HEPATOCAARCINOGENESIS BY PEROXISOME PROLIFERATORS

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ABSTRACT — It is well known that various kinds of hypolipidemic drugs induce marked changes in the livers of rats and mice. The initial hepatic responses in rodents are marked hepatomegaly, proliferation of peroxisomes in association with changes in peroxisome structure and enzyme composition. Furthermore, since many of hypolipidemic peroxisome proliferators induce hepatocellular carcinomas in both rats and mice, the relationship between peroxisome proliferation and hepatocarcinogenicity of these drugs has become extremely important. However, it has not yet been established whether there are any direct relationships among pharmacological action, peroxisome proliferation and carcinogenicity of these drugs.

In order to clarify this task, we have studied the involvement of HGF in hepatocarcinogenesis caused by peroxisome proliferators. After male F-344 rats were orally given Wy-14,643, hepatocarcinomas and (pre) neoplastic nodules were observed in the livers. At that time, the content of HGF and the expression of HGF mRNA were significantly decreased in the liver tumors.

These findings may indicate that decreases in hepatic HGF levels are specific events induced by peroxisome proliferators but not by genotoxic carcinogenesis, and that those changes play an important role in the promotion of neoplastic or preneoplastic cell growth induced by peroxisome proliferators. Decrease in HGF induced by peroxisome proliferators such as Wy-14,643 would inhibit the growth of normal hepatocytes and then lend an advantageous circumstance for the selective growth of neoplastic or preneoplastic cells, resulting in the development of growth of tumors.

KEY WORDS: Hepatocarcinogenesis, Peroxisome proliferator (PP), Nongenotoxic carcinogenesis, Wy-14,643, Hepatocyte growth factor (HGF), Peroxisome proliferator-activated receptor (PPAR)

INTRODUCTION

Peroxisome proliferators (PPs) are known as nongenotoxic hepatocarcinogens, which include hypolipidemic drugs, industrial plasticizers, herbicides and endogenous substances such as fatty acids and dehydroepiandrosterone. The initial hepatic responses in rodents are marked hepatomegaly and proliferation of peroxisomes in association with the induction of enzymes. However, the safety of these compounds in humans has not been evaluated, since the detailed mechanism of carcinogenesis has not been clarified yet.

In order to clarify this, we have studied the involvement of HGF in hepatocarcinogenesis caused by peroxisome proliferators. Up to 78 weeks after male F-344 rats were orally given Wy-14,643, the hepatocarcinomas and (pre) neoplastic nodules in the livers were observed. At this time, the levels of HGF and the expression of HGF mRNA were significantly lowered in the liver tumors. In the present review, the author will discuss the characteristics of peroxisome proliferation and hepatocarcinogenesis by peroxisome proliferators.

THE CHARACTERISTICS OF PEROXISOME PROLIFERATION

Chemical structures and the mode of action of peroxisome proliferators

There are many kinds of chemical compounds by which the enzymes as described above are induced, especially in the livers of rodents as shown in Fig. 1. Those include medical drugs such as hypolipidemic...
drugs (clofibrate, bezafibrate and other fibrates) (Watanabe et al., 1987), anti-inflammatory drugs (fenbufen, aminopyrin, acetylsalicylic acid and others) (Ishii and Suga, 1979; Watanabe and Suga, 1985), anticonvulsant (valproic acid) (Horie and Suga, 1985), inhibitor of thromboxane synthetase (OKY-1581) (Watanabe et al., 1986), industrial solvents (perfluorinated octane sulfonic acid and heptamethylnonane) (Ikeda et al., 1987, 1988), phenoxyacetic acid herbicides (2,4-D and 2,4,5-T) (Kozuka et al., 1991) and many other chemical compounds in addition to natural and endogenous components such as fatty acids and dehydroepiandrosterone (DHEA). On the basis of results obtained from structure-inducibility relationships, we concluded that an unmetabolizable lipophilic anion is the ultimate structure to induce peroxisome proliferation.

