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REVIEW

Mechanistic Insights into N-Oleoylethanolamide-Mediated Hepatoprotection via PPAR-α

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ABSTRACT: The high prevalence of obesity and associated nonalcoholic fatty liver disease (NAFLD) in the population determines the increased interest in identifying molecular targets for regulating the processes underlying these pathologies. The search for new endogenous bioregulators of lipid metabolism and their inclusion in therapeutic regimens for the treatment of patients is becoming a potentially promising direction in science and medicine. Oleoylethanolamide (OEA) is an endogenous lipid mediator capable of exerting multiple hypolipidemic, anti-inflammatory, and hepatoprotective effects mediated by agonism with receptors of the peroxisome proliferator-activated receptor (PPAR) family (PPAR-α and PPAR-γ). This review focuses on a detailed description of the PPAR-dependent mechanisms of the hepatoprotective activity of OEA in the development of NAFLD. The main attention is paid to such topics as reduction of oxidative stress and inflammation, inhibition of liver fibrogenesis, suppression of hepatocyte death, and changes in various parameters of lipid metabolism.

KEYWORDS: NAFLD; liver; inflammation; N-Oleoylethanolamide; OEA; PPAR-α

1 Introduction

Due to the worldwide obesity epidemic and the ongoing rise in the incidence of associated metabolic disorders, nonalcoholic fatty liver disease (NAFLD) is becoming a major worry for the healthcare system. According to recent meta-analysis data, the global prevalence of NAFLD is significantly higher than previously estimated and continues to increase at an alarming rate. The global prevalence of NAFLD is estimated to be 32.4% in 2022, significantly higher than in 2005 (25.5%). In addition, the incidence and prevalence of NAFLD are significantly higher in men than in women [1]. In addition, NAFLD is projected to become the leading cause of cirrhosis requiring liver transplantation in the next decade [2]. It is commonly established that NAFLD has a strong correlation with the onset of obesity [3] as well as with metabolic conditions that directly coexist with obesity, including hypertension [4], insulin resistance [5], and hypercholesterolemia [6]. NAFLD is often defined by a fairly broad range of liver lesions, including damage to hepatocytes, which are functioning liver cells, the growth of the inflammatory process, and the creation of cirrhosis and fibrosis on top of the inflammation [7].

Based on its histologic characteristics, NAFLD is commonly divided into nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL) [8]. With a more benign course, NAFL is characterized by fatty liver dystrophy and mild inflammation of the hepatic lobules [9]. In addition to more severe diffuse

lobular inflammation progressing to cirrhosis and fibrosis, NASH is associated with significant hepatocyte destruction, including fat necrosis [10].

In the development of obesity, under conditions of increased caloric intake, *de novo* fat synthesis increases, with the main source of material for triacylglycerides (TAG) synthesis coming from white adipose tissue [11]. Also, one of the most significant pathogenetic aspects of NAFLD is insulin resistance, which, as a rule, also develops in the background of obesity [12].

In the context of excessive sugar intake, insulin has an antilipolytic effect, encourages the synthesis and storage of TAGs in adipose tissue, and increases the fatty acid synthesis and esterification processes [13]. In adipocytes, fatty acids (FA) are mostly stored as TAGs [14]. In instances of low energy experienced by the body due to insulin resistance, TAGs are known to respond to counterregulatory hormones, such as cortisol and epinephrine, by undergoing a process of breakdown into glycerol and free fatty acids (FAs). Sharp increases in FAs intake in the liver can produce mitochondrial dysfunction and poor beta-oxidation, which can then cause inflammation and concurrent activation of lipid peroxidation, which can ultimately lead to oxidative stress, damage, and hepatocyte death [15,16].

There are two key pathogenetic phases in the development of NAFLD [17]. Insulin resistance and the accumulation of excess fat in the liver are features of the first stage. As a result, insulin resistance increases even more, starting a vicious loop [18]. Molecular and cellular changes that eventually result in the development of chronic, long-lasting inflammation and fibrosis are the hallmarks of the second stage. These molecular alterations include immune cells producing proinflammatory cytokines, lipid peroxidation being activated [19], oxidative stress developing [20], lipotoxicity, and extracellular matrix remodeling [21].

Hepatocytes overexposed to free fatty acids (FFA) undergo oxidative stress that damages their mitochondria, produces more reactive oxygen species (ROS) [22,23], stresses the endoplasmic reticulum (ER) and ultimately leads to persistent inflammation [24] (Fig. 1).

Peroxisome proliferator-activated receptor (PPAR) agonists are currently one of the most promising options for the comprehensive treatment of NAFLD and are attracting increasing research attention. The therapeutic areas related to lipid and glucose metabolism, inflammation, obesity [25,26], insulin resistance, and atherosclerosis [27,28], which often lead to secondary liver damage, are well aware of the potential benefits of PPAR agonists. The versatility of their therapeutic effects determines their advantage over other pharmacological targets.

