Review

The role of peroxisome proliferator-activated receptor in the treatment of non-alcoholic fatty liver disease

XIN SUN[1]
YAN ZHANG[2,3*]
MEILIN XIE[3*]

[1] *Department of Pharmacy*
Wuxi No. 2 People's Hospital
The Affiliated Hospital of Nanjing
Medical University, Wuxi, Jiangsu
214002, China

[2] *Department of Gynecology and*
Obstetrics, Wuxi Maternal and Child
Health Hospital, The Affiliated Hospital
of Nanjing Medical University, Wuxi
Jiangsu, 214002, China

[3] *Department of Pharmacology*
College of Pharmaceutical Sciences
Soochow University, Suzhou, Jiangsu
215123, China

Non-alcoholic fatty liver disease (NAFLD) has been defined as a spectrum of histological abnormalities and is characterized by significant and excessive accumulation of triglycerides in the hepatocytes in patients without alcohol consumption or other diseases. Current studies are targeting new molecular mechanisms that underlie NAFLD and associated metabolic disorders. Many therapeutic targets have been found and used in clinical studies. Peroxisome proliferator-activated receptors (PPARs) are among the potential targets and have been demonstrated to exert a pivotal role in modulation of NAFLD. Many drugs developed so far are targeted at PPARs. Thus, the aim of this paper is to summarize the roles of PPARs in the treatment of NAFLD.

Keywords: non-alcoholic fatty liver disease, peroxisome proliferator-activated receptors, agonists, insulin resistance, inflammation

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of liver disease in humans. Its main characteristic is excessive accumulation of triglycerides in the hepatocytes without consumption of alcohol or other drugs (1). NAFLD includes a wide variety of conditions, from simple steatosis to non-alcoholic steatohepatitis (NASH) and can eventually lead to cirrhosis, liver failure, and/or hepatocellular carcinoma (2, 3). According to the literature, about 10–29 % of NASH patients might progress to liver cirrhosis within 10 years and about 4–27 % of liver cirrhosis patients might develop hepatocellular carcinoma (HCC) (Fig. 1) (4, 5). The diagnosis of NAFLD remains unclear because many patients are asymptomatic until late stages of the disease. In clinics, liver biopsy is recognized as the

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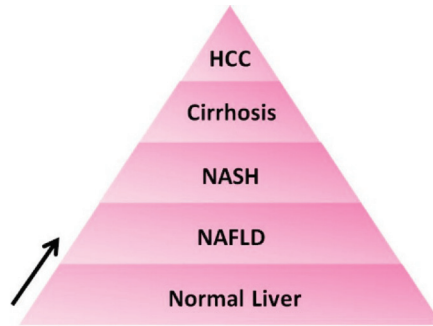* Correspondence; yaoxue2030@163.com, xiemeilin@suda.edu.cn

Fig. 1. Natural history of nonalcoholic fatty liver disease. NAFLD – nonalcoholic fatty liver disease, NASH – non-alcoholic steatohepatitis, HCC – hepatocellular carcinoma.

major and also the most accurate tool to diagnose NAFLD. However, liver biopsy often carries a serious risk of complications (6). Hence, more research is needed to discover new drugs.

PATHOGENESIS OF NAFLD

The natural history and pathogenesis of NAFLD are still poorly understood. The key factors in the progress of NAFLD are still not clearly defined. In recent years, many literature sources have reported the pathogenesis of NAFLD, mainly including *two-hit* (Fig. 2, red frame) (7), and *multiple parallel hit* (Fig. 2, blue frame) (8, 9) hypotheses.

