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Effects of hypolipidaemics cetaben and clofibrate on mitochondrial and peroxisomal enzymes of rat liver

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Abstract—Clofibrate or cetaben was administered to male rats for 10 days. Peroxisomal and mitochondrial enzymes were assayed in liver subcellular fractions. Clofibrate affected the specific activities of both mitochondrial enzymes (glycerol-3-phosphate dehydrogenase and nicotinamide-linked isocitrate dehydrogenase) and peroxisomal enzymes (fatty acyl-CoA oxidase, glycerone phosphate acyltransferase, urate oxidase, and D-amino-acid oxidase). In contrast, cetaben raised only the peroxisomal enzymes, acyl-CoA oxidase, glyceronephosphate acyltransferase, D-amino-acid oxidase, catalase, and urate oxidase. Thus, the hypolipidaemic activity of these drugs may be exclusively related to stimulated peroxisomal functioning, while mitochondria play only a minor role.

Although only a few mitochondrial enzymes have been shown to be influenced by clofibrate, mitochondria have received particular interest in studies on the hypolipidaemic action of the drug. Mitochondrial enzymes which are induced by clofibrate include glycerol-3-phosphate dehydrogenase (Hess et al 1965), choline dehydrogenase (Kramar et al 1984), outer carnitine palmitoyltransferase (Markwell et al 1977), and nicotinamide dependent isocitrate dehydrogenase (Schön et al 1991).

Cetaben has been identified as an anti-atherosclerotic hypolipidaemic substance (Hollander et al 1978; Fort et al 1983). It is structurally quite different from clofibric acid but is also an amphipathic carboxylate. Hypolipidaemic peroxisome proliferators often have this structural feature. Cetaben has been shown to act similarly in some respects to clofibrate. In rats, cetaben treatment at a dose of 200 mg kg⁻¹ day⁻¹ raised liver weight slightly and the number of peroxisomes increased, as did liver catalase activity (Fort et al 1983).

The effect of cetaben on mitochondrial and other peroxisomal enzymes has not been investigated so far; we have, therefore, compared the action of cetaben with that of clofibrate by

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measuring the activities of selected mitochondrial and peroxisomal enzymes in rat liver cell fractions.

Materials and methods

Materials. Cetaben was a generous gift from Lederle Arzneimittel GmbH & Co. (Wolfratshausen, Germany). Clofibrate was purchased from Serva (Heidelberg, Germany). D-[U-¹⁴C] Fructose 1,6-bisphosphate (sp. act. 12·5 MBq mM⁻¹) was purchased from Amersham (Buckinghamshire, UK). Triose-phosphate isomerase (5 k units mg⁻¹) and fructose-bisphosphate aldolase (9 units mg⁻¹) were obtained from Boehringer Mannheim GmbH (Germany). All other reagents were purchased from Sigma Chemical Co. (St Louis, MO, USA).

Animals and treatment. Male Sprague-Dawley rats, 181 ±25 g, were allowed free access for 10 days to a standard laboratory chow (controls), or one containing either 1·0 g kg⁻¹ cetaben or 7·5 g kg⁻¹ clofibrate. Food for the drug treatment was impregnated with cetaben dissolved in chloroform/methanol (3:1) or with clofibrate dissolved in diethylether. Solvents were removed by evaporation to dryness. The mean daily intake of clofibrate was 840 mg kg⁻¹ day⁻¹ and that of cetaben 112 mg kg⁻¹ day⁻¹ calculated from the daily food consumption of 20·2 g. The cetaben dose was chosen after preliminary experiments: 56 mg kg⁻¹ day⁻¹ did not lower the plasma triglycerides significantly, whereas 335 mg kg⁻¹ day⁻¹ caused the death of three out of six rats during a feeding period of 10 days. A comparable toxicity of cetaben has been reported (Oker-Blom 1981). The clofibrate dose was within the range used in other experimental studies on rat liver (Hess et al 1965; Kurup et al 1970). No animal died under this regimen. This was also the case in our extensive animal studies on clofibrate (Kramar et al 1984; Schön et al 1991; Prager et al 1993). The 10-day feeding period was adopted in accordance with the literature (Hess et al 1965).

