Alterations by peroxisome proliferators of acyl composition of hepatic phosphatidylcholine in rats, mice and guinea-pigs

Role of stearoyl-CoA desaturase

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1. Rats, mice and guinea-pigs were administered *p*-chlorophenoxyisobutyric acid (clofibric acid) or 2,2'-(decamethylenedithio)diethanol (tiadenol). 2. The treatments of rats and mice with either clofibric acid or tiadenol increased markedly the activities of stearoyl-CoA desaturase, palmitoyl-CoA chain elongation, 1-acylglycerophosphate (1-acyl-GP) acyltransferase and 1-acylglycerophosphocholine (1-acyl-GPC) acyltransferase, but not 2-acylglycerophosphocholine (2-acyl-GPC) acyltransferase in liver microsomes. 3. The treatment of guinea-pigs with clofibric acid did not cause any change in the activities of these enzymes. The treatment of guinea-pigs with tiadenol caused a slight, but significant, increase in the activities of 1-acyl-GP acyltransferase and 1-acyl-GPC acyltransferase. 4. The treatment of rats and mice with either clofibric acid or tiadenol increased markedly the proportion of 18:1 and decreased greatly the proportion of 18:0 in liver microsomal phosphatidylcholine. However, there is a considerable difference in the effects of the two peroxisome proliferators on the composition of polyunsaturated fatty acids in phosphatidylcholine between rats and mice. The treatment of guinea-pigs with either of the two peroxisome proliferators caused no change in acyl composition of phosphatidylcholine. 5. The possible role of stearoyl-CoA desaturation in the regulation of acyl composition of phosphatidylcholine was discussed.

INTRODUCTION

Alterations in nutritional state and hormonal state of rats have been reported to influence the activity of hepatic stearoyl-CoA desaturation and the changes in desaturation activity have been considered to cause the alterations in acyl composition of glycerolipids (Brenner, 1974; Holloway, 1983). Recently, it has been found that the treatment of rats with clofibric acid increases markedly the activities of both stearoyl-CoA desaturation and palmitoyl-CoA chain elongation in hepatic microsomes (Kawashima & Kozuka, 1982, 1985). The administration of clofibric acid to rats has been found to cause an increase in the activities of 1-acyl-GPC acyltransferase and 1-acyl-GP acyltransferase as well as marked changes in acyl composition of glycerolipids, especially phosphatidylcholine (Kawashima *et al.*, 1984b). Although these findings may be of interest in a biochemical or pharmacological sense, cellular reactions to many drugs have been known to depend on species. In fact, a marked species difference has been reported for clofibric acid with regard to peroxisome proliferation and inductions of peroxisomal β -oxidation enzymes and cytosolic acyl-CoA hydrolase in livers (Svoboda *et al.*, 1967; Kawashima *et al.*, 1983a). Moreover, numerous compounds, having diverse structures from clofibric acid, have been found to cause peroxisomes to proliferate (Lalwani *et al.*, 1983). Therefore, to advance our knowledge about the effects of peroxisome proliferators on the regulation of acyl composition of glycerolipids, it is necessary to know whether clofibric acid causes similar biochemical changes in other species of animals than rats and whether

peroxisome proliferators other than clofibric acid cause the same biochemical alterations as does clofibric acid. In this context, we have studied (1) the effects of two peroxisome proliferators, clofibric acid and tiadenol, on the activities of the enzymes which participate in fatty acid modification and fatty acid incorporation into phosphatidylcholine, and (2) the relationship between stearoyl-CoA desaturase and acyl composition of phosphatidylcholine, in hepatic microsomes of rats, mice and guinea-pigs.

EXPERIMENTAL

Materials

[2-¹⁴C]Malonyl-CoA (50.0 Ci/mol) and [1-¹⁴C]oleoyl-CoA (56.7 Ci/mol) were obtained from New England Nuclear Co. (Boston, MA, U.S.A.). Palmitoyl-CoA, stearoyl-CoA, oleoyl-CoA, malonyl-CoA, clofibric acid, cytochrome *c*, snake venom (from *Crotalus adamanteus*) and bovine serum albumin were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.); tiadenol was from Aldrich Chemical Co. (Milwaukee, WI, U.S.A.); 1-acyl-GP was from Serdary Research Laboratories (London, Ontario, Canada); NADH and NADPH were from Oriental Yeast Co. (Tokyo, Japan). 1-Acyl-GPC and 2-acyl-GPC were prepared as described previously (Kawashima *et al.*, 1984a).

