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TOPIC HIGHLIGHT

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Role of peroxisome proliferators-activated receptors in the pathogenesis and treatment of nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent and can result in nonalcoholic steatohepatitis (NASH) and progressive liver disease including cirrhosis and hepatocellular carcinoma. A growing body of literature implicates the peroxisome proliferators-activated receptors (PPARs) in the pathogenesis and treatment of NAFLD. These nuclear hormone receptors impact on hepatic triglyceride accumulation and insulin resistance. The aim of this review is to describe the data linking PPARα and PPARγ to NAFLD/NASH and to discuss the use of PPAR ligands for the treatment of NASH.

Key words: Non-alcoholic fatty liver disease; Peroxisome proliferators-activated receptors; Insulin resistance; Metabolic syndrome; Pharmacologic ligands

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BACKGROUND ON NAFLD/NASH

An estimated 30% of adults and 10% of children and adolescents in the United States have nonalcoholic fatty liver disease (NAFLD), defined as liver fat content exceeding 5% (Figure 1)[1-3]. Non-alcoholic fatty liver disease is associated with obesity, non-insulin dependent diabetes, and hypertriglyceridemia and represents the hepatic manifestation of the metabolic syndrome[4]. A subset of persons with NAFLD progresses to nonalcoholic steatohepatitis (NASH), consisting of hepatic steatosis accompanied by inflammation and fibrosis (Figure 1)[5]. Nonalcoholic steatohepatitis affects approximately 3% of the lean population and 19% of obese persons, making it the most prevalent cause of chronic liver disease in the country[6]. Moreover, NASH represents a progressive form of liver disease. Cirrhosis developed in 5% of patients with NASH in a community-based cohort and 20% of NASH patients in a referral population[7,8]. Nonalcoholic steatohepatitis accounts for up to 75% of cases of cryptogenic cirrhosis and patients with NASH and cirrhosis are at risk for hepatocellular carcinoma[9,10].

The pathogenesis of NASH is often conceptualized as a two-step process, consisting of hepatic triglyceride accumulation, followed by the development of oxidative stress and cytokine expression leading to steatohepatitis[11]. Multiple metabolic processes can result in hepatocellular triglyceride accumulation including: (1) Excess dietary intake. Dietary triglycerides are delivered to the liver in the form of chylomicrons. In addition, dietary calories stored in adipose tissue as fat represent a source of fatty acids and triglycerides that can be delivered to the liver in the form of lipoprotein particles and free fatty acids. (2) Increased rates of lipogenesis resulting from the *de novo* synthesis of fatty acids and triglycerides in the liver. (3) Decreased rates of β-oxidation of fatty acids in the liver. (4) Decreased rates of export of cholesterol esters and triglycerides from the liver as very low density lipoprotein (VLDL)[12]. As shown in Figure 2, the PPARs impact on multiple processes involved in lipid trafficking and metabolism.

Insulin resistance and hyperinsulinemia seem to be central to the development of NAFLD. Insulin resistance is associated with increased lipolysis and reduced postprandial uptake and storage of fatty acids in adipose tissue, leading to increased fatty acid flux to the liver[13]. In turn, increased liver fat content contributes to hepatic insulin resistance[14]. Hyperinsulinemia induces sterol regulatory element-binding protein-1c (SREBP-1c) expression and hyperglycemia activates carbohydrate response element binding protein (ChREBP), both of which increase hepatic fatty acid synthesis[15].