The initial hepatic responses to peroxisome proliferators in rodents are: (1) hepatomegaly, (2) proliferation of the smooth endoplasmic reticulum and (3) marked proliferation of peroxisomes in association with induction of several enzymes which are related to lipid metabolism (Table 1). Since many of hypolipidemic peroxisome proliferators induce hepatocarcinomas after long-term administration of drugs in both mice and rats, the relationships between peroxisome proliferation and hepatocarcinogenicity of these drugs have become extremely important. Though it is not

![Chemical structures of peroxisome proliferators.](image)

Table 1. The characteristics of the mode of action of peroxisome proliferators (PPs).

<table>
<thead>
<tr>
<th>Morphological changes</th>
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<tbody>
<tr>
<td>Hepatomegaly</td>
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<tr>
<td>Hepatocarcinogenesis</td>
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<table>
<thead>
<tr>
<th>Biochemical changes</th>
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<tbody>
<tr>
<td>Decrease in serum lipids: triglyceride, cholesterol</td>
</tr>
<tr>
<td>Enzyme induction</td>
</tr>
<tr>
<td>Peroxisomes: acyl-CoA oxidase, bifunctional enzyme, carnitine acetyltransferase</td>
</tr>
<tr>
<td>Mitochondria: acyl-CoA dehydrogenase, carnitine palmitoyltransferase</td>
</tr>
<tr>
<td>Microsomes: CYP 4A</td>
</tr>
<tr>
<td>Cytosol: acyl-CoA hydrolase, malic enzyme</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors affecting enzyme induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species differences: rat, mouse &gt; hamster, guinea pig &gt; rabbit, dog, monkey</td>
</tr>
<tr>
<td>Sex differences: male &gt; female</td>
</tr>
<tr>
<td>Organ differences: liver &gt; kidney, heart, small intestine &gt; other organs</td>
</tr>
</tbody>
</table>
established as yet whether there are direct relationships among pharmacological action, peroxisome proliferation and carcinogenicity, it is well known that the mode of actions of peroxisome proliferators is apparently different from that of inducers for microsomal enzymes such as cytochrome P-450s which are induced by many compounds such as phenobarbital and methyl[a]cholanthrene. Peroxisome proliferators do not induce most of the microsomal enzymes, but induce other enzymes, most of which are related to lipid metabolism in the liver cell.

**Proliferation of peroxisomes and enzyme induction in the rat liver treated with peroxisome proliferators**

Photo 1 shows the electron micrographs of livers from rats treated with peroxisome proliferators for 78 weeks. (A) control, (B) clofibrate, (C) bezafibrate, (D) DEHP.

**Photo 1.** Electron micrographs of the liver from male rats fed with peroxisome proliferators for 78 weeks. (A) control, (B) clofibrate, (C) bezafibrate, (D) DEHP.
weeks (Tamura et al., 1990a). These data show a marked increase in number of peroxisomes and peroxisome proliferation in the liver of rats treated with clofibrate (B), bezafibrate (C) and di(2-ethylhexyl) phthalate (DEHP)(D), which are called “peroxisome proliferators”.

Fig. 2 shows the enzymes induced by clofibrate (CPIB) and dehydroepiandrosterone (DHEA) in the rat livers (Yamada et al., 1991; Suga et al., 1996). These drugs induced many enzymes located in most of the intracellular compartments, and the enzymes thus induced were related to lipid metabolism. It is interesting that dehydroepiandrosterone has a similar mode of action and comparable potency of enzyme induction to clofibrate, a typical peroxisome proliferator. It must be noted that peroxisomal enzymes were induced most preferentially among many enzymes related to lipid metabolism which are located in other intracellular compartments.

**Peroxisome proliferator-activated receptors (PPAR)**

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. PPARs are ligand-modulated transcription factors that are activated by structurally diverse xenobiotic chemicals called peroxisome proliferators as well as by naturally occurring and synthetic fatty acids. PPARs activate transcription of a wide spectrum of genes involved in metabolism and homeostasis of lipid metabolism, including those encoding peroxisomal β-oxidation enzymes and many other enzymes.