The first hit is the development of hepatic steatosis while the second hit includes cellular stresses such as oxidative stress, apoptosis stress and gut-derived lipopolysaccharide stress (LPS). In these two hypotheses, insulin resistance is regarded as the most important
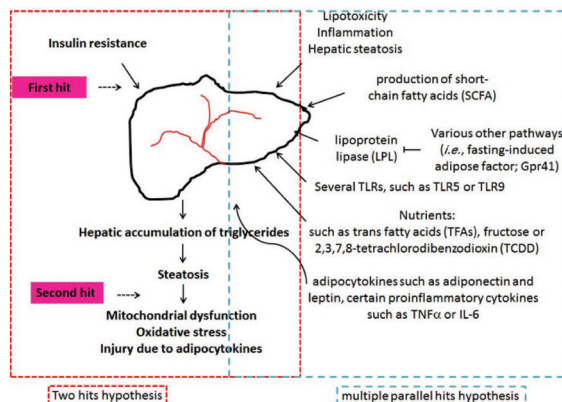

Fig. 2. The two hits hypothesis and the multiple parallel hits hypothesis.

factor. In the two-hits hypothesis, hepatic steatosis develops after a first hit and progresses to NAFLD by a subsequent hit including cellular stresses (such as oxidative stress, gut--derived lipopolysaccharide stress, etc.). Although fatty liver is usually non-progressive, it can progress in patients harboring the risk allele of many genes that play an important role in the development of NASH, such as patatin-like phospholipase 3 (PNPLA3) (10). Thus, the development of NAFLD is regarded a multiple hit process.

In the parallel hits hypothesis, there are multiple parallel hits, such as fasting-induced adipose factor, adipocytokines, certain proinflammatory cytokines, *etc*. (see details in Fig. 2). Hepatic steatosis occurs due to the imbalance between triglyceride accumulation and elimination in the liver. Insulin resistance (IR) is closely and frequently related to the development of NAFLD because it can alter nutrient metabolism (11). Hepatic inflammation is caused by the increase of many inflammatory cytokines, such as interleukin 6 (IL6), tumor necrosis factor TNFα, *etc*. It can be also caused by a decrease of many anti-inflammatory cytokines, such as adiponectin (12).

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR

There are many important regulators among the main discovered mechanisms. Peroxisome proliferator-activated receptor (PPAR) is one of these factors. PPARs are associated with nutrient metabolism and cellular proliferation. There are four subtypes in the PPAR family, namely, PPARα, PPARβ, PPARγ and PPARδ. PPARα (NR1C1) is highly expressed in the tissues with high fatty acid oxidation such as liver (13). PPARβ/δ (NR1C2) is highly expressed in liver, cardiac, kidney and skeletal muscles, brain, adipose tissues, colon and vasculature (14). PPARγ (NR1C3) is highly expressed in adipose tissues (15). PPARγ plays an important role in the transcription process, glucose metabolisms and other events (16).

PPARs are nuclear receptors that are parts of the steroid, retinoid, and thyroid hormone receptor superfamily of ligand-activated transcription factors (16, 17). PPAR isoforms have four functional domains, termed A/B domain, DNA-binding domain (DBD), hinge domain (HD) and ligand-binding domain (LBD). Among these domains, the A/B domain contains the activation function (AF)-1 and is ligand-independent. AF-1 plays an important role in the progress of kinase phosphorylation. DBD domain contains two highly conserved zinc finger motifs and promotes the binding of receptors to a DNA sequence in the promoter region of target genes. It is known as the peroxisome proliferator response element (PPRE). The HD domain acts as a docking site used for cofactors. The LBD is responsible for ligand specificity and increases target gene transactivation (18) (see details in Fig. 3).

Due to the important role of PPARs in the treatment of NAFLD, researchers have paid great attention to drug discovery based on PPARs, especially PPAR agonists. As shown below, there are two main mechanisms of PPAR agonists.