Animals and preparation of microsomes

Male Wistar rats (weighing 170–250 g), male ddy mice (weighing 30–40 g) and male Hartley guinea-pigs

Table 1. Effects of clofibric acid and tiadenol on microsomal stearoyl-CoA desaturation system in livers

The animals were fed a commercial diet or a diet containing 0.5% (w/w) clofibric acid or tiadenol for 7 days. The enzymes were assayed as described in the text. The values are the means $\pm$ S.D. The numbers in parentheses represent the numbers of animals used. ^a*P* < 0.001 relative to control.

Species and treatment		NADH–ferricyanide reductase (μ mol/min per mg of protein)	NADH–cytochrome <i>c</i> reductase (μ mol/min per mg of protein)	Cytochrome <i>b</i> ₅ (μ mol/mg of protein)	Desaturase <i>k</i> ⁺ (min ⁻¹)
Rat					
Control	(8)	3.59 $\pm$ 0.30	0.82 $\pm$ 0.18	0.41 $\pm$ 0.05	0.97 $\pm$ 0.33
Clofibric acid	(8)	4.11 $\pm$ 0.42	0.62 $\pm$ 0.18	0.45 $\pm$ 0.04	5.95 $\pm$ 2.45 ^a
Tiadenol	(10)	3.43 $\pm$ 0.40	0.42 $\pm$ 0.08 ^a	0.46 $\pm$ 0.31	6.15 $\pm$ 1.85 ^a
Mouse					
Control	(6)	4.62 $\pm$ 0.37	0.73 $\pm$ 0.06	0.38 $\pm$ 0.06	2.22 $\pm$ 0.73
Clofibric acid	(6)	5.68 $\pm$ 1.12	0.78 $\pm$ 0.16	0.53 $\pm$ 0.08	11.77 $\pm$ 2.36 ^a
Tiadenol	(5)	4.58 $\pm$ 0.68	0.76 $\pm$ 0.10	0.53 $\pm$ 0.07	10.17 $\pm$ 3.21 ^a
Guinea-pig					
Control	(8)	1.66 $\pm$ 0.19	0.53 $\pm$ 0.08	0.77 $\pm$ 0.07	0.27 $\pm$ 0.10
Clofibric acid	(9)	1.66 $\pm$ 0.22	0.65 $\pm$ 0.25	0.77 $\pm$ 0.05	0.22 $\pm$ 0.11
Tiadenol	(6)	1.72 $\pm$ 0.05	0.44 $\pm$ 0.07	0.75 $\pm$ 0.04	0.23 $\pm$ 0.09

(weighing 300–400 g) were used. Animals were fed *ad libitum* a commercial diet or a diet containing 0.5% (w/w) clofibric acid or tiadenol. Animals were killed and their livers were isolated. Microsomes were prepared by differential centrifugation as described previously (Kawashima & Kozuka, 1982). Protein concentrations in microsomal suspensions were determined by the method of Lowry *et al.* (1951), with bovine serum albumin as standard.

