Peroxisome Proliferation and Lipid Peroxidation in Rat Liver

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ABSTRACT

Male F344 rats were fed a diet containing the peroxisome proliferators 2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropionic acid [ciprofibrate (0.025%) or [4-chloro-6-(2,3-xylyldino)-2-pyrimidinylthio]acetic acid [Wy-14643 (0.1%)] for up to 14 months to determine whether hepatic peroxisome proliferation caused by these agents results in the induction of membrane lipid peroxidation in the liver. Peroxidative damage of membrane lipids from whole liver, postnuclear, heavy-particle, microsomal, and nuclear membranes was evaluated by determining the extent of formation of conjugated dienes (ultraviolet absorption, 233 nm). Increased generation of diene conjugates was noted in whole-liver, postnuclear, and heavy-particle membrane lipids of rats fed peroxisome proliferators for 6 months or longer when compared to controls. An additional, more intense absorption profile in the ultraviolet absorption range of ~276 nm was noted in the membrane lipids derived from whole liver, postnuclear, and heavy particle pellets, but not in the nuclear and microsomal membrane lipids of livers with peroxisome proliferation. Although the exact chemical nature of this A276 nm peak is not clear, it is attributed to the formation of ketone dienes and/or conjugated trienes. The excess lipid peroxidation correlates with the previous observation of accumulation of abundant quantities of lipofuscin in hepatocytes of rats chronically exposed to peroxisome proliferators. The generation of conjugated dienes and ketone dienes and/or trienes together with increased levels of H2O2 generation by peroxisomal enzymes, and decreased levels of hepatic glutathione peroxidase, glutathione reductase, and glutathione-S-transferases, enzymes responsible for the defense against H2O2 damage, suggest the occurrence of membrane lipid peroxidation and oxidative stress in livers of rats treated with carcinogenic peroxisome proliferators.

INTRODUCTION

Currently, several structurally dissimilar hypolipidemic drugs and certain phthalate ester plasticizers constitute two major categories of carcinogenic peroxisome proliferators (1–6). These two classes of chemicals play an important role in our society today, the hypolipidemic agents in the control of hyperlipidemia, a major risk factor for coronary heart disease, and the phthalate ester plasticizers in the formulation and manufacture of highly versatile polyvinyl plastics. It is also expected that new classes of peroxisome proliferators will most likely be identified because of the current emphasis on the development of nonmutagenic chemicals for use as pharmacological, industrial, herbalicidal, and pesticidal agents, since such nonmutagenic agents are now screened for peroxisome proliferative activity. In view of the widespread use of peroxisome proliferators, it is imperative to understand their effects on biological systems and delineate the underlying mechanisms of toxicity and carcinogenicity. It is becoming increasingly evident that peroxisome proliferators induce a very high incidence of hepatocellular carcinomas in rats and mice (4, 7–9) although they are neither mutagenic in Ames assays (10, 11) nor DNA damaging (12, 13). This led to the hypothesis that their carcinogenicity is related to biologically active products of the proliferated peroxisomes rather than to a direct chemical effect on cellular macromolecules (4, 8). Therefore, the proposed relationship between persistent proliferation of peroxisomes and hepatocarcinogenicity implies that peroxisome proliferator induced increase in the synthesis of H2O2 generating peroxisomal β oxidation enzyme system can cause profound intrahepatic oxidative stress leading to endogenous initiation of neoplastic change in liver (8, 14). This mechanism is consistent with the current recognition that cellular prooxidant states can modulate gene expression, differentiation, aging, and neoplastic transformation (15, 16).

