

## Peroxisome proliferator-activated receptors as targets to treat non-alcoholic fatty liver disease

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and microsomal omega-oxidation, being markedly decreased by high-fat (HF) intake. PPAR-beta/delta is crucial to the regulation of forkhead box-containing protein O subfamily-1 expression and, hence, the modulation of enzymes that trigger hepatic gluconeogenesis. In addition, PPAR-beta/delta can activate hepatic stellate cells aiming to the hepatic recovery from chronic insult. On the contrary, PPAR-gamma upregulation by HF diets maximizes NAFLD through the induction of lipogenic factors, which are implicated in the fatty acid synthesis. Excessive dietary sugars also upregulate PPAR-gamma, triggering *de novo* lipogenesis and the consequent lipid droplets deposition within hepatocytes. Targeting PPARs to treat NAFLD seems a fruitful approach as PPAR-alpha agonist elicits expressive decrease in hepatic steatosis by increasing mitochondrial beta-oxidation, besides reduced lipogenesis. PPAR-beta/delta ameliorates hepatic insulin resistance by decreasing hepatic gluconeogenesis at postprandial stage. Total PPAR-gamma activation can exert noxious effects by stimulating hepatic lipogenesis. However, partial PPAR-gamma activation leads to benefits, mainly mediated by increased adiponectin expression and decreased insulin resistance. Further studies are necessary aiming at translational approaches useful to treat NAFLD in humans worldwide by targeting PPARs.

**Key words:** Peroxisome proliferator-activated receptors; Non-alcoholic fatty liver disease; Obesity; Treatment; Insulin resistance; Beta-oxidation; Lipogenesis

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### Abstract

Lately, the world has faced tremendous progress in the understanding of non-alcoholic fatty liver disease (NAFLD) pathogenesis due to rising obesity rates. Peroxisome proliferator-activated receptors (PPARs) are transcription factors that modulate the expression of genes involved in lipid metabolism, energy homeostasis and inflammation, being altered in diet-induced obesity. Experimental evidences show that PPAR-alpha is the master regulator of hepatic beta-oxidation (mitochondrial and peroxisomal)

**Core tip:** Multiple pathways disrupted in obesity and non-alcoholic fatty liver disease (NAFLD) are regulated by genes encoded by peroxisome proliferator-activated receptors (PPARs). Thus, PPARs emerged as potential targets to alleviate NAFLD. The use of PPAR-alpha agonist yields increased mitochondrial beta-oxidation coupled with reduced lipogenesis. Both of them are essential to tackle insulin resistance and hepatic steatosis. PPAR-

beta/delta agonist is still not available as a medicine, but PPAR-beta/delta agonist elicited expressive reduction in hepatic glucose production in murine models. PPAR-gamma agonist is extensively used, and beneficial effects come from partial activation as total PPAR-gamma activation leads to hepatic lipogenesis, being harmful to the liver.

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## INTRODUCTION

The current obesity epidemics have resulted in a significant rise in its comorbidities prevalence<sup>[1]</sup>. Liver is often significantly affected by obesity and, hence, the non-alcoholic fatty liver disease (NAFLD) is regarded as the hepatic manifestation of metabolic syndrome, showing rising prevalence regardless of economic status or age worldwide<sup>[2]</sup>. Despite being a benign process at first, the continuation of the triggering stimuli can lead to harmful conditions such as non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma<sup>[3]</sup>.

Excessive energy intake concomitant with sedentism are considered essential underpinnings of lipid droplets accumulation<sup>[4]</sup>. When the metabolism faces obesity, excessive adipose tissue fat pads elicit low-grade inflammation, which is linked to insulin resistance development<sup>[5,6]</sup>. The resulting hyperinsulinemia yields high lipolysis rate in the white adipose tissue coupled with reduced fatty acid oxidation within the hepatocytes<sup>[7]</sup>. The balance between fatty acid input and output in the liver is controlled by integrated enzymes that act in the catalysis of hepatic uptake, lipogenesis, oxidation and exportation of fatty acids<sup>[8]</sup>. Whenever the hepatic fatty acid synthesis and/or uptake surpass the liver oxidative and/or the exportation capacity, lipid droplets accumulate within the hepatic parenchyma, configuring NAFLD<sup>[9]</sup>.