Enzyme assays

Stearoyl-CoA desaturase was assayed by the method of Oshino *et al.* (1971) as described previously (Kawashima & Kozuka, 1982) and the activity was presented as the rate constant for stearoyl-CoA stimulated-reoxidation of NADH-reduced cytochrome *b*₅. NADH–cytochrome *c* reductase and NADH–ferricyanide reductase were assayed by the method of Oshino *et al.* (1966) and Rogers & Strittmatter (1973), respectively. The content of cytochrome *b*₅ in hepatic microsomes was estimated according to the method of Omura & Sato (1964). Palmitoyl-CoA chain elongation in hepatic microsomes of rats and guinea-pigs was assayed as described previously (Kawashima & Kozuka, 1985). Palmitoyl-CoA chain elongation in mouse liver microsomes was assayed with some modifications as follows; the reaction mixture contained 15 nmol of palmitoyl-CoA, 120 nmol of [2-¹⁴C]malonyl-CoA, 1 μ mol of NADH, 1 μ mol of NADPH, 0.5 μ mol of KCN, 50 μ mol of Tris/HCl buffer (pH 7.4) and 250 μ g of microsomal protein in a final volume of 0.5 ml. The mixture was incubated at 37 °C for 3 min under N₂. 1-Acyl-GPC acyltransferase and 1-acyl-GP acyltransferase were assayed with oleoyl-CoA as a substrate by the method of Lands & Hart (1965), as described previously (Kawashima *et al.*, 1984a,b). 2-Acyl-GPC acyltransferase was assayed with palmitoyl-CoA as a substrate by the method of Lands & Hart (1965), as described previously (Kawashima *et al.*, 1984a).

Lipid analyses

Lipids were extracted from microsomal suspension by the method of Bligh & Dyer (1959). Phosphatidylcholine was isolated by t.l.c. as described previously (Kawashima *et al.*, 1984b). To analyse acyl composition in C-1 and C-2 positions of phosphatidylcholine, phosphatidylcholine was hydrolysed by phospholipase A₂ from snake venom, and 1-acyl-GPC and free fatty acid formed by the hydrolysis were separated by t.l.c. as described previously (Kawashima *et al.*, 1984b). The analyses of fatty acid were performed by g.l.c. as described previously (Kawashima & Kozuka, 1982).

Statistical analyses were performed using Student's *t* test from two means.

RESULTS

Effects of peroxisome proliferators on stearoyl-CoA desaturation and palmitoyl-CoA chain elongation

Animals were administered clofibric acid or tiadenol to study the effects of these drugs on the activities of the enzymes which make up liver microsomal stearoyl-CoA desaturation system in rats, mice and guinea-pigs (Table 1). It has been demonstrated that the desaturation of stearoyl-CoA is catalysed by system composed of three proteins, NADH–cytochrome *b*₅ reductase, cytochrome *b*₅ and desaturase (Holloway, 1983). The administration of tiadenol to rats caused a 6-fold increase in stearoyl-CoA desaturase activity, as was observed with clofibric acid. Similarly, the administration of these two peroxisome proliferators to mice increased the activity of stearoyl-CoA desaturase approx. 5-fold. The administration of either of the two peroxisome proliferators did not affect the activities of NADH–ferricyanide reductase and NADH–cytochrome *c* reductase, or the content of cytochrome *b*₅ in hepatic microsomes of rats and mice, except that the treatment of rats with tiadenol reduced substantially the activity of NADH–cytochrome *c* reductase. No component of stearoyl-CoA desaturation system was influenced

Table 2. Effects of clofibric acid and tiadenol on palmitoyl-CoA chain elongation in hepatic microsomes

The animals were fed a commercial diet or a diet containing 0.5% (w/w) clofibric acid or tiadenol for 7 days. The activity of palmitoyl-CoA chain elongation was assayed as described in the text. The values are the mean $\pm$ S.D. Numbers in the parentheses represent the numbers of animals used. ^a*P* < 0.001, ^b*P* < 0.01, ^c*P* < 0.05 relative to control.

Species	Chain elongation (nmol/min per mg of protein)		
	Control	Clofibric acid	Tiadenol
Rat	0.24 $\pm$ 0.03 (6)	0.91 $\pm$ 0.11 ^a (4)	1.30 $\pm$ 0.29 ^a (3)
Mouse	0.71 $\pm$ 0.23 (3)	1.32 $\pm$ 0.22 ^c (3)	1.56 $\pm$ 0.14 ^b (3)
Guinea-pig	0.23 $\pm$ 0.06 (3)	0.37 $\pm$ 0.15 (5)	0.24 $\pm$ 0.06 (6)