PPAR agonists and insulin resistance in NAFLD

As insulin resistance is the major mechanism in the progression of NAFLD, many researchers and physicians are paying increasing attention to the potential therapeutic effects of insulin sensitizers. Insulin binds with its specific receptor and activates the in-
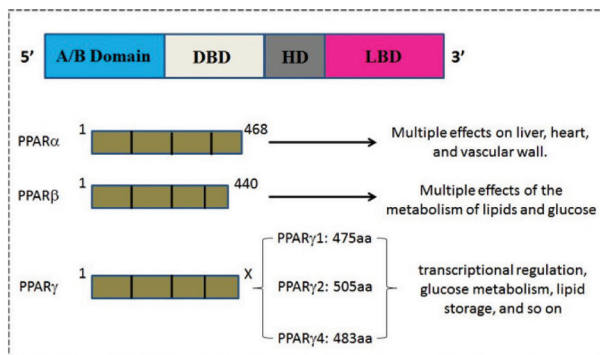
Fig. 3. Schematic structure of peroxisome proliferator-activated receptor (PPARs).

tracellular signaling pathway. Insulin receptor then phosphorylates itself and insulin receptor family members such as IRS1 and IRS2. IRS1 and IRS2 regulate insulin homeostasis by mediating insulin signaling and inducing insulin sensitivity in the liver (19). Insulin resistance (IR) has been demonstrated in many research reports to lead to inflammation and inflammatory response in the progress of NAFLD (20).

Thiazolidinediones (TZDs) contain two heteroatoms, nitrogen and sulfur. They can activate the nuclear transcription factor named peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ can upregulate specific genes that decrease insulin resistance, inflammation, proliferation, *etc.*, and increase insulin sensitivity. Among them, the representatives of TZDs are troglitazone, rosiglitazone and pioglitazone. In addition to being reported as cancer treatment drugs, they have also been approved for the treatment of diabetes mellitus type II (21). Clinically, troglitazone is the first TZD that is widely used in the treatment for diabetes. The first clinical study revealed that seven of ten NASH patients who received troglitazone (400 mg per day for 6 months) normalized alanine aminotransferase (ALT) at the end of the treatment (22).

Ample data have suggested the potential therapeutic effects of TZDs on NAFLD and liver steatosis, presumably due to their action of decreasing insulin resistance, beneficial effects of glucose, *etc.* (23, 24). As far as rosiglitazone and pioglitazone are concerned, many researchers have demonstrated that they show severe side effects, such as cardiovascular morbidity of rosiglitazone and facilitation of bladder cancer of pioglitazone (24, 25). According to the PROspective pop]itazone (PROactive) clinical trial database, pioglitazone reduced cardiovascular complications compared to the control patients (26).

PPAR agonists and inflammation in NAFLD

As confirmed by many researchers, along with insulin resistance, inflammation has also been demonstrated to be a key pathway in the development of hepatic diseases such as NAFLD. Hepatic pro-inflammatory cytokines are also regarded as important markers of the increasing severity of liver disease, such as transcription factor NF-κB, *etc.* (23). NF-κB plays a crucial role in the process of inflammation chain, including cellular proliferation, chemokines, *etc.* (27). Many literature sources have revealed that insulin resistance could

enhance inflammation in NAFLD/NASH. Also, inflammation could disrupt insulin signaling, for example, serine phosphorylation of insulin receptor substrate by inflammatory signal transducers such as NF-κB inhibitor (27). Interleukin 6 (IL-6) is an interleukin that acts both as a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene, a target gene of NF-κB, and its expression was more than 100-fold higher in adipose tissue compared to its expression in liver tissue (28). On the other hand, another important inflammatory factor in NAFLD patients is the tumor necrosis factor (TNF-α). Researchers have demonstrated that the severity of NAFLD might be associated with the increased level of TNF-α in NAFLD patients (29, 30). TNFα could bind to trimerized TNF receptor type I and activate NF-κB *via* the inhibitor of the nuclear factor kappa-B kinase (IKK) pathway. TNF-α could induce c-Jun N-terminal kinase (JNK) activation, which is associated with the induction of hepatocyte death (31, 32). On the other hand, Lv and his colleagues (33) found that TNF-α could directly induce lipid accumulation through the AMP-activated protein kinase (AMPK) pathway, which is known as an important factor in the process of energy homeostasis. In addition, lipopolysaccharides (LPS) could induce activation of mitogen-activated protein kinases (MAPKs) and liver injury (28).