Subcellular preparation. A large particle fraction (Leighton et al 1968), consisting of mitochondria, lysosomes, and peroxisomes, was prepared by centrifuging the 1000 g postnuclear supernatant at 20 000 g for 20 min and suspending the pellet in 5 mL 250 mM sucrose (g tissue)$^{-1}$. All steps were carried out at 4°C.

Enzyme assays. Enzyme activities were measured after two cycles of freezing and thawing. Fatty acyl-CoA oxidase and D-amino-acid oxidase were assayed as described by Small et al (1980), by measuring the palmitoyl-CoA- and D-alanine-depen-

dent formation of H_2O_2. Leuko-2,7-dichlorofluorescein was used as peroxidase substrate. For the urate oxidase assay the disappearance of uric acid was determined in a reaction mixture containing 19 mM borate buffer, pH 9·5, 1 g L^{-1} Triton X-100 and 0·19 mM uric acid (Böck et al 1975). Glycerone phosphate acyl transferase was measured with 18·5 kBq D-[U-^{14}C]fructose-1,6-bisphosphate (sp. act. 12·5 kBq mM^{-1}) as the source of glycerone phosphate in the presence of 65 μM palmitoyl-CoA, 15 units mL^{-1} triose-phosphate isomerase and 0·45 units mL^{-1} fructose-bisphosphate aldolase (Bates & Saggerson 1979). Car-

Table 1. Effects of cetaben and clofibrate intake on body weight, relative liver weight, and tissue protein fractions of rat liver.

	Control	Cetaben	Clofibrate
Food intake (g day^{-1})	27·1 ± 4·0	20·2 ± 2·7*	20·3 ± 2·1*
Change in body wt (g)	54·0 ± 3·5	16·3 ± 0·7**	82·7 ± 2·6**
Weight of liver/100 g body wt (g)	5·2 ± 0·5	5·3 ± 0·5•	6·6 ± 0·8**
Protein in post nuclear supernatant (mg g^{-1})	120 ± 18	136 ± 21	143 ± 27*
Protein in large-particle fraction (mg g^{-1})	31·5 ± 5·9	40·7 ± 7·7	46·5 ± 8·9*
Serum triglycerides (g L^{-1})	0·87 ± 0·21	0·55 ± 0·18*	0·24 ± 0·028**
Serum total cholesterol (g L^{-1})	1·03 ± 0·08	0·63 ± 0·23**	0·63 ± 0·18**

$*P < 0.05$, $**P < 0.01$ compared with controls. $•P < 0.01$ compared with clofibrate values. There were nine animals in each group.

Table 2. Effect of cetaben and clofibrate on selected peroxisomal and mitochondrial enzymes in the large-particle fraction prepared from rat liver homogenate.