THE PPARS

PPARs play a key role in modulating hepatic triglyceride

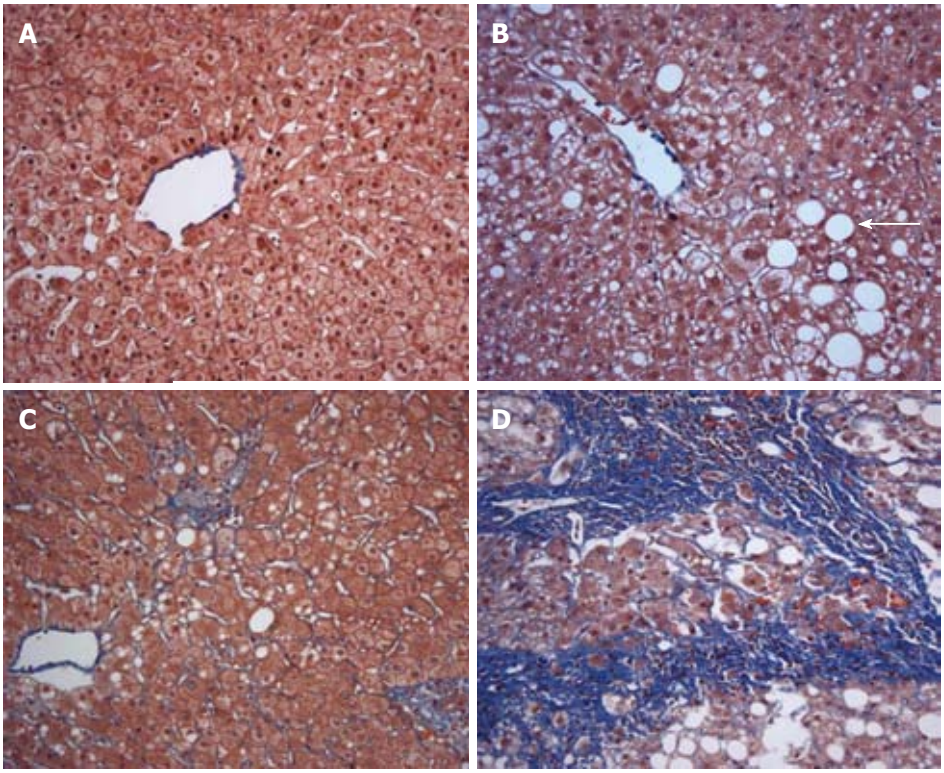

Figure 1 Liver histology ranging from normal liver to steatohepatitis with fibrosis. **A**: Normal liver. Cytoplasmic fat globules are absent in hepatocytes and there is no fibrosis in this trichrome stained specimen (× 20); **B**: Steatosis without steatohepatitis. Moderate cytoplasmic fat infiltration (arrow) is present without fibrosis (× 20); **C**: Steatohepatitis with minimal fibrosis. There is focal hepatocyte ballooning, inflammation, and minimal fibrosis (accentuated in blue by trichrome stain) (× 20); **D**: Steatohepatitis with fibrosis. There is nodular scarring in this fat laden liver with advanced fibrosis depicted in blue by trichrome stain (× 20).

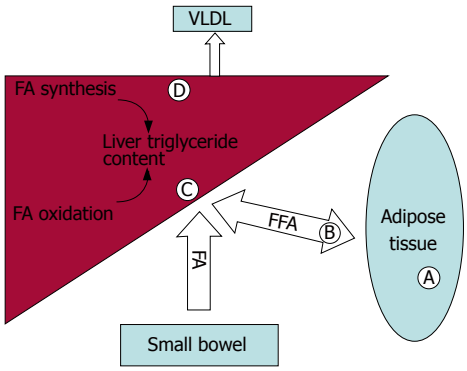

Figure 2 Mechanisms by which PPARs and their ligands can modulate triglyceride accumulation are highlighted by letters in the figure. A: PPARγ increases expression of genes associated with fatty acid uptake and triglyceride storage in adipocytes. Release of adiponectin from adipocytes improves insulin sensitivity and activates PPARα; B: PPARγ increases lipoprotein lipase expression, liberating circulating fatty acids from lipoproteins for import into adipocytes; C: PPARα activity up regulates β-oxidation of fatty acids in the liver; D: PPARα and TZDs upregulate stearoyl-CoA desaturase-1, a necessary enzyme for VLDL synthesis and export, and TZDs increase arachidonic acid content in triglycerides, which is associated with increased insulin sensitivity.

accumulation. PPARα regulates fatty acid β-oxidation. PPARγ increases insulin sensitivity as well as regulating triglyceride storage in adipose tissue. Fat labeling studies indicated that the majority of hepatic triglycerides originate from adipose tissue as non-esterified fatty acids[16].