Dietary quality has a paramount importance for the hepatic fatty acid metabolism<sup>[10]</sup>. Excessive intake of simple carbohydrate such as fructose and sucrose are implicated in high rates of *de novo* lipogenesis (DNL) in the liver, which is defined as the synthesis of fatty acids from a non-lipid source<sup>[11]</sup>. In conjunction with a high intake of dietary fats that generates lipotoxicity through the excessive production of ceramides from palmitate and aggravates insulin resistance, the high DNL due to excessive dietary carbohydrate makes a great demand for hepatic oxidation of fatty acids, which exceeds the oxidative capacity of hepatic peroxisomes, mitochondria and microsomes (endoplasmic reticulum). In turn, hepatic lipid metabolic equilibrium is disrupted due to abnormal fat partitioning within hepatocytes<sup>[11-13]</sup>.

The carbohydrate and lipid intake, as well as the adipokines and insulin levels, exert considerable influence upon key transcription factors that can modulate hepatic lipid metabolism<sup>[14]</sup>. Peroxisome proliferator-activated receptors (PPARs) are at the crossroads of NAFLD pathogenesis, once recent evidences point to the modulation of hepatic beta-oxidation and lipogenesis by different PPAR isoforms<sup>[15,16]</sup>. Thus, even though weight management and exercise are the most efficient approach to treating NAFLD, adjunctive pharmacological intervention is utterly indicated. PPARs emerge as a target to treat NAFLD by modulating diverse pathways that are impaired by obesity<sup>[17,18]</sup>. The role that total or partial PPAR alpha, beta/delta and gamma activation play in lipogenesis and hepatic oxidation as well as in carbohydrate metabolism through the gluconeogenesis, and DNL are relevant targets to fasten the treatment of NAFLD and obesity.

## PPAR PHYSIOLOGY IN EXPERIMENTAL MODELS NAFLD

Hepatic metabolic pathways can be disturbed differently according to the nutrient that is excessive in the diet<sup>[19]</sup>. Experimental dietary models of NAFLD are influenced by the dietary scheme duration, diet composition, and animal age, all of which directly affect the spectrum of NAFLD pathogenesis<sup>[20]</sup>.

When there is excessive dietary intake of lipids, hepatic PPAR-alpha expression decreases significantly parallel to an expressive increase of PPAR-gamma<sup>[16,21]</sup>. Obese mice fed during 16 wk a high-fat (HF) diet made up of 60% of energy as lipids, predominantly saturated fatty acids from lard, exhibited overweight, insulin resistance and 34.57% of volume density of hepatic steatosis concomitant to a proinflammatory adipokine profile and activation of hepatic stellate cells (HSCs)<sup>[21]</sup>. Hepatic PPAR-alpha expression was substantially reduced<sup>[21]</sup>, agreeing with a reduced number in the numerical density of hepatic mitochondria<sup>[21,22]</sup>. PPAR-alpha is related to mitochondrial beta-oxidation of fatty acids, which has got carnitine palmitoyl transferase-1 (CPT-1) as a pivotal enzyme that allows the fatty acid to go through the inner mitochondrial membrane and reach the mitochondrial matrix to be metabolized<sup>[23]</sup>. In the absence of a typical PPAR-alpha expression in the liver, the transcription of its target gene CPT-1 is impaired and excessive fatty acids, which are usually stemmed from lipolysis and delivery to the liver of obese individuals, tend to accumulate in the form of triglycerides<sup>[24,25]</sup>.

A similar dietary scheme (50% of energy as fat for 12 wk) elicited 2.3 fold increase in liver triglycerides, followed by 0.7 fold decrease in PPAR-alpha and a 0.4 fold increase in PPAR-gamma protein expression in the liver. These observations feature a frame that predisposes to NAFLD because PPAR-gamma is linked to lipogenesis and its target gene expression, SREBP-1c, was 0.5 fold increased in HF fed animals<sup>[16]</sup>. SREBP-1c

is implicated in the DNL, induced by high insulin levels. Once activated, SREBP-1c activates others lipogenic genes and leads to the conversion of pyruvate into fatty acids. During this process, there is a great production of malonyl co-A, which inhibits CPT-1 and prevents fatty acids from reaching the mitochondrial matrix to be metabolized through mitochondrial beta-oxidation<sup>[26,27]</sup>. Alternative pathways, peroxisomal beta-oxidation, and microsomal omega-oxidation are upregulated to try to compensate insufficient mitochondrial oxidative activity. Mitochondrial damage found in NAFLD and increased peroxisomal and microsomal oxidation of fatty acids leads to oxidative stress and the consequent progression to NASH if an adequate intervention is not implemented<sup>[28,29]</sup>. The pivotal role that oxidative stress plays in NAFLD progression to NASH was verified through positive immunoreactions for oxidized phosphatidylcholine close to activated stellate cells and in apoptotic hepatocytes in samples of human liver autopsy. Moreover, immunostaining intensity correlated positively with the degree of steatosis<sup>[30]</sup>.