PPAR was cloned from the liver by Issemann and Green in 1990. PPARs belong to the nuclear hormone receptor superfamily (Fig. 3). To date, three different subtypes of PPAR (α, β or NUC1/δ and γ) coded by three separate genes have been described in amphibians, rodents and man (Table 2). Early studies showed that PPARα was activated by peroxisome proliferators, hence their name.

Sensitive rodent species such as rats and mice undergo a pleiotropic response to PPs. This is characterized in the short term by upregulation of peroxisomal fatty acid β-oxidation enzymes in the liver, peroxisome proliferation and cell proliferation in addition to hepatomegaly. In long-term experiments, preneoplastic lesions and eventually carcinomas can be observed in the liver. It is important to establish what role, if any, PPARs have in mediating these diverse responses. It is well established that enzyme upregulation following PP treatment occurs at the transcriptional level, and it is now clear that PPARα is directly involved in this process.

Analyses of the promoter of several PPAR target genes has led to the definition of the consensus PPAR-responsive element (PPRE) as a direct repeat of two AGGTCA half-sites separated by a single intervening

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**Fig. 2.** Effect of dehydroepiandrosterone (DHEA) and clofibrate (CPIB) on hepatic enzyme activities of male Wistar rats. DHEA and/or CPIB were orally administered to rats at a dose of 300 mg/kg body weight for 2 weeks. Data are expressed as relative activities to the control ± SD.
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nucleotide (DR-1) (Tugwood et al., 1992). PPARs are strictly dependent upon the retinoid X receptor (RXR) as a heterodimerization partner to bind to DNA. All the PPAR target genes identified thus far code for enzymes involved in important pathways of lipid metabolism.

PPARα is required for the pleiotropic effects induced by peroxisome proliferators in the liver, such as the stimulation of PPAR target genes, the induction or inhibition of enzymes and peroxisome proliferation itself.

**THE CHARACTERISTICS OF HEPATOCARCINOGENESIS BY PEROXISOME PROLIFERATORS**

**The characteristics and mechanism of hepatocarcinogenesis induced by peroxisome proliferators**

It is known that peroxisome proliferators are non-genotoxic carcinogens, which do not have an initiation activity in the multistep mechanism of chemical carcinogenesis (Fig. 4). Cell proliferation, an important factor in carcinogenesis, is regulated by various onco-genes, tumor suppressor genes and growth factors. In hepatocytes, cell proliferation is mainly regulated by growth factors such as hepatocyte growth factor (HGF), epidermal growth factor (EGF) and transforming growth factor-α and -β (TGF-α and -β). If changes in the balance of these factors are caused by peroxisome proliferators, this could be favorable for the promotion of growth of preneoplastic cells, resulting in the development of tumors.

In order to examine whether paroxisomal hydrogen peroxide (H₂O₂) plays an important role in peroxisome proliferator-induced hepatocarcinogenesis, we followed the change in metabolism of hepatic H₂O₂ in vivo and in vitro using male Fischer-344 rats fed clof

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**Table 2. Peroxisome proliferator-activated receptors (PPARs).**

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Ligands</th>
<th>Biological events</th>
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<tbody>
<tr>
<td>PPARα</td>
<td>Hypolipidemic agents</td>
<td>Decrease in serum lipids</td>
</tr>
<tr>
<td></td>
<td>Fibrates, Wy-14,643</td>
<td>&lt;Rodent animals&gt;</td>
</tr>
<tr>
<td></td>
<td>Platicizers</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td></td>
<td>Phthalate esters</td>
<td>Peroxisome proliferation</td>
</tr>
<tr>
<td></td>
<td>Herbicides</td>
<td>Induction of enzymes related to lipid metabolism</td>
</tr>
<tr>
<td></td>
<td>2,3-D, 2,4,5-T</td>
<td>Liver injury</td>
</tr>
<tr>
<td></td>
<td>Endogenous substances</td>
<td>Hepatocarcinogenesis</td>
</tr>
<tr>
<td></td>
<td>Fatty acids, DHEA</td>
<td></td>
</tr>
<tr>
<td>PPARβ (δ)</td>
<td>Synthetic PGs</td>
<td>Unestablished</td>
</tr>
<tr>
<td></td>
<td>Ilopost</td>
<td></td>
</tr>
<tr>
<td>PPARγ</td>
<td>Antidiabetic agents</td>
<td>Decrease in serum glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver injury</td>
</tr>
</tbody>
</table>

