-transferases dropped, however statistically not significant, to 80% of controls (Table 3).

Treatment of these alloxan-diabetic rats s.c. with two daily doses of 10 I.U./kg of bovine depot insulin for 10 consecutive days starting 5 days after induction of diabetes stabilized serum glucose levels slightly above controls of 105 mg/dl. This stabilization was also reflected by a 2.4% body weight gain during the experimental time period compared with 10.7% of controls and a normalized liver/body weight ratio of 4.1% for both groups.

The activities of both, peroxisomal β-oxidation and cytosolic epoxice hydrolase were apparently, but not statistically significantly, elevated 1.4-fold after 10 days of insulin treatment, while microsomal epoxide hydrolase and cytosolic glutathione *S*-transferase activity had approximately reached control levels (Table 3).

Starvation

Starvation of Fischer-344 rats (220–260 g) for 48 hr caused a 10% and 25% decrease in body and liver weight. The corresponding liver/body weight ratio dropped from initially 3.7% to 3.2%, and the serum glucose was reduced 47% from 97.6 ± 11.6 mg/dl to 51.8 ± 21.7 mg/dl.

Fasting increased peroxisomal β-oxidation 1.3-fold and cytosolic epoxide hydrolase activity 1.2-fold compared with control activities. Microsomal epoxide hydrolase activity was reduced to 57% of control. In contrast to the other enzymes glutathione *S*-transferases were not significantly affected (Table 4).

Starvation of Fischer-344 rats initially weighing 300–330 g for 5 days caused a 19% and 46% loss in body and liver weight respectively, and shifted the initial liver/body weight ratio from 3.2% to 2.2%. The activities of peroxisomal β-oxidation and cytosolic epoxide hydrolase were elevated 2.1-fold and 1.6-fold compared to controls. Microsomal epoxide hydrolase activity was significantly reduced to 61% of control while glutathione *S*-transferase activity

Table 3. Effect of alloxan diabetes and prolonged insulin treatment on the activities of peroxisomal β-oxidation, epoxide hydrolases and glutathione S-transferase

Treatment	Peroxisomal β-oxidation†	Cytosolic epoxide hydrolase‡	Microsomal epoxide hydrolase†	Glutathione S-transferase†
Control	2.95 ± 0.41	25.7 ± 2.8	4.41 ± 0.57	288 ± 66
Alloxan	4.29 ± 0.91*	65.3 ± 15.7***	3.13 ± 0.73*	228 ± 52
Control/NaCl	2.79 ± 0.75	22.1 ± 3.8	3.85 ± 0.40	195 ± 49
Alloxan/20 I.U. Insulin/kg	3.82 ± 0.54	30.2 ± 6.6	3.59 ± 0.64	296 ± 59

Diabetes was induced in rats weighing 220–260 g by a single s.c. injection of 120 mg alloxan/kg body wt. Bovine depot insulin was given twice a day at 10 I.U./kg body wt for 10 consecutive days starting 5 days after the induction of diabetes. Controls received the equivalent volume of saline twice a day. Enzyme activities were determined from three animals each.

† Specific activity is given in nmol/min × mg protein.

‡ Specific activity is given in pmol/min × mg protein.

P values for results significantly different (Student's *t*-test) from controls at * $P < 0.1$; *** $P < 0.02$.

Table 4. Effect of 48 hours starvation on the activities of peroxisomal β-oxidation, epoxide hydrolases and glutathione S-transferase

Treatment	Peroxisomal β-oxidation*	Cytosolic epoxide hydrolase†	Microsomal epoxide hydrolase*	Glutathione S-transferase*
Control	4.7 ± 0.3	44.6 ± 3.6	5.8 ± 0.9	1572 ± 188
Starvation	6.0 ± 0.5****	53.6 ± 2.8****	3.3 ± 0.7****	1435 ± 54

Enzyme activities were determined from four control and five starved rats initially weighing 220–260 g after 48 hr of starvation.

* Specific activity is given in nmol/min × mg protein.

† Specific activity is given in pmol/min × mg protein.

P values for results significantly different (Student's *t*-test) from controls at **** $P < 0.01$.