by the treatment of guinea-pigs with either clofibric acid or tiadenol. It should be noted that the activity of stearoyl-CoA desaturase in control mouse liver is twice that in control rat liver and that the activity of stearoyl-CoA desaturase in guinea-pig liver was one-third that in control rat liver. Moreover, the rates of *p*-cresol-stimulated reoxidation of NADH-reduced cytochrome *b*₅ of hepatic microsomes of control rats and guinea-pigs are 2.78 and 0.35 min⁻¹, respectively, and the rate of *p*-cresol-stimulated reoxidation of NADH-reduced cytochrome *b*₅ was increased by the treatment of rats with clofibric acid. The effects of the two peroxisome proliferators on microsomal palmitoyl-CoA chain elongation were studied with rats, mice and guinea-pigs (Table 2). The administration of tiadenol to rats caused a marked increase in the activity of palmitoyl-CoA chain elongation, as was observed with clofibric acid. Although these two peroxisome proliferators increased the activity of microsomal palmitoyl-CoA chain elongation in mouse liver, the specific activity of chain elongation in control mouse liver is two or three times higher compared with that in control rat liver. No increase in the activity was brought about in guinea-pig livers.

Effects of peroxisome proliferators on microsomal acyltransferases

Animals were treated with clofibric acid or tiadenol to examine the effects of these drugs on the activities of 1-acyl-GP acyltransferase, 1-acyl-GPC acyltransferase and 2-acyl-GPC acyltransferase in hepatic microsomes of rats, mice and guinea-pigs (Table 3). The treatment of mice with these peroxisome proliferators caused a considerable increase in the activity of 1-acyl-GP acyltransferase, as was observed with rats. The activity of 1-acyl-GPC acyltransferase in hepatic microsomes was increased more markedly than that of 1-acyl-GP acyltransferase by the treatment of rats and mice with either the two drugs. Although the administration of clofibric acid to guinea-pigs did not cause any increase in either 1-acyl-GP acyltransferase or 1-acyl-GPC acyltransferase, the treatment of guinea-pigs with tiadenol increased slightly, but significantly, the activities of both 1-acyl-GP acyltransferase and 1-acyl-GPC acyltransferase. These results regarding guinea-pigs were confirmed by using [1-¹⁴C]oleoyl-CoA as a substrate (results not shown). 2-Acyl-GPC acyltransferase was not affected by the treatment of any animals used with either clofibric acid or tiadenol.

Effects of peroxisome proliferators on acyl composition of phosphatidylcholine in hepatic microsomes

To examine the influence of the alterations in the activities of the enzymes which participate in both modification of fatty acids and incorporation of fatty acids into phosphatidylcholine, microsomal phosphatidylcholine was isolated and its acyl composition was analysed (Table 4). There is no great difference in acyl composition of phosphatidylcholine between mice and rats, although the proportion of 20:4 is lower by 40% in mice and the proportion of 22:6 in mice is approx. 1.7 times that of rats. On the other hand, there is a marked difference in the acyl composition of liver microsomal phosphatidylcholine between guinea-pigs and rats. Namely, phosphatidylcholine of guinea-pig liver contained 20:3, 20:4 and 22:6 in extremely small proportions;

Table 3. Effects of clofibric acid and tiadenol on acyltransferases in hepatic microsomes

The animals were fed a commercial diet or a diet containing 0.5% (w/w) clofibric acid or tiadenol for 7 days. The activity of these enzymes was assayed as described in the text. The values are the mean $\pm$ S.D. Numbers in the parentheses represent the numbers of animals used. ^a*P* < 0.001, ^b*P* < 0.01, ^c*P* < 0.05 relative to control.