In previous studies we have shown accumulation of abundant quantities of autofluorescent lipofuscin in liver during hepatocarcinogenesis by peroxisome proliferators (14, 17). Lipofuscin is widely accepted as the end product of a free radical-induced oxidative polymerization reaction involving proteins and lipids (18, 19). Therefore, it appeared necessary to investigate whether xenobiotic-induced peroxisome proliferation leads to oxidation of membrane fatty acids, initiating lipid peroxidation. In this report we present evidence of increased lipid peroxidation in rat livers with peroxisome proliferation induced by ciprofibrate, a peroxisome proliferator (20). The data on hepatic H2O2 generation and on the levels of enzymes which play a role in the regulation of defenses against oxidative stress are also included.

MATERIALS AND METHODS

Chemicals. The hypolipidemic peroxisome proliferators used in this study were generous gifts from the following sources: ciprofibrate (purity, >99.99%) from Sterling Winthrop Research Institute, Rensselaer, NY; and Wy-14643 (purity, >99.9%) from Wyeth Laboratories, Inc., Radnor, PA. NAD+, coenzyme A, and palmitoyl-CoA were obtained from Sigma Chemical Co., St. Louis, MO. [1-14C]Palmitoyl-CoA (specific activity, 59 mCi/mmol) was obtained from Radiochemical Center Corp., Amersham, Arlington Heights, IL. All other chemicals were obtained from sources listed elsewhere (21, 22).

Animals and Treatment. Male F-344 rats weighing 100–150 g were obtained from Charles River Breeding Laboratories, Wilmington, MA. They were housed in individual cages on a 12-h light, 12-h dark photoperiod in the containment facility of the center for Experimental Animal Care of the Northwestern University Medical School, and had free access...
to water and food. Peroxisome proliferators were administered in powdered rat chow at concentrations estimated. The diets were mixed thoroughly in a mechanical mixer, once weekly, and stored in a refrigerator. The daily consumption of diet by each rat was estimated at ~10–14 g. Control rats were fed rat chow without the drug. At the end of the treatment period the animals were killed under light ether anesthesia and the livers were removed and processed as described below.

Subcellular Fractionation of Liver. The livers were homogenized (10% homogenate, w/v) in ice-cold 0.25 M sucrose containing 0.003 M EDTA (pH 7.4) using a Potter-Elvehjem homogenizer. The homogenates were fractionated into heavy particle (mitochondria, peroxisomes, and lysosomes), postnuclear (mitochondria, peroxisomes, lysosomes, and microsomes), and, and microsomal pellets according to the method outlined by Kurup et al. (23) as described before (24). Nuclei were obtained by the method of Bresnick et al. (25) as modified by Patton et al. (26). The subcellular fractions so obtained were suspended in 0.25 M sucrose containing 0.003 M EDTA and were used for lipid extraction either immediately or after storage at ~70°C.

Extraction of Lipids and Detection of Conjugated Dienes. Lipids from various subcellular fractions were extracted in 20 ml of chloroform:methanol (2:1) according to the method of Bligh and Dyer (27). Lipids in the chloroform phase were recovered by evaporation the chloroform under oxygen-free N2 (ultrapure carrier, Grade 99.99% N2). From various subcellular fractions were extracted in 20 ml of chloroform:methanol (2:1) according to the method of Bligh and Dyer (27). Lipids in the chloroform phase were recovered by evaporation of the chloroform under oxygen-free N2 (ultrapure carrier, Grade 99.99% N2). From these 300 ml of 220 nm against a cyclohexane blank in a Beckman Model 25 spectrophotometer. Total lipid content was measured by the method of Chiang et al. (28). Lipids extracted from liver postnuclear membranes of rats treated with carbon tetrachloride served as a positive control for detection of diene conjugates (29).