When the HF diet (49% of energy as lipids) was administered to dams during 8 wk prior to gestation, gestation, and lactation, similar hepatic alterations were detected in the offspring. Pups from HF dams had overweight and glucose intolerance at 3 mo of age, both of which agree with the 1.4 fold increase in hepatic steatosis rate in these animals. PPAR-alpha gene and protein expression were reduced in the liver of offspring of HF dams parallel to increased gene and protein expression of PPAR-gamma. As a result, the hepatic expression of the PPAR-alpha target gene *CPT-1* was decreased, because the expression of the PPAR gamma target genes *SREBP-1c* was elevated<sup>[31]</sup>. This pattern of gene and protein expression explains the early NAFLD onset in the offspring of obese dams<sup>[32]</sup>, albeit with a discrete overweight. Besides the compromised mitochondrial beta-oxidation through the reduced CPT-1 activity and the enhanced DNL, favored by over-expression of SREBP-1c, the offspring presented with expressive reduction in fatty acid translocase (FAT)/CD36 expression, which limits long chain fatty acids (more than 20 carbons) oxidation. FAT/CD36 can shorten the fatty acid chain in order to allow CPT-1 to catalyze its transport to the mitochondrial matrix<sup>[33]</sup>. This represents an additive failure in hepatic lipid metabolism due to maternal obesity.

Additionally, hepatic insulin resistance was detected in obese dams offspring through enhanced hepatic expression of glucose 6 phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK)<sup>[34,35]</sup>. Both enzymes are crucial to hepatic gluconeogenesis and are activated by glucagon during the fasting period and inhibited by insulin at the postprandial stage. When insulin resistance occurs, insulin, at high levels, loses its capacity to inhibit gluconeogenesis by the downregulating G6Pase and PEPCK expression<sup>[34,35]</sup>. Hence, high hepatic glucose production aggravates insulin resistance. PPAR-beta/delta induces forkhead box-containing protein O

subfamily-1 (FOXO-1), which can regulate G6Pase and PEPCK expression, and might be a viable approach to restoring this pathway<sup>[36]</sup>. In addition, PPAR-beta/delta is described to induce HSCs proliferation in fibrogenesis activation *in vitro* and *in vivo*. HSCs constitutively express PPAR-beta/delta and their activation aim at the hepatic recovery from chronic insult. However, the collagen synthesis by HSCs leads to hepatic fibrosis in the long run, being involved in the progression of simple NAFLD to more dangerous types of liver diseases<sup>[37,38]</sup>.

Excessive intake of sucrose (32% of energy as sucrose) yielded similar effects to liver histology and PPAR expression in C57BL/6 mice. Although animals did not become obese, excessive sucrose supply, elicited 1.3-fold increase in hepatic steatosis coupled with 0.5 fold decrease in PPAR-alpha expression and 0.8 increase in SREBP-1c expression<sup>[19]</sup>. Likewise, the intake of 34% of energy as fructose impaired hepatic cytoarchitecture and lipid metabolism in the same mouse model. Even in the absence of significant overweight, mice fed a high-fructose diet presented nearly 55% volume density of hepatic steatosis, which can be accounted for by augmented hepatic expression of PPAR-gamma (0.5 fold) and reduced hepatic expression of PPAR-alpha (-0.25 fold)<sup>[39]</sup>. PPAR-gamma increases the transcription of SREBP-1c, leading to higher lipogenesis, and little PPAR-alpha expression favors high hepatic glucose production. There is the interplay between white adipose tissue and liver as a glucose/glycerol cycle that guarantees energy transport (as glucose) from liver to peripheral tissues<sup>[40]</sup>. This process relies on PPAR-alpha, being impaired in the fructose-fed animals<sup>[39,40]</sup>. In addition, high fructose intake augmented the hepatic expression of PEPCK and GLUT2<sup>[39]</sup>, indicating high hepatic glucose output, which aggravates insulin resistance and favors the NAFLD progression to NASH<sup>[41]</sup>.