	Activity (nmol/min per mg of protein)		
	Control	Clofibric acid	Tiadenol
1-Acyl-GP acyltransferase			
Rat	77.0 $\pm$ 12.1 (6)	12.3 $\pm$ 27.7 ^b (6)	169.1 $\pm$ 10.7 ^a (3)
Mouse	205.4 $\pm$ 31.9 (6)	310.3 $\pm$ 4.3 ^a (4)	339.6 $\pm$ 65.7 ^a (6)
Guinea-pig	166.3 $\pm$ 16.5 (6)	173.3 $\pm$ 26.7 (6)	218.4 $\pm$ 24.8 ^c (6)
1-Acyl-GPC acyltransferase			
Rat	33.5 $\pm$ 1.9 (6)	124.4 $\pm$ 34.4 ^a (6)	183.3 $\pm$ 13.8 ^a (3)
Mouse	41.1 $\pm$ 4.2 (6)	135.2 $\pm$ 24.5 ^a (4)	250.0 $\pm$ 33.6 ^a (6)
Guinea-pig	42.5 $\pm$ 10.4 (6)	44.9 $\pm$ 7.7 (6)	79.8 $\pm$ 10.2 ^b (6)
2-Acyl-GPC acyltransferase			
Rat	36.3 $\pm$ 1.1 (3)	30.6 $\pm$ 4.2 (3)	24.3 $\pm$ 3.9 (3)
Mouse	35.7 $\pm$ 6.2 (6)	31.8 $\pm$ 2.8 (4)	29.0 $\pm$ 3.1 (6)
Guinea-pig	47.6 $\pm$ 2.4 (4)	43.6 $\pm$ 4.3 (3)	49.4 $\pm$ 4.1 (6)

Table 4. Effects of clofibric acid and tiadenol on acyl composition of phosphatidylcholine in hepatic microsomes

The animals were fed a commercial diet or a diet containing 0.5% (w/w) clofibric acid or tiadenol for 7 days. The values are the mean $\pm$ S.D. Numbers in parentheses are the numbers of animals used. ^a*P* < 0.001, ^b*P* < 0.01, ^c*P* < 0.05 relative to control.

		Composition (mol %)								
Conditions		16:0	16:1	18:0	18:1	18:2	20:3 (<i>n</i> −9)	20:3 (<i>n</i> −6)	20:4	22:6
Rats										
Control	(3)	23.3±1.7	1.4±0.3	24.1±1.8	8.1±1.0	16.4±0.5	0	2.0±0.5	20.8±0.7	4.0±0.8
Clofibric acid	(4)	31.5±1.2 ^a	2.2±1.0 ^b	14.2±1.0 ^a	17.8±2.0 ^a	10.3±2.6 ^b	1.4±0.3 ^a	3.5±1.3	17.4±5.4	1.8±1.3 ^c
Tiadenol	(3)	28.6±1.6 ^b	1.8±0.3	15.3±1.5 ^b	17.4±0.3 ^a	9.8±0.7 ^a	1.7±0.3 ^a	3.5±0.5 ^b	19.1±1.4	2.8±0.4
Mouse										
Control	(3)	32.6±0.4	1.8±0.4	13.8±0.9	9.8±0.9	19.9±0.9	0	3.1±0.8	11.9±1.4	7.0±0.5
Clofibric acid	(3)	39.0±2.8 ^c	3.0±0.1 ^b	6.0±0.8 ^a	19.9±2.0 ^b	15.8±1.0 ^c	0	6.1±1.1 ^c	5.9±0.8 ^b	4.3±0.8 ^b
Tiadenol	(3)	35.9±0.8 ^b	3.9±0.4 ^b	3.7±0.6 ^a	19.1±0.4 ^a	18.5±2.3	0	7.2±0.6 ^b	7.1±0.6 ^b	4.5±0.5 ^b
Guinea-pig										
Control	(3)	14.5±0.7	0.7±0.1	30.4±1.3	9.4±0.4	38.1±0.6	0	1.3±0.1	2.8±0.3	1.1±0.2
Clofibric acid	(3)	14.9±0.5	0.7±0.0	30.1±1.0	9.5±1.0	37.9±1.1	0	1.3±0.1	2.6±0.2	0.9±0.1
Tiadenol	(3)	13.2±0.5	0.6±0.1	29.9±0.9	9.7±0.4	38.9±0.8	0	1.4±0.1	2.9±0.2	0.9±0.1