Measurement of H2O2. The basal levels of H2O2 in liver homogenates were measured by the ferrithiocyanate method as described by Thurman et al. (30). Liver homogenates (5%, w/v) were prepared in 0.25 M sucrose solution containing 1 mM sodium azide. Proteins were precipitated by cold 50% trichloroacetic acid. To 1 ml of supernatant, 0.2 ml of 10 mM ferrous ammonium sulfate and 0.1 ml of 2.5 mM potassium thiocyanate were added, and the absorption of red ferrithiocyanate complex formed by incubating aliquots of liver homogenates in 50 mM Tris HCl, pH 8.3, containing NADH (0.2 mM); CoA (0.1 mM); flavin adenine dinucleotide (0.01 mM); diithiothreitol (0.01 mM); Triton X-100 (0.1%); bovine serum albumin (0.0075%); MgCl2 (5 mM); ATP (2.5 mM); sodium azide (1 mM), and substrate palmitate (15 μM) in a total reaction mixture of 1.0 ml. The reaction mixture was incubated at 37°C for 40 min. The reaction was terminated by adding 50% cold trichloroacetic acid to get a final concentration of 5%. The hydrogen peroxide was measured by the ferrithiocyanate method as described above.

Enzyme Activities. Enzymatic activities in liver homogenates were measured as follows: peroxisomal palmitoyl-CoA oxidizing activity by the method described by Neut and Osmundsen (31) using antimycin A (10 μg/ml) to block β-oxidation due to mitochondria; catalase was measured by the method of Luck (32) as described elsewhere (33). GSH content was determined by the method of Cohn and Lyle (34) as modified by Hissin and Hilf (35); GST was assayed according to the procedure of Habig et al. (36) with 1,2-dichloro-4-nitrobenzene and 1-chloro-2,4-dinitrobenzene as substrates; GSH-P was measured using GSH and H2O2 as substrates according to the procedure described by Hafeman et al. (37), and GSH-R was assayed according to the method outlined by Racke (38). Protein concentration was determined by the method of Lowry et al. (39), using bovine serum albumin as a standard.

Electron Microscopy. Postnuclear and heavy particle pellets obtained from livers of rats exposed to ciprofibrate for 6 months or longer were fixed in 2% OsO4, dehydrated, and embedded in Epon. Semithin sections were examined by a light microscope. Ultrathin sections cut from selected regions showing a uniform layer of particles were stained with lead citrate and examined in an electron microscope.

RESULTS

Lipid Peroxidation. Lipid peroxidation in membranes obtained from whole-liver homogenates and in membranes of subcellular fractions was compared in rats fed control and peroxisome proliferator-containing diets. Since the major sites of lipid peroxidation damage within the cell are in the biomembranes of subcellular organelles, it appeared necessary to compare the extent of lipid peroxidation damage in microsomal, nuclear, large-particle, and postnuclear membranes. Lipid peroxidation-induced double-bond rearrangements in the hydrocarbon chain of polyunsaturated fatty acids result in the appearance of conjugated dienes which exhibit characteristic UV absorption pattern at 233 nm (40). Lipids extracted from isolated membranes of whole liver homogenates of rats fed ciprofibrate (0.025%, w/w) and Wy-14643 (0.1%, w/w) for 6 months yielded a clear peak of conjugated dienes at 233 nm, when compared to rats fed a regular diet (Fig. 1). In addition, in the membrane lipids from ciprofibrate- and Wy-16463-treated rats, a second peak was noted in the 276 nm range (Fig. 1). Analysis of UV spectra of extracted lipids from postnuclear pellets (Fig. 2) and heavy-particle pellets (Fig. 3) of rats fed ciprofibrate for 6 months also revealed two distinct peaks, one at 233 and the other at 276 nm. Such increases were not evident in lipids derived from microsomal pellets. As can be seen from Fig. 2, the 276 nm peak was not prominent either in control or in carbon tetrachloride-treated rat liver postnuclear pellets. The 233 and 276 nm peaks were only slightly prominent.
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Fig. 2. UV absorption patterns of lipids extracted from membranes from post-nuclear pellets, which contain all membranes except nuclear membranes of rats fed (a) control diet; and (c) ciprofibrate (0.025%, w/w) in chow for 6 months. The spectrum (b) represents the profile of lipids derived from the liver of a rat treated with CCl₄ (0.25 ml/100 g body wt) by gavage and killed 16 h later. Note the increased absorption of ~233 nm in ciprofibrate- and CCl₄-treated rats (ΔABS₂₃₃), indicating increased lipid peroxidation. The increase in absorption at ~276 nm is very striking in ciprofibrate-treated animals, when compared to control and CCl₄-treated rats.