PPARs are part of the nuclear receptor superfamily[17]. There are three isotypes in mammals designated PPARα [NR1C1], PPARδ [NR1C2] and PPARγ [NR1C3][18]. PPARα is activated by ligands termed peroxisome proliferators, which were named for their effects on peroxisomes in rodent livers[19,20]. Lipids are natural PPAR ligands, leading to regulation of lipid metabolism and fuel partitioning[17]. PPARs form a heterodimer with the retinoid X receptor (RXR). The PPAR:RXR heterodimer, when bound to a ligand, changes conformation and binds to DNA at PPAR response elements, resulting in gene transcription[21,22].

PPARα AND NAFLD

PPARα is expressed in the liver and other metabolically active tissues including striated muscle, kidney and pancreas[23,24]. Many of the genes encoding enzymes involved in the mitochondrial and peroxisomal fatty acid β-oxidation pathways are regulated by PPARα. In particular, the acyl-CoA synthetase, the carnitine palmitoyl transferase I, the very long-chain acyl-CoA dehydrogenase and the tri-functional protein genes encoding enzymes in the mitochondrial fatty acid β-oxidation pathway are induced by peroxisome proliferators that activate PPARα[25-28]. Similarly, the acyl-CoA synthetase, the straight-chain acyl-CoA oxidase, the L-bifunctional protein and the 3-ketoacyl-CoA thiolase genes encoding enzymes in the peroxisomal fatty acid β-oxidation pathway are induced by peroxisome proliferators that active PPARα[26,27,29,30]. Loss of expression of the PPARα gene in mice results in hepatic steatosis under conditions of increased fatty acid metabolism in the liver such as fasting or a high fat diet[31,32]. Administration of a potent PPAR agonist decreases hepatic steatosis in mice receiving a methionine and choline deficient diet[33]. These observations indicate that under conditions of increased hepatic fatty acid influx or decreased hepatic fatty acid efflux, PPARα activation prevents the accumulation of triglycerides by increasing the rate of fatty acid catabolism.

Additional factors appear to interact with PPARα to regulate hepatic triglyceride content. These include adiponectin, which is an adipocyte produced peptide

hormone that limits fat accumulation in the liver by a number of mechanisms including activation of PPARα to increase hepatic fatty acid oxidation[34]. In cell culture models, treatment with adiponectin resulted in increased activity of PPARα target genes such as acyl-CoA oxidase, carnitine palmitoyl transferase- I , and fatty acid binding protein[35]. PPARα ligands can increase steaoryl-CoA desaturase-1 (SCD1) activity, which is necessary for VLDL secretion[36]. A PPAR response element was found in the SCD1 promoter[37]. Adiponectin is upregulated by PPARγ, providing a connection between the two isotypes[38].

Most of the data regarding PPARα and hepatic lipid homeostasis comes from mouse models. However, there are important differences in PPARα activity between rodents and humans. PPARα DNA binding activity and PPARα expression in human hepatocytes is less than 10-fold that observed in mice[39,40]. Certain PPAR response elements, such as the acyl CoA oxidase gene, do not respond to PPAR ligands in humans as they do in rodent models[41]. Finally, PPARα activation in rodent models resulted in peroxisomal proliferation, hepatomegaly, and hepatocellular carcinoma[39,42,43], whereas similar changes were not observed in humans[44,45]. Further research is needed to determine the relative importance of PPARα in regulating hepatic triglyceride metabolism in humans.