the proportion of 18:2 in phosphatidylcholine was 38% and the proportion of 18:2 in the C-2 position of phosphatidylcholine was 71%. These values were twice those of phosphatidylcholine in rat liver. In accordance with our previous findings (Kawashima *et al.*, 1984b), marked changes were observed in the proportions of 18:0, 18:1, 18:2 and 20:3 (*n*−9) in phosphatidylcholine from the rats which had been treated with clofibric acid. Almost the same changes in acyl composition of phosphatidylcholine was brought about by the treatment of rats with tiadenol. Although a marked increase in the proportion of 18:1 and a marked decrease in the proportion of 18:0 were brought about in phosphatidylcholine from the mice which had been administered either of the two peroxisome proliferators, no appreciable changes in the proportion of 18:2 and 20:3 (*n*−9) was observed. On the other hand, a great increase in the proportion of 20:3 (*n*−6) and marked decrease in the proportions of 20:4 and 22:6 were evident in phosphatidylcholine when mice were treated with either of the two peroxisome proliferators.

To confirm the changes in acyl composition in C-1 and C-2 positions separately, phosphatidylcholine was hydrolysed by phospholipase A₂ and fatty acids were analysed with g.l.c. The administration of either of the peroxisome proliferators to rats caused no considerable change in the acyl composition in C-1 position of phosphatidylcholine. On the other hand, treatment of mice with clofibric acid caused a 54% decrease in the proportion of 18:0 and a 1.6-fold increase in the proportion of 18:1. A 63.3% decrease in the proportion of 18:0 and a 2-fold increase in the proportion of 18:1 were brought about by the treatment of mice with tiadenol. Treatment of rats with either clofibric acid or tiadenol caused an approx. 3-fold increase in the proportion of 18:1 and an approx. 50% decrease in the proportion of 18:2 in the C-2 position of phosphatidylcholine. On the other hand, a 1.6–2.1-fold increase in the proportion of 18:1 occurred in the C-2 position of phosphatidylcholine from mice when administered either of the two peroxisome proliferators. No appreciable change in the proportion of 18:2 was observed. For the acyl moiety at the C-2 position of phosphatidylcholine in

liver microsomes of mice, a 2.1–2.5-fold increase in the proportion of 20:3 (*n*−6) and an approx. 44% decrease in the proportion of 20:4 were evident after the administration of either clofibric acid or tiadenol; these changes were not obvious in the acyl composition of phosphatidylcholine of rats. It should be noted that no increase in the proportion of 20:3 (*n*−9) in the C-2 position of phosphatidylcholine in mouse liver was observed, although a marked increase in that in rat liver was observed. No significant change in acyl composition of phosphatidylcholine was observed in hepatic microsomes of guinea-pigs.

DISCUSSION

Many attempts have been made to understand the regulation of fatty acid modification (desaturation and chain elongation) and fatty acid incorporation into glycerolipids in rat liver (Allmann *et al.*, 1965; Ellingson *et al.*, 1970; Faas & Carter, 1980; Kawashima *et al.*, 1984b). Little, however, is known about the regulation in livers of other species than rats. The present study showed that, with regard to stearoyl-CoA desaturase, palmitoyl-CoA chain elongation and 1-acyl-GP acyltransferase in hepatic microsomes, mice had two to three times higher activity than rats. Although the activity of palmitoyl-CoA chain elongation in microsomes of guinea-pig liver was comparable with that of rat liver and the activity of 1-acyl-GP acyltransferase in guinea-pig liver was twice that in rat liver, the activity of stearoyl-CoA desaturase in guinea-pig liver is about one-third that in rat liver and about one-eighth that in mouse liver. Oshino & Sato (1971) have suggested that the rate of *p*-cresol-stimulated reoxidation of NADH-reduced cytochrome *b*₅ is mediated by stearoyl-CoA desaturase. We confirmed that the rate of *p*-cresol-stimulated reoxidation of NADH-reduced cytochrome *b*₅ in liver microsomes of guinea-pigs is one-eighth that of rats, suggesting that the low activity of stearoyl-CoA desaturase in guinea-pig liver is not due to its low activity of desaturase for acyl-CoA alone, but due to the low amount or activity of desaturase protein. A great species difference in the response of animals to clofibric acid has been reported in the induction of