Fig. 3. UV absorption patterns of lipids derived from membranes of heavy particle pellets (composed predominantly of mitochondria, peroxisomes, and lysosomes) obtained from rats fed (a) control chow, and (o) ciprofibrate (0.025%, w/w) in rat chow for 6 months. For other details about the difference spectrum of absorption at 233 and 276 nm, see the legend for Fig. 1.

in postnuclear-pellet lipids of rats fed ciprofibrate for a short duration of 4 weeks (Fig. 4). In comparison, the 276 nm peak was very large in the lipids extracted from postnuclear pellets (Fig. 5) prepared from nontumorous portions of liver from rats bearing hepatocellular carcinomas induced by chronic administration of ciprofibrate or Wy-14643 (Fig. 6). This 276 nm peak, however, was only slightly intense in the lipids of highly purified nuclear pellets (Fig. 7) and microsomes (not illustrated) of peroxisome proliferator-treated rats. As illustrated in Fig. 5, the postnuclear pellet contains numerous lipofuscin pigment profiles, abundant peroxisomes, and several mitochondria. The highly prominent 276 nm peak in the livers of rats chronically treated with peroxisome proliferators most likely reflects the formation of conjugated trienes and ketone dienes which have an absorbance in the range of 275–283 nm (40-42). It is also pertinent to point out that proteolipids, rich in tryptophan and tyrosine, can also give intense absorbance at ~280 nm (41, 42).

H₂O₂ Generation. The basal and substrate (palmitate)-generated H₂O₂ levels were measured in the liver homogenates of rats treated with ciprofibrate (Table 1). Basal H₂O₂ levels were higher in peroxisome proliferator-treated rat livers when compared to untreated controls. Addition of palmitate, a substrate for peroxisomal fatty acid β oxidation system, resulted in >6-fold increase in the H₂O₂ level (Table 1).

GSH, GST, and Related Enzyme Activities. Administration of the peroxisome proliferator, ciprofibrate, for 5 weeks resulted in a marked decrease in the activity of hepatic GST (Table 2). In contrast, the GSH levels in the livers of ciprofibrate-treated rats were slightly elevated (Table 2). The time course of changes in hepatic catalase, β oxidation enzyme system, and GSH and GST levels in rats fed ciprofibrate for up to 22 days are shown in Fig. 8. Dose-response studies indicated that ciprofibrate administered at 0.001% dietary level for 4 weeks reduced hepatic GST level by more than 50%. At 0.01 and 0.02% dietary levels, ciprofibrate caused ~90% reduction in GST activity (Fig. 9). The activity of selenium dependent GSH-P, which utilizes H₂O₂ as well as hydroperoxide as substrates (43, 44) was also reduced in the livers of ciprofibrate-treated rats (Table 2). Ciprofibrate also inhibited the activity of hepatic GSH-R (Table 2).

DISCUSSION

Several studies have now established that the currently identified carcinogenic peroxisome proliferators are not mutagenic and that they do not covalently interact with or damage cellular nuclear pellets (Fig. 7) and microsomes (not illustrated) of peroxisome proliferator-treated rats. As illustrated in Fig. 5, the postnuclear pellet contains numerous lipofuscin pigment profiles, abundant peroxisomes, and several mitochondria. The highly prominent 276 nm peak in the livers of rats chronically treated with peroxisome proliferators most likely reflects the formation of conjugated trienes and ketone dienes which have an absorbance in the range of 275–283 nm (40-42). It is also pertinent to point out that proteolipids, rich in tryptophan and tyrosine, can also give intense absorbance at ~280 nm (41, 42).