Table 5. Effect of 5 days starvation and refeeding on the activities of peroxisomal β-oxidation, epoxide hydrolases and glutathione S-transferase

Treatment	Peroxisomal β-oxidation*	Cytosolic epoxide hydrolase†	Microsomal epoxide hydrolase*	Glutathione S-transferase*
Control (5 days)	2.03 ± 0.46	25.1 ± 4.4	9.11 ± 1.44	744 ± 192
Starvation (5 days)	4.21 ± 0.36****	39.1 ± 7.5*	5.57 ± 0.91****	686 ± 110
Control II (15 days)	2.29 ± 0.50	18.3 ± 4.5	8.90 ± 1.17	925 ± 268
Starvation (5 days)/ refeeding (10 days)	2.52 ± 0.75	20.2 ± 1.7	9.77 ± 1.91	603 ± 114

Except for control II, which comprised four animals enzyme activities were determined from three rats each initially weighing 300–330 g.

* Specific activity is given in nmol/min × mg protein.

† Specific activity is given in pmol/min × mg protein.

P values for results significantly different (Student's *t*-test) from controls at * $P < 0.01$; **** $P < 0.01$.

towards CDNB was not significantly changed (Table 5).

Refeeding for 10 days with a standard diet following 5 days of starvation normalized body and liver weights and all investigated enzyme activities which had been significantly changed by starvation (Table 5).

DISCUSSION

Numerous alterations in hepatic ultrastructure and metabolism occur during diabetes and starvation [22]. These changes also seem to include the drug metabolizing enzymes as has been demonstrated for cytochrome P-450-dependent monooxygenases [20, 21] and glutathione S-transferases [23, 24]. We have now investigated the effects of diabetes and fasting on the activities of cytosolic glutathione S-transferases, microsomal and cytosolic epoxide hydrolases as well as peroxisomal β-oxidation in Fischer-344 rats, and observed changes similar to those obtained upon treatment with hypolipidemic drugs.

Both diabetogenic compounds, alloxan and streptozotocin, caused a 3- to 6-fold elevated serum glucose level comparable to that observed in previous

studies [20, 25] and independent of the age and initial body weight of the experimental animals. At the same time the activities of peroxisomal β-oxidation and cytosolic epoxide hydrolase were increased 1.3- to 1.5-fold and 2.0- to 2.7-fold respectively, whilst the activities of microsomal epoxide hydrolase and soluble glutathione *S*-transferases were reduced to about 70% and 80% of controls (Tables 1–3).

Similar results were obtained upon fasting with 1.3- to 2.1-fold elevated levels of peroxisomal β-oxidation and 1.2- to 1.6-fold increased cytosolic epoxide hydrolase activity depending on the period of starvation. Reduction of microsomal epoxide hydrolase activity was more pronounced in this metabolic state, while glutathione *S*-transferase showed only a marginal decrease in activity which did not reach statistical significance (Tables 4 and 5).

Both metabolic states, diabetes as well as starvation are characterized by an extensive accumulation of long chain fatty acids and their corresponding acyl-CoA derivatives in the liver [22, 25, 26]. As a consequence rates of fatty acid β-oxidation are accelerated [26].

Hepatic fatty acid oxidation is catalysed by the mitochondrial and peroxisomal β-oxidation system. Horie *et al.* [25] have shown that the activity of peroxisomal β-oxidation was elevated in alloxan treated rats. We have now confirmed their results and extended this observation to streptozotocin (Table 1). Both compounds leading to identical effects, provides strong evidence that these changes are in fact due to the altered metabolism following induction of diabetes and not caused by an unrelated property of the diabetogenic compound itself.

In recent studies we have shown that peroxisomal β-oxidation and cytosolic epoxide hydrolase were concomitantly regulated after treatment of rats or guinea-pigs with various hypolipidemic drugs [7, 13]. Similar results were obtained with mice [11, 12]. We have now observed a concomitant increase of both enzyme activities under the conditons of diabetes (Tables 1–3) and short term as well as prolonged starvation (Tables 4 and 5). These changes, caused by an altered metabolism, are significantly less than those after treatment of rats with xenobiotic peroxisome proliferators. Nevertheless, they are of special interest as they may help to identify "natural" peroxisome proliferators and must be considered in a hypothesis describing the concomitant regulation of peroxisomal β-oxidation and cytoslic epoxide hydrolase. Lalwani *et al.* [27, 28] presented evidence for a cytosolic binding protein, which should mediate the effects of peroxisome proliferators. However, this receptor could not be confirmed in a recent study [29]. Instead Sharma *et al.* [30] have proposed a mechanism in which long-chain fatty acids, which may be elevated in the hepatocyte as a result of the action of hypolipidemic compounds after hydroxylation by cytochrome P-452 and further cytosolic oxidation to dicarboxylic acids may be responsible for the proliferation of peroxisomes.