peroxisomal β -oxidation enzymes (Kawashima *et al.*, 1983a). In the present study, we showed that the administration of clofibric acid or tiadenol increased markedly the activity of stearoyl-CoA desaturase in hepatic microsomes of both rats and mice without appreciable influence on the other components which make up microsomal desaturation system. Moreover, treatment of rats and mice with these two peroxisome proliferators caused an increase in the activity of palmitoyl-CoA chain elongation, 1-acyl-GP acyltransferase and 1-acyl-GPC acyltransferase. These results suggest that peroxisome proliferators, regardless of the marked difference in their structures, induce concomitantly these enzymes in livers of rats and mice. No change was brought about in the activity of these enzymes by the treatment of guinea-pigs with clofibric acid. However, it should be noted that the administration of tiadenol to guinea-pigs increased slightly the activities of both 1-acyl-GP acyltransferase and 1-acyl-GPC acyltransferase, although tiadenol did not change the activity of either stearoyl-CoA desaturase or palmitoyl-CoA chain elongation in guinea-pig livers. Moreover, we found that the administration of tiadenol did not cause any increase in the activity of peroxisomal β -oxidation in guinea-pig livers (results not shown). These results suggest that guinea-pigs do not always lack all the ability to induce enzymes in response to peroxisome proliferators. The mechanism by which peroxisome proliferators induce many enzymes in liver of rodents has not been clarified. There may be two conceivable mechanisms, namely a direct inducing effect of peroxisome proliferators on liver and indirect inducing effect of peroxisome proliferators through endocrine changes. However, we found previously that changes in various hormonal states of rats failed to prevent clofibric acid from inducing stearoyl-CoA desaturase, palmitoyl-CoA chain elongation, peroxisomal β -oxidation and cytosolic long chain acyl-CoA hydrolase (Kawashima & Kozuka 1982, 1985; Kawashima *et al.*, 1983b).

The present study showed that the administration of peroxisome proliferators caused a marked increase in the proportion of 18:1 in phosphatidylcholine in livers of rats and mice, but not of guinea-pigs. These changes in the proportion of 18:1 in microsomal phosphatidylcholine correlated well with the changes in the activity of stearoyl-CoA desaturase. In the previous study (Kawashima *et al.*, 1984b), we found that stearoyl-CoA desaturase participates actively in the regulation of acyl composition of phosphatidylcholine in rat liver. The present results indicate probably that stearoyl-CoA desaturase plays an important role in the regulation of acyl composition of hepatic phosphatidylcholine of not only rats, but also other species. Octadecenoic acid is known to be formed from 16:0 by the concerted action of chain elongation and desaturation (Nakagawa *et al.*, 1976), suggesting that the activity of palmitoyl-CoA chain elongation increases to supply 18:0 to stearoyl-CoA desaturase when the desaturase actively makes 18:1. In good agreement with this possibility, our results showed that the activity of palmitoyl-CoA chain elongation was changed in association with stearoyl-CoA desaturase activity. In livers of rats and mice, octadecenoic acid

formed by the action of desaturation may be incorporated actively into the C-2 position of phosphatidylcholine by the action of 1-acyl-GP acyltransferase and 1-acyl-GPC acyltransferase which had been induced by peroxisome proliferators. It has not been clarified yet why the proportion of 18:1 in the C-1 position of phosphatidylcholine in mouse liver was increased markedly by the treatment with peroxisome proliferators, despite the fact that 2-acyl-GPC acyltransferase was not induced by the peroxisome proliferators. It is plausible, however, that 18:1 is incorporated into the C-1 position of phosphatidylcholine of mouse liver instead of 18:0, because the amount of 18:0 has been reduced by the treatment of mice with peroxisome proliferators. It should be noted here that there is a great difference in the regulation of polyunsaturated fatty acid metabolism in livers among rats, mice and guinea-pig.

Our present study showed that peroxisome proliferators, regardless of their chemical structures, may be an useful tool to study glycerolipid metabolism in livers of animals.

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