All studies have clearly revealed that inflammatory factors are important regulators involved in NAFLD/NASH. Hence, suppressing inflammation might be an attractive therapeutic approach for improving inflammatory liver disease and the associated insulin resistance. Recent studies have shown that PPARs could produce anti-inflammatory effects. PPARs could accelerate lipid catabolism, which might reduce liver steatosis. Many experiments have revealed that PPAR agonists could attenuate the symptoms of NAFLD/NASH (33). Mechanisms of the beneficial metabolic effects of PPAR activation may be the following: (*i*) insulin resistance associated with pro-inflammatory microenvironment, (*ii*) effects of the tumor necrosis factor-alpha (TNFα) in adipocytes, (*iii*) activation of cytokine-mediated signaling (*e.g., via* NF-κB) enhancing insulin action, (*iv*) reducing circulating levels of proteins that serve as markers of inflammation, (*v*) inducing the expression of adiponectin implicated as having anti-inflammatory activity (see details in Fig. 4).
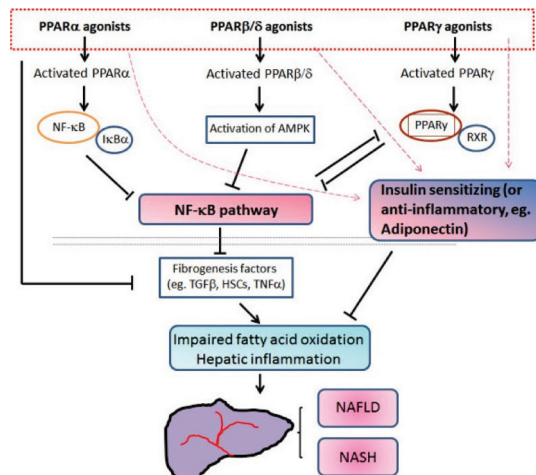

Fig. 4. PPARs regulate the inflammation in the NAFLD.

Based on the above mentioned important role of PPARs in NAFLD, researchers and clinicians have discovered many PPAR agonists besides the above mentioned ones. Thus, according to the different subtypes of PPARs, we have summarized all the PPAR agonists that have been reported (see Table I).

PPARα

N-3 polyunsaturated fatty acids (n-3 PUFAs) are PPAR α-ligands. PUFA can ameliorate insulin sensitivity through binding PPARα. Patients treated with n-3 PUFA showed reduction of triglyceride and alanine transaminase (ALT) serum levels (27, 34–37). Oleoylethanolamine (OEA) has been demonstrated as an endogenous high-affinity PPARα. Researchers have revealed that 5 mg kg^{-1} per day OEA (*i.p.*) could ameliorate the development of NAFLD compared to control groups after treatment for 6 weeks through detecting the levels of plasma triglycerides (TG), serum total cholesterol (TC), alanine aminotransferase (ALT) and aspartate transaminase (AST) as well as liver inflammatory cytokines (38).

Another classic agonist of PPARα is fenofibrate. Fenofibrate could activate lipolytic enzymes, reduce the synthesis of apolipoprotein and remove plasma triglycerides. Fenofibrate is widely used for the treatment of NAFLD. Fenofibrate has been demonstrated to protect against inflammatory injury in NAFLD. The probable mechanism is associated with the endoplasmic reticulum (ER) stress pathway (39). In another report, researchers divided mice into two groups (fructose-fed and fructose-fenofibrate treated groups). The results revealed that after the treatment with 100 mg kg^{-1} (*p.o.*), fatty acids (FAs) and very low-density lipoprotein (VLDL), secretions were decreased more than in the control group (40). In a clinical trial, Piyush Patel *et al.* (41) found that the TG level was reduced in patients who were administered fenofibrate (116 patients were administered choline fenofibrate and 116 patients were administered micronized fenofibrate). Another research group also found that adding pentoxifylline to fenofibrate had a beneficial effect on a direct marker linked to matrix deposition (hyaluronic acid), a cytokine/growth factor linked to liver fibrosis (transforming growth factor beta 1), the inflammatory pathway, insulin resistance and liver stiffness, in non-alcoholic fatty liver patients treated with fenofibrate (300 mg daily) plus pentoxifylline (1200 mg per day) for 24 weeks (42).