	Control	Cetaben	Clofibrate
Peroxisomal enzymes			
Acyl-CoA oxidase			
(units (g liver)$^{-1}$)	0·110 ± 0·001	1·24 ± 0·07**	1·09 ± 0·09**
(m units (mg protein)$^{-1}$)	3·5 ± 0·72	30·5 ± 2·6**†	23·4 ± 4·1
D-Amino-acid oxidase			
(units (g liver)$^{-1}$)	0·020 ± 0·004	0·103 ± 0·015**‡	0·0060 ± 0·0001**
(m units (mg protein)$^{-1}$)	0·637 ± 0·089	2·54 ± 0·51**‡	0·136 ± 0·027**
Urate oxidase			
(units (g liver)$^{-1}$)	1·27 ± 0·06	2·24 ± 0·10**‡	0·916 ± 0·057**
(m units (mg protein)$^{-1}$)	40·3 ± 7·0	56·4 ± 4·9**‡	19·7 ± 1·3**
Glycerone phosphate acyltransferase			
(units (g liver)$^{-1}$)	0·0016 ± 0·0003	0·0113 ± 0·0003**‡	0·0046 ± 0·0004*
(m units (mg protein)$^{-1}$)	0·05 ± 0·01	0·277 ± 0·010**‡	0·10 ± 0·01**
Catalase			
(rate constant, (mg tissue)$^{-1}$)	1·19 ± 0·06	1·98 ± 0·39**	1·90 ± 0·12**
(rate constant, (mg protein)$^{-1}$)	37·7 ± 7·6	48·7 ± 3·2*	42·5 ± 8·5
Mitochondrial enzymes			
Glycerol-3-phosphate dehydrogenase			
(units (g liver)$^{-1}$)	0·067 ± 0·009	0·103 ± 0·015**‡	0·502 ± 0·057**
(m units (mg protein)$^{-1}$)	2·14 ± 0·43	2·54 ± 0·40‡	10·8 ± 2·1**
Nicotinamide-dependent isocitrate dehydrogenase			
(units (g liver)$^{-1}$)	0·299 ± 0·039	0·374 ± 0·077†	0·693 ± 0·138**
(m units (mg protein)$^{-1}$)	9·48 ± 1·89	9·19 ± 0·75†	14·9 ± 3·1*
Succinate dehydrogenase			
(units (g liver)$^{-1}$)	0·300 ± 0·051	0·510 ± 0·066*†	0·637 ± 0·015**
(m units (mg protein)$^{-1}$)	9·52 ± 1·62	12·4 ± 2·4	13·7 ± 1·1**
Malate dehydrogenase			
(units (g liver)$^{-1}$)	31·7 ± 0·6	41·1 ± 1·2**†	51·0 ± 6·43**
(m units (mg protein)$^{-1}$)	1016 ± 192	1009 ± 157	1096 ± 216
Fumarate hydratase			
(units (g liver)$^{-1}$)	8·17 ± 0·76	11·0 ± 0·3**†	12·3 ± 0·415**
(m units (mg protein)$^{-1}$)	260 ± 25·3	270 ± 9·9	261 ± 11·4
Peroxisomal and mitochondrial enzyme			
Carnitine acetyltransferase			
(units (g liver)$^{-1}$)	0·084 ± 0·011	0·220 ± 0·045**‡	1·47 ± 0·27**
(m units (mg protein)$^{-1}$)	2·67 ± 0·46	5·31 ± 0·87**‡	31·6 ± 6·3**

$*P < 0.05$, $**P < 0.01$ compared with control values; $†P < 0.05$, $‡P < 0.01$ compared with corresponding clofibrate values.

nitine acetyltransferase was assayed with 2,2'-dinitro-5,5'-dithiodibenzoic acid as acceptor for the release CoASH (Markwell et al 1973).

Mitochondrial glycerol-3-phosphate dehydrogenase and succinate dehydrogenase were determined with 2-(p-iodophenyl)-3-(p-nitrophenyl)-5-phenyltetrazolium-chloride as electron acceptor (Kramar 1971). Nicotinamide-dependent isocitrate dehydrogenase was assayed according to Schön et al (1991), fumarate hydratase according to Kanarek & Hill (1964), and malate dehydrogenase according to England & Siegel (1969). Catalase was assayed by following the decomposition of H_2O_2 (Böck et al 1975).

Protein and blood lipids. Protein was measured by the method of Lowry et al (1951). Serum total triglycerides and cholesterol concentration were measured after enzymatic hydrolysis as described by Wahlefeld (1974) and Seidel et al (1983).

Statistics. Results obtained from control and treated rats are given as arithmetic means ± s.d. and analysed by the unpaired Student's t-test. The observed differences between groups were considered to be significant at $P < 0.05$.

Results and discussion

Cetaben and clofibrate had a significant effect on the weight of the animals (Table 1). Whereas the clofibrate group showed a much stronger increase of body weight than the controls, the cetaben-treated rats had a lower weight gain despite similar food consumption. Clofibrate significantly increased the relative liver weight by 27% and protein (g liver)$^{-1}$ in the part nuclear supernatant by 19%. Serum total cholesterol and triglycerides were lowered by both drugs (Table 1).

The effects of clofibrate on selected enzymes were established to obtain an internal control against which the action of cetaben could be evaluated (Table 2). Clofibrate raised the specific activities of the mitochondrial enzymes glycerol-3-phosphate dehydrogenase, nicotinamide-dependent isocitrate dehydrogenase and succinate dehydrogenase. Of the peroxisomal enzymes studied, only fatty acyl-CoA oxidase and glycerone phosphate acyltransferase activities were elevated, whereas catalase activity remained unchanged. Urate oxidase and D-amino-acid oxidase activities decreased. These findings agreed with previous data (Hess et al 1965; Lazarow & De Duve 1976; Pollard & Brindley 1982; Panchenko et al 1982). Clofibrate treatment increased weight gain but decreased food consumption.