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Fig. 5. Low-power survey electron micrograph of the postnuclear pellet obtained from the nontumorous portions of liver of a rat fed ciprofibrate. The uninvolved liver was separated from the liver tumors, homogenized, and the postnuclear pellets were obtained by differential centrifugation. Note the presence of numerous peroxisomes (P), most of which show partial loss of matrix proteins. Mitochondria (M), and several profiles of lipofuscin (L) are also seen. X 6800.

DNA (9–13). Therefore, it appears that the mechanism of carcinogenesis by peroxisome proliferators may be mediated by a process other than the direct chemical-DNA interactions. A strong positive correlation between hepatic peroxisome proliferation and the development of hepatocellular carcinomas prompted us to postulate that the peroxisome proliferator-induced liver carcinogenesis is linked to the oxidative stress emanating from sustained increase in peroxisome population and the attendant enhanced synthesis of H₂O₂ generating peroxisomal β oxidation enzymes (4, 6, 8). Although the precise mechanisms by which intracellular oxidative stress influences initiation and promotion of carcinogenesis remains unknown, it is generally held that H₂O₂ and other reactive oxygen species (OH; O₂⁻, and •O₂) can cause DNA damage either directly or by initiating lipid peroxidation (15, 21, 45, 46). Alternatively, it is conceivable that the oxidative stress may lead to the activation of oncogene(s) or may give rise to resistant hepatocyte population lacking peroxisome proliferator receptors. The postulated link between peroxisome proliferation-mediated oxidative stress and carcinogenicity implies that tumors should develop only in organs (tissues) displaying profound peroxisome proliferation in animals exposed to peroxisome proliferators.

The results of the present study demonstrate increased lipid peroxidation in the liver of rats fed for 6 months or longer a diet containing ciprofibrate or Wy-14643, two potent carcinogenic peroxisome proliferators (3, 20). In contrast, the results of the same analyses on rats fed these agents for a relatively short period of 4 weeks are somewhat equivocal in that the difference spectra of less than 0.1 A units in this semiquantitative assay of conjugated dienes is not convincing. This suggests that sustained injury to liver cells by persistent peroxisome proliferation may be necessary to induce peroxidative damage to membrane lipids. Lipid peroxidation is known to cause double bond rearrangements in the hydrocarbon chain of fatty acids (40–42, 44–45). This results in the appearance of conjugated dienes which absorb intensely at 233 nm, whereas the intact polyenoic fatty acids with unconjugated double bonds absorb strongly only below about 225 nm in the UV spectrum (40). Increased levels
lipids observed in the present study suggests that peroxisome proliferator-induced lipid peroxidation occurs predominantly in the membranes of large subcellular organelles (peroxisomes, mitochondria, or lysosomes). The lipids from these membranes also showed an additional more intense absorbance pattern at 276 nm, which is generally attributed to ketone dienes and or conjugated trienes (40). Similar dramatic increase of absorbance in this region has not been reported in the literature dealing with lipid peroxidation abnormalities (40, 47, 48). The absence of substantial increase in this 276 nm peak in microsomal and nuclear membrane lipids suggests that ketone diene formation may also be restricted to the membranes of the large subcellular organelles.