In some publications, however, researchers reported that fenofibrate exerted side effects, such as nephrotoxicity (leading to renal vasoconstriction) (43) and hepatotoxicity (enhanced the fatty liver mass) (44).

PPARβ/δ

GW4064 is a PPARβ agonist that has highly selective farnesoid X receptor (FXR) affinity. FXR is a member of the nuclear receptor superfamily of ligand activated receptors and is mainly expressed in the liver, intestines, kidneys and adrenal glands. FXR has been found to be a key regulator of lipid metabolism and to improve peripheral insulin sensitivity. Xin *et al.* (45) found that GW4064 could increase the expression of adiponectin, leptin, adiponectin receptor 2 (AdipoR2) and leptin receptors (OB-Rb).

Chehaibi *et al.* (46) found that GW0742 is another PPARβ/δ agonist and could upregulate serum HDL-C and HDL phospholipids in NAFLD mice. The effects of GW0742 could be completely abolished in PPAR-β/δ-deficient mice (45). GW501516 could prevent endo-

Table I. PPAR agonists

Agonist	Drug	Mechanism	Adverse effect(s)	Reference(s)
		Single PPAR agonists		
	Oleoylethanol-amine (OEA)		Not reported	53
PPARα	Z-551	Enhances insulin sensitivity, reduces inflammatory injury		39
	n-3 PUFAs			36
	Fenofibrate		Enhances fatty liver weight nephrotoxicity	54
PPARβ	GW4064 GW0742	Farnesoid X receptor agonist, modulate macrophage cholesterol efflux	Not reported	44, 55
PPARγ	Thiazolidinedio-nes (TZDs) Rosiglitazone Pioglitazone	Enhance insulin sensitivity and anti-inflammatory	Fluid retention, hemodilution edema, heart failure	45–47
		Dual PPAR agonists		
PPARα/δ	GFT505	Inhibition of hepatic gluconeogenesis and anti-inflammatory	Not reported	23, 56
PPARα/γ	Tesaglitazar LT175	Improve insulin mediated control of glucose and FFA fluxes	Not reported	52, 57
PPARβ/δ	GW501516	Anti-inflammatory	Not reported	58
PPARγ/δ	Alkoxy-3-indolylacetic acid	Inhibition of the level of hepatic triglycerides	Not reported	59

plasmic-reticulum (ER) stress associated with inflammation and insulin resistance. The published data showed that the mechanisms might be related to activation of the AMP activated protein kinase (AMPK) pathway and inhibition of the extracellular-signal-regulated kinase (ERK)1/2 pathway (46).

PPARγ

PPARγ plays an indispensable role in adipogenesis, which is frequently impaired under pathological conditions such as nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Many drugs were developed based on the activation of PPARγ, such as telmisartan (47), rivoglitazone (48), *etc*.

Rivoglitazone is a novel agonist of PPARγ that has been demonstrated in rats and monkeys. It has significant stereoselectivity and is very efficacious. Rivoglitazone could enhance adiponectin levels in plasma and decrease adipose mRNA levels in mice. Rivoglitazone could also ameliorate insulin resistance (49). In clinics, rivoglitazone has been used to treat type 2 diabetes, but rivoglitazone has many adverse effects such as peripheral edema and weight gain (50).