## TARGETING PPARS TO TREAT NAFLD

PPARs encompass a subfamily of a superfamily of nuclear receptors. There are three different isoforms: PPAR-alpha, PPAR-beta/delta, and PPAR-gamma, which are differently expressed in various tissues. They are ligand-dependent transcription factors that regulate the expression of their target genes through specific binding to peroxisome proliferation response elements (PPERs). Each isoform heterodimerize with its retinoid X receptor alpha, beta/delta or gamma and binds to its respective PPRE, forming a structure able to recognize specific DNA sequences (AGGTCA) to activate the transcription of its target genes<sup>[42-44]</sup>.

Briefly, PPAR-alpha is closely linked to the transcription of genes related to hepatic beta-oxidation, such as CPT-1 and is highly expressed in the liver<sup>[45,46]</sup>. Thus, treatment with PPAR-alpha agonist usually yields body mass loss as this isoform is implicated in lipid metabolism pathways<sup>[43]</sup>. PPAR-beta/delta is ubiquitously expressed and is crucial to beta-oxidation in skeletal muscle, not in the liver. In the liver, anti-inflammatory

properties by the activation of macrophages and the protection against lipotoxicity are reported. The induction of Stearoyl-CoA desaturase 1 by PPAR-beta/delta activation promotes monounsaturated fatty acids formation instead of saturated fatty acids, decreasing oxidative stress, emerging as a promising approach to the tackle insulin resistance<sup>[47,48]</sup>. PPAR-gamma is expressed at low concentrations in the liver (9%-12% of the expression in the white adipose tissue), being related to adipogenesis and insulin-sensitizing effects through the diversion of fatty acids to adipose tissue storage. Patients with NAFLD exhibit abnormal high expression of PPAR-gamma in the liver, which coincides with overexpression of SREBP-1c and the consequent hepatic lipogenesis<sup>[49,50]</sup>.

Taking into account the above-mentioned PPAR related effects, the use of PPAR agonist to treat NAFLD seems to be a viable strategy. In this regard, the activation of PPAR-alpha by fenofibrate markedly ameliorated the hepatic insulin resistance by the upregulation of enzymes involved with beta-oxidation in fructose-fed mice and the expressive reduction of DNL, albeit with high endoplasmic reticulum stress<sup>[51]</sup>. In addition, fenofibrate significantly ameliorated microcirculatory perfusion in a HF mice mouse model of NAFLD, besides the upregulation of genes involved in hepatic lipid oxidation<sup>[52]</sup>. These reported effects comply with a significant decrease in hepatic steatosis percentage after the activation of PPAR-alpha by fenofibrate<sup>[51,52]</sup>. Activation of PPAR-alpha by fish oil, a nutraceutical, yielded alleviation of hepatic insulin resistance through low G6Pase and PEPCK expression in the liver and reduced steatosis by upregulation of mitochondrial beta-oxidation (high CPT-1 expression) concomitant to reduced lipogenesis (low fatty acid synthase expression)<sup>[53]</sup>.

In humans, the evaluation of fenofibrate use to treat NAFLD is difficult as it is usually taken with others drugs. It seems that insulin-sensitizing action of fenofibrate is more important to counter hepatic steatosis than its lipid-lowering property. A recent study showed a significant decrease in hepatic transaminases coupled with a marked decrease of hepatocellular ballooning in humans<sup>[54,55]</sup>.

As far as mice models of NASH are concerned, APOE2 mice fed a western diet showed decreased hepatic macrophage accumulation, which precedes lipid accumulation within hepatocyte, and expressive reduction of lipotoxicity after treatment with fenofibrate. A marked reduction in the expression of proinflammatory genes, great expression of genes implicated in  $\beta$ -oxidation and the suppression of procollagen type 1 expression underlie these findings<sup>[56,57]</sup>.