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Fig. 3. The regulation of gene expression by PPAR (Escher and Wahli, 2000). PPAR: peroxisome proliferator-activated receptor, RXR: retinoid X receptor AGGTCAXAGGTCA: PPAR-response element (PPRE), ▼: ligand.
brane, bezafibrate and di(2-ethylhexyl) phthalate (DEHP) for up to 78 weeks (Tamura et al., 1990a, 1990b). Although hepatic H$_2$O$_2$ levels were increased slightly by these agents, the changes did not correlate with the changes in peroxisomal fatty acyl-CoA oxidase activity which is one of H$_2$O$_2$-generating enzymes located in peroxisomes. During this period, hepatic capacities of H$_2$O$_2$-degrading enzymes, catalase and GSH peroxidase apparently exceeded the H$_2$O$_2$-generating levels obtained on the basis of peroxisomal β-oxidation activities in the livers of both control and treated rats throughout the experimental period. In isolated hepatocytes, the rate of leakage of peroxisomal H$_2$O$_2$ from peroxisomes into cytosol and the hepatocellular H$_2$O$_2$ content was measured. The rate of leakage of peroxisomal H$_2$O$_2$ into cytosol increased 2.5–4-fold when peroxisomal β-oxidation activity was induced by peroxisome proliferators, and the increases in this rate corresponded with changes in the peroxisomal β-oxidation activity. In contrast, the hepatocellular H$_2$O$_2$ contents were not affected by induced peroxisomal β-oxidation (data not shown). These data show that H$_2$O$_2$ leaked from peroxisome into cytosol would be quickly decomposed, and thus peroxisomal H$_2$O$_2$ does not appear to play an important role in hepatocarcinogenesis by such an oxidative stress mechanism after long-term treatment with peroxisome proliferators.

Other results obtained from our studies described elsewhere (Tamura et al., 1991; Hayashi et al., 1994, 1995, 1998) also supported the above conclusion.

So far many marker enzymes for preneoplastic and neoplastic lesions induced by chemical carcinogens in rat livers have been described and used for analyses of the process involved in hepatocarcinogenesis as well as for screening of carcinogens and carcinogenic modifiers (promoters and inhibitors) (Sato, 1989). Among them, the placental form of GSH S-transferase has been established as one of the most reliable markers for preneoplastic lesions induced by mutagenic hepatocarcinogens. However, this enzyme has not been described to be expressed in hepatic hyperplastic nodules and hepatomas induced by peroxisome proliferators (Reddy and Rao, 1986).

It was found that peroxisomal enzymes in hepatic foci, nodules and hepatocellular carcinomas induced by peroxisome proliferators were either completely absent or expressed very weakly as compared to levels in the surrounding normal hepatocytes (Yokoyama et al., 1992). These results suggest that immunohistochemical staining of peroxisomal enzymes is a useful approach for detection of putative preneoplastic and neoplastic lesions induced by non-genotoxic peroxisome proliferator carcinogens in rat livers.

**The involvement of hepatocyte growth factor (HGF) in hepatocarcinogenesis induced by peroxisome proliferators**

Hepatocyte growth factor (HGF) has been known to enhance the growth of normal hepatocytes, but, on the other hand, to inhibit the growth of neoplastic cells. We have studied the involvement of HGF in hepatocarcinogenesis caused by peroxisome proliferators (Motoki et al., 1997, 1999; Suga et al., 2000).