PPARα AS A TARGET FOR THE TREATMENT OF NAFLD

Fibric acid derivatives, which are available for use in humans as lipid lowering agents, serve as PPARα activators[46,47]. In a mouse model of fatty liver disease, fenofibrate treatment improved steatosis and increased expression of genes involved in fatty acid metabolism[48]. Trials with fibrates in humans have yielded mixed results. A study involving potential living liver donors with steatosis showed that a combination of diet, exercise, and benzafibrate significantly reduced steatosis and resulted in normalization of alanine aminotransferase levels[49]. However, it was not clear whether the therapeutic benefit was related to benzafibrate or to a 1000 kilocalorie/day diet and a 600 kilocalorie/day exercise regimen. In addition to being a PPARα ligand, benzofibrate activates PPARγ and improves insulin sensitivity in animal models[46,47], an effect not seen with fenofibrate[50]. Another study demonstrated that 42% of 62 patients with NAFLD had biochemical and ultrasound improvement on fenofibrate, but histologic data were not collected[51]. A small controlled study of gemfibrozil *versus* placebo for four weeks found improved aminotransferase levels with the use of gemfibrozil in patients with NAFLD[52]. These studies are in contrast to a another small series, which demonstrated no change in aminotransferases and no histologic improvement after one year of clofibrate therapy for NAFLD[53].

Omega-3 polyunsaturated fatty acids (PUFA) present in fish oil, and their metabolites, provide another source of PPARα ligands. Omega-3 PUFA also inhibit lipogenesis by antagonizing activation of LXR[54,55], thus reducing expression of SREBP-1c[56], which results in the down regulation of key enzymes involved in hepatic lipid biosynthesis. In mouse models, omega-3 PUFA supplementation was associated with improvement in hepatic steatosis and insulin sensitivity, as well as lower fasting free fatty acid concentrations and lower serum triglyceride levels[57,58]. Two human studies reported a decline in serum aminotransferase levels and improvement in ultrasound features of fatty liver with omega-3 PUFA supplementation[59,60]. However, no histologic data were provided. Omega-3 PUFA supplementation also reduces serum triglyceride levels in the fasting and postprandial state[61-63], but was not found to improve insulin sensitivity in humans[62,64,65].

PPARγ AND NAFLD

PPARγ is expressed in high levels in adipose tissue[66] and plays a role in increasing insulin sensitivity as well as in promoting fatty acid uptake into adipocytes and adipocyte differentiation. The net effect of these processes is to increase triglyceride storage in adipocytes, reducing delivery of fatty acids to the liver. Patients with dominant negative mutations in PPARγ have NAFLD and the metabolic syndrome while lacking adipose tissue suggesting increased triglyceride delivery to the liver[67]. PPARγ is present in the liver to a lesser degree than in adipose tissue. Liver-specific PPARγ deficient mice are protected against the development of steatosis suggesting a role for hepatic PPARγ in liver triglyceride accumulation[68,69].

Insulin resistance is integral to the development of NAFLD, leading to increased fatty acid flux to the liver and increased hepatic fatty acid synthesis[13,15]. PPARγ increases insulin sensitivity by upregulating GLUT4, an insulin dependent glucose transporter in adipose tissue and striated muscle[70], and inducing expression of the c-Cbl associated protein, which is involved in insulin signaling[71]. Additionally, in mouse models of insulin resistance, PPARγ activation attenuated induction of supressor of cytokine signaling 3 (SOCS3), which is involved in the development of insulin resistance[72].

PPARγ also promotes adipocyte differentiation and expression of proteins in adipocytes involved in fatty acid uptake[17,73], fatty acid transport[74,75] and fatty acid synthesis[76]. Differentiation of preadipocytes to adipocytes requires transcription factors including the CCAT-enhancer-binding proteins (C/EBPs) and the adipocyte differentiation and determination factor (ADD)-1/SREBP-1[77-80]. C/EBP plays an important role in inducing and maintaining PPARγ expression in adipogenesis[81,82]. ADD-1/SREBP-1 is strongly adipogenic, is enhanced by PPARγ, and results in the expression of lipogenic genes including fatty acid synthase[80]. These transcription factors guide the cell through proliferation, clonal expansion, growth arrest, and eventually adipocyte specific genes are activated resulting in lipid accumulation[82]. PPARγ also increases expression of lipoprotein lipase, an enzyme that serves to partition fat to adipocytes, limiting fatty acid flux to the liver. Similar to PPARα, PPARγ ligands upregulate SCD1 activity, which promotes VLDL secretion. Thiazolidinediones (TZDs), ligands for PPARγ have also been shown to increase arachidonic acid content in triglycerides through SCD1, which has been associated with increased