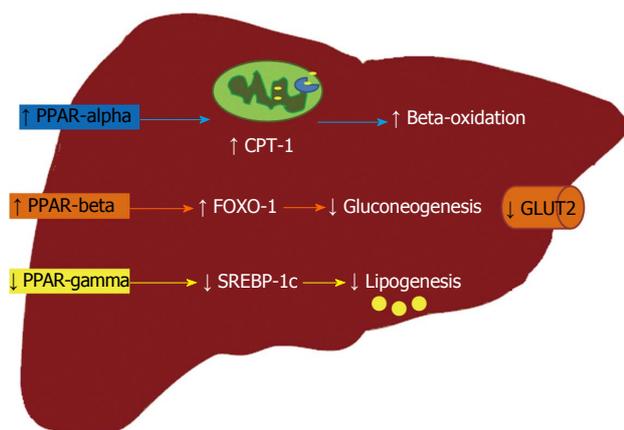
Total PPAR-gamma activation by rosiglitazone counters insulin resistance, but do not manage to reduce NAFLD in HF mouse models. It can be argued that full activation of PPAR-gamma favors the transcription of lipogenic transcription factors, such as SREBP-1c, and even though animals benefit from anti-inflammatory effects of high adiponectin levels, the upregulation of lipogenesis

results in obesity, increased hepatic triglycerides and the maintenance of NAFLD<sup>[16,58]</sup>. In contrast, mice with NASH benefit from the use of rosiglitazone as it inhibited cell proliferation and diminished collagen expression in hepatic stellate cells *in vivo* and *in vitro*<sup>[59,60]</sup>. In addition, the increase in insulin sensitivity due to enhanced adiponectin transcription and reduced levels of tumor necrosis factor (TNF)-alpha is crucial to the treatment of NASH with rosiglitazone in murine models<sup>[61,62]</sup>.

Humans with NASH also benefit from the regular use of rosiglitazone. The randomized placebo-controlled Fatty Liver Improvement With Rosiglitazone Therapy (FLIRT) trial revealed that 47% of the patients with histologically proved NASH had marked reduction (> 30%) in steatosis score after one year of treatment. Moreover, 38% of the patients achieved normalization of alanine aminotransferase (ALT) values, albeit with no significant improvement of NASH histological features such as hepatocyte ballooning, fibrosis and lobular inflammation/necrosis. In agreement with experimental background, rosiglitazone significantly increased insulin sensitivity and adiponectin levels and the former was correlated with the reduction in the percentage of steatosis in patients of FLIRT trial<sup>[63]</sup>.

When the same set of patients were revisited two years later (FLIRT 2 extension trial), the long-term efficacy of rosiglitazone was attested by the maintenance of reduced ALT levels and reduced HOMA-IR and insulin levels. However, once again, no beneficial effect on liver histology was perceived. It can be argued that even though rosiglitazone exhibited an antisteatogenic effect during the first year and normalized insulin sensitivity and ALT levels, these effects were not enough to tackle NASH features and additional treatments are encouraged<sup>[64]</sup>. In agreement to the FLIRT trial, the Pioglitazone vs Vitamin E vs Placebo for the Treatment of Nondiabetic Patients with nonalcoholic steatohepatitis trial showed that vitamin E and pioglitazone were able to reduce ALT levels, increase insulin sensitivity, decrease hepatic steatosis and ameliorate lobular inflammation, but without significant improvement in hepatic fibrosis and hepatocyte ballooning. The significant weight gain after pioglitazone treatment was an adverse effect<sup>[65]</sup>.

Recently, the partial activation of PPAR-gamma coupled with the selective activation of PPAR-alpha in the liver by telmisartan (also an AT1 receptor blocker) elicited positive effects to hepatic cytoarchitecture and ultrastructure in mice fed a HF diet<sup>[21,66]</sup>. Animals showed normal volume density of hepatic steatosis when compared to the untreated group, followed by reduced SREBP-1c expression and insulinemia parallel to greater mitochondrial numerical density revealed by transmission electron microscopy<sup>[21]</sup>. The same drug was also able to counter steatohepatitis in a murine model through the suppression of macrophage infiltration within hepatocytes, induction of high adiponectin levels and reduction of adipocyte size<sup>[66]</sup>. In humans, telmisartan showed beneficial effects when compared to losartan (pure AT1 receptor blocker) in the management of



**Figure 1** Effects of each peroxisome proliferator-activated receptor isoform in the treatment of non-alcoholic fatty liver disease. PPAR-alpha activation leads to the transcription of CPT-1, a target gene that is crucial to beta-oxidation as it allows the fatty acid to reach the mitochondrial matrix; PPAR-beta/delta activation is involved with FOXO-1 transcription, which reduces the hepatic expression of enzymes involved in gluconeogenesis. Thus, GLUT2 and hepatic glucose production are also significantly reduced; conversely, the partial activation of PPAR-gamma or, even, its reduced expression is linked to diminished lipogenesis. All these events are efficient to tackle NAFLD. PPAR: Peroxisome proliferator-activated receptor; CPT-1: Carnitine palmitoyl transferase-1; FOXO-1: Forkhead box-containing protein O subfamily-1; GLUT2: Glucose transporter 2; SREBP-1c: Sterol regulatory element-binding protein-1c.