The very similar results obtained in this study for the induction of peroxisomal β-oxidation and cytosolic epoxide hydrolase with diabetic and starved animals support the view that the inductive response is triggered by endogenous factors common to both metabolic states, namely high hepatic levels of free fatty acids and/or relative endogenous excess of glucagon. These may give rise to an induction of cytochrome P-452 as proposed by Sharma *et al.* [30] with increased rates of fatty acid ω-hydroxylation and formation of dicarboxylic acids. But the increased levels of free fatty acids may as well lead to a rapid consumption of coenzyme A with concomitant formation of long chain fatty acyl-CoA derivatives which may on the other hand express intrinsic inductive potency. The concomitant induction of cEH with peroxisomal β-oxidation may provide an important protective mechanism against increased lipid peroxidation and fatty acid epoxide formation under conditions of elevated peroxisomal fatty acid metabolism and H_2O_2 production.

The changes caused by diabetes (Tables 1–3) could, with the exception of peroxisomal β-oxidation, be largely restored to control levels under conditions of controlled application of depot insulin for 10 consecutive days (Table 3). A single daily i.v. injection of insulin over a period of 5 days, however, as an example for badly controlled treatment of diabetes, did not affect elevated peroxisomal β-oxidation and only marginally reduced elevated cytosolic epoxide hydrolase activity (Table 2).

Alterations in enzyme activities induced by starvation were basically abolished upon refeeding (Tables 4 and 5).

These results argue for a reversible enzyme induction/repression process depending on imbalanced metabolite and/or hormone levels. Although it has not been investigated in detail, the latter seems to play only a minor role in that the hormone levels upon feeding of hypolipidemic drugs should not be impaired whereas the induction of cEH and peroxisomal β-oxidation is more than 5 times higher [7, 13]. However, despite the evidence from this study and previous reports [7, 13, 25, 26] that primarily increased hepatic fatty acid levels may give rise to altered enzyme activities, the hormonal aspect needs to be considered in future studies in a system such as cultured hepatocytes which allows a better control of substrate and hormone parameters.

The effect of diabetes and insulin on the composition of cytochrome P-450 dependent monooxygenases was shown to depend on the isoenzyme investigated [20, 31]. The same could be demonstrated in the present study for the effect of diabetes and starvation on cytosolic and microsomal epoxide hydrolase. While cytosolic epoxide hydrolase activity was increased the microsomal epoxide hydrolase remained unchanged or was slightly but significantly decreased (Tables 3–5), reflecting the fact that these enzymes are under different if not opposite genetic control. The reproducible slight decrease in glutathione *S*-transferase activity against 1-chloro-2,4-dinitrobenzene as substrate observed in diabetic rats (Tables 1, 3–5) is in agreement with previous studies [24, 32].

The reason why Younes *et al.* [24] have observed an increase in glutathione *S*-transferase activity after fasting, whereas in our experiments the activity remained reproducibly unchanged or was even slightly decreased, is not clear.

The slight suppression of glutathione *S*-transferase

activity as well as the significantly reduced activity of microsomal epoxide hydrolase deserve attention particularly with respect to an increased liberation of accumulated hydrophobic drugs and xenobiotics from fat tissue upon fasting and a potentially increased risk of formation of reactive metabolites under these conditions of impaired detoxification capacities.

Our study demonstrates that the activity of cytosolic epoxide hydrolase can be significantly altered under the influence of pathophysiological conditions and presents further evidence that this enzyme activity is concomitantly regulated with peroxisomal β-oxidation. In addition the results of this investigation, which are similar to those obtained upon feeding of hypolipidemic compounds with peroxisome proliferating activity, indicate that high levels of free fatty acids or their metabolites which are known to accumulate in liver during starvation and diabetes may act as endogenous peroxisome proliferators.

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