Cetaben not only increased the specific activities of peroxisomal fatty acyl-CoA oxidase and glycerone phosphate acyltransferase, but also of the peroxisomal enzymes urate oxidase, D-amino-acid oxidase, and catalase. A simultaneous induction of urate oxidase and D-amino-acid oxidase has also been reported for another amphipathic hypolipidaemic carboxylate, MLM-160 (Yokota 1990). The mitochondrial enzymes studied were not influenced by cetaben. Thus cetaben exerted its effects selectively on peroxisomal enzymes, leaving the specific activities of mitochondrial enzymes unchanged. The strong correlation between peroxisomal β-oxidation and mitochondrial glucose-3-phosphate dehydrogenase found with a number of peroxisome proliferators (Holloway & Orton 1979; Mitchell et al 1986) was absent in the case of cetaben. Carnitine acetyltransferase, an enzyme which is both mitochondrial and peroxisomal (Markwell et al 1973), was induced by clofibrate more than by cetaben. Presumably cetaben induced only the peroxisomal isoenzyme of carnitine acyltransferase, whereas clofibrate also acted on the mitochondrial isoenzyme (Markwell et al 1977).

The specific response of some enzymes to the proliferative stimuli of clofibrate and cetaben was demonstrated by observing changes in specific activities. The specific activities of the mitochondrial enzymes, glycerol-3-phosphate dehydrogenase, succinate dehydrogenase, malate dehydrogenase and fumarate hydratase, were not affected by cetaben but showed some increase when their activities were normalized for liver weight. This may be partly explained by the decrease in absolute liver weight observed with cetaben treatment.

The enzymatic changes observed after cetaben and clofibrate treatment corresponded well with morphological alterations reported previously. Cetaben (like clofibrate) drastically increased the number of peroxisomes (Fort et al 1983). This agreed with our previous study (Böck et al 1992) which also showed that the mitochondria of cetaben-fed rats were inconspicuous in number and morphology, whereas they were augmented after clofibrate. Compared with clofibrate treatment, .this selective peroxisomal effect of cetaben was presumably reflected by the lower increase in liver protein. As urate oxidase is firmly bound to crystalline cores of mammalian peroxisomes, the scarcity of cores in clofibrate-proliferated peroxisomes clearly corresponded to the observed decrease of urate oxidase activity (Hess et al 1965). Cetaben-proliferated peroxisomes were well provided with cores (Böck et al 1992) and urate oxidase activity increased correspondingly.

Hypolipidaemic doses of cetaben lowered plasma triglycerides and cholesterol levels without hepatomegaly and mitochondrial proliferation. This might be a favourable aspect in the therapeutic use of this drug.

Our results show that while the biochemical effects of clofibrate encompass hepatic peroxisomes and mitochondria, cetaben selectively stimulates the peroxisomal compartment. This raises some doubts on a common proliferation mechanism for peroxisomes and mitochondria triggered by a common receptor for the drugs.

On the other hand certain systemic effects of hypolipidaemic peroxisome proliferators are relevant to their pharmacological action. Clofibrate and related fibrates enhance lipoprotein lipase activity in skeletal muscle (Lithell et al 1978), adipose tissue (Taylor et al 1977), and blood (Heller & Harvengt 1983). In addition clofibrate decreases the low density lipoprotein cholesterol and triglycerides by raising the expression of low density lipoprotein receptors (Kleinman et al 1985) and lowers the activity of hydroxymethylglutaryl-CoA reductase, the rate-limiting enzyme in cholesterol synthesis (Stahlberg et al 1989). Therefore, some caution should be exercised when interpreting the results: the action of these drugs on liver cell organelles may have nothing to do with their pharmacological capacity and may only be a side-effect. This view is encouraged by the pathology of the Zellweger cerebrohepatorenal syndrome. In this autosomal recessive peroxisomal defect, the tissues of the patients are totally devoid of peroxisomes and the mitochondria exhibit severe abnormalities. However, a marked increase of plasma lipid concentrations has not been observed (Kelley 1983).

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