After treatment with Wy-14,643 for 78 weeks, hepatocellular carcinomas and/or adenomas were observed in all the rats. We first examined the changes

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**Fig. 4.** Multistep mechanism of hepatocarcinogenesis by peroxisome proliferators.
in the expression of hepatic HGF mRNA levels in the tumor or nontumor portions induced by the agent. In the nontumor portions in the liver of Wy-14,643-treated rats, HGF mRNA levels decreased to 79% of the control level (Fig. 5). In the liver tumors, the amount of HGF mRNA had significantly decreased to 45% of the control level. The degree of reduction in mRNA levels was more apparent in the tumor portions than in nontumor portions. The expression of TGFα and TGFβ, on the other hand, tended to decrease slightly, but not significantly.

We examined the effect of HGF on formation of preneoplastic and neoplastic cells and tumors induced by Wy-14,643 in rat liver. In order to demonstrate that HGF suppresses the proliferation of preneoplastic, neoplastic cells or tumor cells, we examined the in vivo effect of HGF on the growth of preneoplastic and neoplastic cells and tumor formation that was induced by Wy-14,643. Rats were dosed with Wy-14,643 and human recombinant HGF was injected intravenously for the last 4 weeks before sacrifice. At 39 weeks after administration of Wy-14,643, formation of ACO-negative lesions, which were detected by the immunohistochemical method using anti-ACO-antibody, were clearly seen in the liver as shown in Fig. 6. When HGF was injected into those rats, the formation of the lesions was apparently suppressed. The effect of HGF on the formation of tumors in the liver was also examined after the treatment with Wy-14,643 and HGF. When HGF was injected into those rats, tumor formation decreased to about half that of the Wy-14,643 group at low dose of HGF (Suga et al., 2000) (data not shown).

To confirm the hypothesis that the reduction of HGF caused by Wy-14,643-treatment promotes the development of hepatocarcinogenesis, we examined whether the growth of the neoplastic or preneoplastic cells induced by Wy-14,643 was inhibited by HGF in a subsequent experiment according to colony assay method. The colonies formed from liver neoplastic or preneoplastic cells induced by Wy-14,643 were tightly packed, and HGF had no effect on the form of the colonies even at a concentration of 300 ng/mL (Fig. 7). The growth of the colonies, on the other hand, was significantly suppressed by HGF at concentrations of 100 and 300 ng/mL HGF. The number of colonies decreased to 77-68% of the control level at low concentrations (5-15 ng/mL) of HGF. The suppression of colony formation was dependent on the concentration of HGF. From the results obtained here, it is apparent that HGF can inhibit the growth of tumor cells directly and can act effectively at a low concentration of HGF.

Cell proliferation is an important factor in carcinogenesis, which is regulated by a balance between proliferative and suppressive factors. If this balance is changed, carcinogenesis could be promoted. In the present study, Wy-14,643 significantly reduced the level of hepatic HGF. This decrease corrupted the hepatic HGF mRNA, and persisted throughout the long-term treatment period. Furthermore, HGF mRNA level was significantly reduced in the tumor portions of the liver. So far as the authors know, this is the first time that chemical hepatocarcinogens have been shown to reduce hepatic HGF levels. These findings
suggest that reduced hepatic HGF levels may stimulate the growth of neoplastic or preneoplastic cells induced by peroxisome proliferators.

These findings may indicate that decreases in hepatic HGF levels are common and specific events induced by peroxisome proliferators, but not by genotoxic carcinogenesis, and that those changes play an important role in the promotion of neoplastic or preneoplastic cell growth (Fig. 8). Decrease in HGF induced by peroxisome proliferators such as Wy-14,643 would inhibit the growth of normal hepatocytes and then give an advantageous circumstance for the selective growth of neoplastic or preneoplastic cells, resulting in the development of growth of tumors.

The mechanism of hepatocarcinogenesis induced by peroxisome proliferators and species differences

Target genes of PPARα are many growth factors such as c-Ha-ras, c-jun, c-fos, c-myc, TGFα, HGF, functional proteins such as fatty acid transporters, fatty acid binding proteins, apo-lipoproteins A-III and C-III and many enzymes related to lipid metabolism such as fatty acid translocase, acyl-CoA synthetase, peroxisomal β-oxidation system and malic enzymes (Escher and Wahli, 2000).