Excessive accumulation of autofluorescent lipofuscin is regularly encountered in livers of rats exposed chronically to peroxisome proliferators (14, 17). This pigment presumably reflects membrane damage due to biologically damaging free radicals (14, 18, 19). Peroxisomal oxidases, such as fatty acyl-CoA oxidase, urate oxidase, d-amino acid oxidase, and α-hydroxy acid oxidase reduce O2 and generate H2O2 (49, 50). The transcriptional activation of fatty acyl-CoA oxidase gene (51) and increased basal and substrate-generated H2O2 levels in the livers of peroxisome proliferator-treated rats are thought to be the basis for the observed increase in lipid peroxidation in the present study. Under normal conditions catalase can efficiently detoxify low rates of H2O2 generated within the peroxisomes (52, 53). However, the high permeability of the peroxisomal membrane to H2O2 (14, 52) results in the diffusion of some H2O2, even at low rates of production. This diffusion may be accelerated in livers with peroxisome proliferation because such peroxisomes contain low levels of catalase and increased concentration of H2O2 producing β oxidation enzymes per unit peroxisome volume (4, 6). H2O2 per se or hydroxyl radicals resulting from the iron-catalyzed decomposition of H2O2 can lead to uncontrolled lipid peroxidation reaction in livers of rats with peroxisome proliferation. It is also of particular interest to note that GSH-P and GSH-R, which are involved in H2O2 metabolism, (52) are also significantly reduced in the livers of rats treated with ciprofibrate. This may result in a further compromise of endogenous defense against excess H2O2 produced by proliferated peroxisomes.

In summary, the present study clearly demonstrates increased lipid peroxidation in the membranes of large subcellular particles of liver in rats chronically exposed to peroxisome proliferators.

of conjugated dienes considered as prima facie evidence of lipid peroxidation have been seen in the lipids of postnuclear and heavy-particle membrane pellets of liver of rats treated with ciprofibrate or Wy-14643 for 6 months or longer. Absence of increase in the absorbance at 233 nm in microsomal membrane

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**Table 1** Changes in liver weight, catalase activity, and H2O2 generation in rats fed ciprofibrate

<table>
<thead>
<tr>
<th>Group</th>
<th>Liver wt (g/100 g body wt)</th>
<th>Catalase (units/mg protein)</th>
<th>Basal levels (μmol/g liver)</th>
<th>Generated levels (palmitate as substrate; μmol/min/g liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.5 ± 0.4</td>
<td>45 ± 3</td>
<td>0.522 ± 0.018</td>
<td>0.326 ± 0.157</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>9.3 ± 0.4**</td>
<td>54 ± 9*</td>
<td>0.052 ± 0.025</td>
<td>1.922 ± 0.345*</td>
</tr>
</tbody>
</table>

* Significantly different from control (P < 0.001) using Student’s t test.

**Fig. 6.** UV absorption patterns of lipids extracted from membranes of postnuclear pellets of rats fed (a) control diet; (b) Wy-14643 (0.1%, w/w); and (c) ciprofibrate (0.025%, w/w) for 14 months. The liver of ciprofibrate- and Wy-14643-treated rats contained multiple liver tumors. The postnuclear pellets were obtained from portions of liver devoid of grossly visible tumors. Note the dramatic increase in the absorbance at 276 nm, which is generally attributed to ketone dienes and or conjugated trienes (40). Similar dramatic increase of absorbance at 233 and 276 nm, which is generally attributed to ketone dienes and or conjugated trienes (40).
This observation is consistent with increased H$_2$O$_2$ generation and excessive accumulation of lipofuscin in hepatocytes. Increased levels of conjugated dienes ($\Delta_{233\text{nm}}$) and ketone dienes ($\Delta_{276\text{nm}}$) are indicative of lipid peroxidation damage to membranes. The intense absorbance at 276 nm, particularly in livers of rats treated for long duration may be due to the contents of lipofuscin, since such structures become abundant in the liver cells of rats chronically exposed to peroxisome proliferators, and are seen in the postnuclear and heavy particle pellets used in this study for lipid extraction (Fig. 5). The results of the present study further substantiate the existence of peroxisome proliferation-associated intrahepatic oxidative stress. It is of interest to note that increased lipid peroxidation has been observed in the livers of rats treated with methyprene hydrochloride (47) and choline-deficient diet (48), both of which induce liver tumors by mechanisms unrelated to direct DMA damage. Additional studies are essential to understand the interrelationships among oxidative stress, lipid peroxidation, oncogene activation, and neoplastic transformation in livers.

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