Dual PPAR agonist

GFT505 is a PPAR agonist with preferential activity on PPARα with half-maximal effective concentration of about 10–20 nmol L^{-1} and additional activity on PPARδ with half-maximal effective concentration of about 100–150 nmol L^{-1}. Researchers have found that GFT505 could improve glycemic control in db/db mice, which is related to its liver-centric effects on hepatic insulin sensitivity and gluconeogenesis (49). Also, in phase II of clinical studies, researchers found that GFT505 treatment decreased alanine aminotransferase, gamma-glutamyl transpeptidase and alkaline phosphatase (51). Shiomi *et al.* (36) found that Z-551, having both PPARα and PPARγ antagonistic activities, could increase the level of molecules involved in fatty acid combustion and thus significantly reduce fasting plasma levels of glucose, triglycerides, free fatty acids, insulin and leptin. This indicated that Z-551 might be clinically useful for preventing or treating metabolic disorders such as type 2 diabetes, dyslipidemia and NAFLD (52).

Zhao *et al.* (53) found that osthole might be a dual agonist of PPAR α/γ and could decrease hepatic lipid accumulation. After treating the rats with 5–20 mg kg^{-1} osthole for 4 weeks, the results showed that the serum alanine aminotransferase, aspartate aminotransferase, total cholesterol, triglyceride, and free fatty acid levels, tumor necrosis factor-α (TNF-α) and liver index were lower in the osthole treated group than in the control group. This demonstrated that osthole was effective in treating rat steatohepatitis (36).

CURRENT PROBLEMS

Although many researchers have revealed the molecular mechanism in the development of NAFLD such as inflammation, the basic and clinical trials are still needed to face additional challenges. Thus far, PPARs have been considered as effective molecular targets that could be used to treat liver disease. However, they also need more clinical evidence before their clinical application. For example, insulin sensitizer might induce some side effects, such as heart attack, heart failure, weight gain, *etc.* (60). The adverse effects of each PPAR agonist are summarized in Table I. In order to overcome these adverse effects, many researchers found that dual PPAR agonists could improve liver injury without side effects induced by single PPAR agonists (13, 61–63). Clinical trials also demonstrated that PPAR agonist therapies may lead to side effects such as paradoxical dissociation of steatosis, inflammation, *etc.* Thus, much work still remains to be done to fully cure the NAFLD in order to separate the beneficial effects of PPAR agonists from unwanted side effects.

CONCLUSIONS

In this review, we focused on and outlined the PPAR agonists in the treatment of NAFLD. Elucidating detailed mechanisms of these drugs could provide new targets for

future therapeutic strategies in NAFLD. The effect and safety of NAFLD management should be taken into account as well.

In summary, further large-scale clinical trials and practice are needed to verify drug treatments.

Acronyms, abbreviations, symbols. – AdipoR2 – adiponectin receptor 2, ALT – alanine aminotransferase, AMPK – AMP activated protein kinase, AST – aspartate transaminase, DBD – DNA-binding domain, ER – endoplasmic-reticulum, FAs – fatty acids, ERK– extra-cellular-signal-regulated kinase, FFA – free fatty acid, FXR – farnesoid X receptor, HCC – hepatocellular carcinoma, HD – hinge domain, IKK – inhibitor of nuclear factor kappa-B kinase, JNK – c-Jun N-terminal kinase, IL6 – interleukin 6, IR – insulin resistance, LBD – ligand-binding domain, LPS – lipopolysaccharide, MAPKs – mitogen-activated protein kinases, n-3 PUFAs – n-3 polyunsaturated fatty acids, NAFLD – non-alcoholic fatty liver disease, NASH – non-alcoholic steato-hepatitis, NF-κB – nuclear factor κB, OEA – oleoyle-thanolamine, PNPLA3 – patatin-like phospholipase 3, PPARα – peroxisome proliferator-activated receptor alpha, PPARβ – peroxisome proliferator-activated receptor beta, PPARδ – peroxisome proliferator-activated receptor delta, PPARγ – peroxisome proliferator-activated receptor gamma, PPARs – peroxisome proliferator-activated receptors, TC – total cholesterol, TG – triglyceride, TNFα – tumor necrosis factor alpha, TZDs – thiazolidinediones, VLDL – very low density lipoprotein.

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