The hypothesis that PPARα plays an essential role in the pleiotropic changes in metabolism of liver...
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cells was confirmed by Gonzalez et al. (1998) using PPARα-knockout mice. In these mice, no hepatomegaly, peroxisome proliferation, cell proliferation or enzyme induction was observed after the treatment with Wy-14,643, a potent peroxisome proliferator. Peters et al. (1997) also demonstrated that the formation of hepatic tumor known to be evoked by peroxisome proliferators was not induced in PPARα-knockout mice even after long-term administration of Wy-14,643 (Table 3). Thus, it was established that PPARα plays an essential role in the regulation of lipid metabolism and non-genotoxic hepatocarcinogenesis induced by peroxisome proliferators.

It has been well known that there are species differences in hepatic responses to hypolipidemic peroxisome proliferators in vivo and in vitro (Blaauboer et al., 1990; Cohen and Grasso, 1981; Foxworthy et al., 1990). This has led to a doubt as to the relevance of the rodent carcinogenicity findings to humans. There have been a few reports concerning species differences in hepatic response to peroxisome proliferators, such as Ly-171,883 (Eacho et al., 1986), ciprofibrate (Reddy et al., 1984) and gemfibrozil (Gray and de la Iglesia, 1984), but there have been no systematic studies on species differences using many animal species on one compound.

We examined in detail the species differences in the effects of bezafibrate as a hypolipidemic peroxisome proliferator on several animals such as rats, mice, guinea pigs, rabbits, dogs and monkeys, on which biochemical data have already been reported (Table 4) (Watanabe et al., 1984, 1989). Dogs and monkeys were given bezafibrate orally at 30 mg/kg body weight daily for 2 weeks and at 125 mg/kg body weight daily for 13 weeks, respectively, and other species at 100 mg/kg daily for 2 weeks. In male rats, marked changes were observed in the activities of especially fatty acyl-CoA oxidizing system (FAOS, 12.9-fold) and carnitine acetyltransferase (CAT, 35.8-fold). In mice, the increase in the enzyme activities of FAOS and CAT were 3.7-fold and 7.9-fold, respectively. In guinea pigs and hamsters also, a significant induction of FAOS and CAT was observed, but the induction ratios were less than in the case of rats and mice. Although rabbits and dogs showed slight increases in CAT activity, no significant response to the drug was seen in monkeys. Therefore, these results may show that there are apparent species differences in the effects of bezafibrate on hepatic peroxisomes, and may indicate that bezafibrate induced hepatic peroxisome proliferation especially in

![Fig. 8. Hypothetical mechanism of peroxisome proliferator-induced hepatocarcinogenesis.](image)

Table 3. Effect of PPARα-knockout on response to peroxisome proliferator, Wy-14,643.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>No. of Animals</th>
<th>No. of Tumor mice</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carcinoma</td>
</tr>
<tr>
<td>PPARα (+/+)</td>
<td>Control</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>(wild)</td>
<td>Wy-14,643</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>PPARα (−/−)</td>
<td>Control</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>(knockout)</td>
<td>Wy-14,643</td>
<td>6</td>
<td>0</td>
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rodents, rats and mice. These facts in addition to many other experimental data including morphological studies (Momose et al., 1993) may suggest that rodents have an exclusively high susceptibility to hepatocarcinogenicity by peroxisome proliferators, but other animal species, especially mammals, are not sensitive.

CONCLUSIONS

In the present review on hepatocarcinogenesis by peroxisome proliferators, the author discussed the chemical structures and the mode of action of peroxisome proliferators, proliferation of peroxisomes and enzyme induction by peroxisome proliferators and a specific receptor (PPARα) which is known as an essential factor for peroxisome proliferation. Next, the author also described the characteristics of hepatocarcinogenesis induced by peroxisome proliferators, including the mechanism of hepatocarcinogenesis such as the involvement of HGF and species differences in the response to peroxisome proliferators.

In recent years, PPARs have been focused on as one of the promising targets for the development of new pharmaceutical drugs by many pharmaceutical industries. For development of this field, further progress of basic and applied research is now expected.

ACKNOWLEDGMENT

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