insulin sensitivity[83]. Other effects of PPARγ include induction of uncoupling protein-2, which might decrease hepatic triglyceride accumulation by increasing energy expenditure[84]. PPARγ expression also might reduce hepatic inflammation by decreasing expression of proinflammatory cytokines, such as TNFα[85].

PPARγ AS A TARGET FOR THE TREATMENT OF NAFLD

TZDs are PPARγ agonists, which improve glycemic control in patients with type 2 diabetes mellitus by increasing insulin sensitivity[86]. The TZD-mediated increase in insulin sensitivity was demonstrated in adipose tissue, the liver, and skeletal muscle[87,88]. TZD therapy increases adiponectin levels, which are associated with improved insulin sensitivity[89]. Furthermore, adiponectin impacts on hepatic fat accumulation by enhancing fatty acid oxidation in muscle, and by activating PPARα to increase fatty acid oxidation in the liver[34].

Thiazolidinediones also increase expression of AMP-activated protein kinase[88,90]. This protein kinase increases fatty acid oxidation as well as decreasing lipogenesis[91,92]. The reduction in lipogenesis is mediated through phosphorylation and inhibition of acetyl-CoA carboxylase, which decreases malonyl CoA formation and down regulates SREBP and the carbohydrate response element binding protein (ChREBP)[93]. Finally, TZDs have anti-inflammatory and anti-fibrotic properties that might be beneficial in NASH. Serum high-sensitivity CRP, IL-6 and IL-18 levels were significantly reduced in patients on TZD therapy[94,95] and the TZD pioglitazone reduced activation of hepatic stellate cells in an animal model[96]. Increased adiponectin may also contribute to the anti-inflammatory effects of TZD therapy. Adiponectin was shown to block TNFα activation of inflammatory genes in endothelial cells[97], decrease macrophage growth and function[98-100], and increase release of the anti-inflammatory cytokines IL-10 and IL-1RA with a concomitant decrease in interferon-γ production[100].

Studies of the TZDs rosiglitazone and pioglitazone demonstrated reduction in aminotransferase levels and improvement in liver histology in patients with NASH[87,101-106]. One study that compared pioglitazone plus vitamin E to vitamin E alone for the treatment of NASH found significant improvement in steatosis, hepatocellular ballooning, and pericellular fibrosis in the combination therapy arm, but not in patients treated with vitamin E alone[103]. In a study of pioglitazone plus diet versus placebo plus diet in patients with biopsy proven NASH and insulin resistance, pioglitazone therapy was associated with a significant reduction in mean serum aminotransferase levels and improved glycemic control[107]. There were significant improvements in hepatic insulin resistance as well as histologic parameters including hepatic steatosis, ballooning, and inflammation, although not fibrosis with six months of treatment. Further evaluation of the efficacy and the cardiovascular risk of TZD therapy[108] is needed before this class of medications is routinely prescribed for the treatment of NASH.

CONCLUSION

The nuclear hormone receptors PPARα and PPARγ appear to play an important role in modulating hepatic triglyceride accumulation, the primary process in the development of NAFLD. PPARα activity reduces liver fat by increasing β-oxidation of fatty acids and PPARγ increases insulin sensitivity as well as reducing fatty acid flux to the liver. PPAR ligands show promise in the treatment of NAFLD, although further human studies are needed to define the therapeutic role of these agents.

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