NAFLD, highlighting the importance of PPAR activation to treat NAFLD. Telmisartan also yields decreased expression of Nuclear factor  $\kappa$ B target genes, such as TNF-alpha and interleukin-6 in diet-induced obese mice, which coupled with increased adiponectin prevent these animals from NASH onset<sup>[21,67]</sup>. In resemblance with telmisartan, ragaglitazar, a dual PPAR-alpha/PPAR-gamma agonist, tackled hepatic insulin resistance, hepatic steatosis and overweight in a mouse model of metabolic syndrome, whereas total PPAR-gamma agonist rosiglitazone elicited visceral adiposity and hepatomegaly<sup>[68]</sup>.

Pan-PPAR activation by bezafibrate triggered beneficial effects in offspring from obese dams derived from PPAR-alpha activation (increased CPT-1 expression in the liver); PPAR-beta/delta activation (reduced gluconeogenesis due to low hepatic G6Pase and PEPCK expression caused by downregulation of FOXO-1 gene); and PPAR-gamma activation (high FAT/CD36 liver expression, causing greater hepatic lipid oxidation in conjunction with the high CPT-1 expression)<sup>[31]</sup>. Bezafibrate and GW501516, a PPAR-delta agonist, inhibited NASH development in mice fed a methionine choline-deficient diet. Both treatments elicited greater expression of genes related to beta-oxidation and lipid transportation in hepatocytes concomitant with reduced levels of genes linked to inflammation<sup>[69]</sup>. An overview of the effects of PPAR activation upon the pathways involved with NAFLD pathogenesis is shown in Figure 1.

PPAR transcriptional activity can be influenced by several kinases as they are phosphoproteins<sup>[70]</sup>. Mitogen-activated protein kinase (MAPK) activation leads to phosphorylation of PPAR-alpha and PPAR-gamma isoforms. Phosphorylated PPAR-alpha exhibits

higher transcription activity, whereas PPAR-gamma shows reduced transcriptional potential after phosphorylation. This knowledge is utterly important when it comes to the attempt to obtain new drugs with huge effectiveness. PPAR-alpha and gamma activate MAPK, while MAPK activation leads to PPAR-alpha and gamma phosphorylation and modulation, configuring an interplay between these two pathways. So, it can be argued that PPAR-alpha beneficial effects are maximized by the interplay with MAPK, which result in favored beta-oxidation in the liver<sup>[71]</sup>. On the other hand, the reduced transcriptional potential of PPAR-gamma due to MAPK activation might also be beneficial provided that insulin-sensitizing effects of PPAR-gamma are more expressive when there is partial activation of this isoform<sup>[72]</sup>.

## CONCLUSION

It is widely understood that PPARs are critically involved in the regulation of hepatic beta-oxidation and lipogenesis pathways, besides influencing hepatic carbohydrate metabolism. These observations prompted the attempt to treat NAFLD by targeting PPARs. Targeting PPAR-alpha has been proved a promising therapeutic approach to control NAFLD through the upregulation of beta-oxidation genes and the inhibition of DNL and gluconeogenesis enzymes. On the other hand, total PPAR-gamma activation shows deleterious effects upon liver histology and physiology based on the increased hepatic lipogenesis. However, partial PPAR-gamma activation as well as dual or pan-PPAR activation shows beneficial effects upon liver structure and functioning. In this way, PPAR modulation by partial activation or selective activation is a promising field of study as it possibilities the reduction of side effects that may stem from total agonism of the receptor. In addition, the role that PPAR-beta/delta has upon liver metabolism remains to be completely unraveled as there is not a PPAR-beta/delta agonist available to the population. Evidences related to this isoform come from experimental studies using selective agonists that are not commercialized or pan-PPAR agonist, which challenges the identification of each isoform properties. Further studies are necessary aiming at translational approaches useful to treat this prevalent metabolic disease in humans worldwide by targeting PPARs.

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