As a lipid mediator, oleoylethanolamide (OEA) belongs to the class of N-acylethanolamines (NAE) and acts by activating the nuclear receptor PPAR-α [29]. OEA is implicated in the pathophysiology of appetite regulation, lipid metabolism, and carbohydrate metabolism, according to an increasing body of studies [30]. Numerous studies have demonstrated that OEA is a promising pharmacological target for the treatment of obesity and eating disorders [31]. It has been demonstrated to increase fullness and reduce appetite in both obese humans [32] and animals [33]. A growing body of experimental data indicates that the hepatoprotective benefits of OEA might be attributed to its capacity to activate PPAR-α.

The aim of this review is to describe point by point the mechanisms of NAFLD formation in the context of potential OEA-mediated therapeutic effects. The main focus is on PPAR-dependent pathways for the implementation of the hepatoprotective effect of OEA.

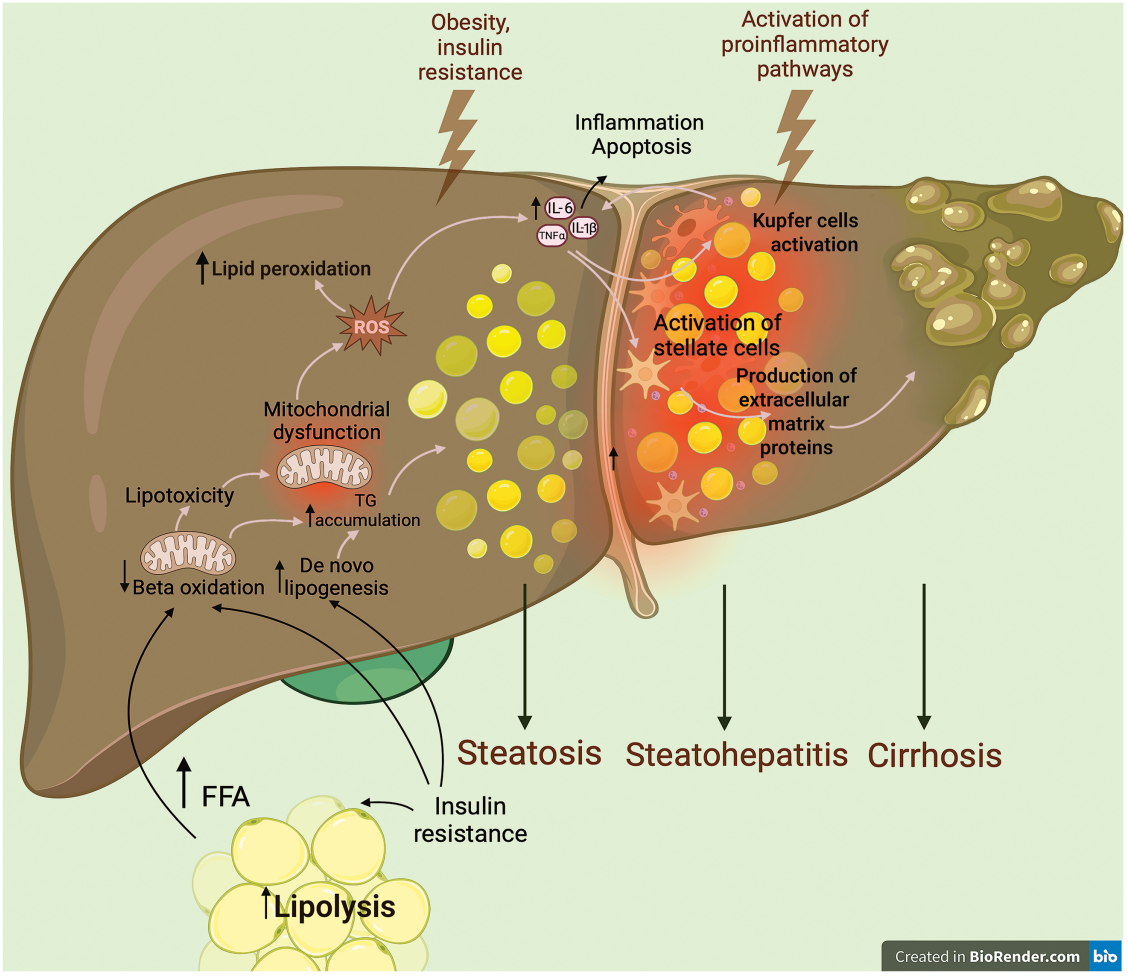

Figure 1: The main pathogenetic stages of NAFLD. In the initial phase, the presence of insulin resistance results in the influx of excessive free fatty acids into the liver. Concurrently, insulin triggers *de novo* lipogenesis and suppresses beta-oxidation of fatty acids. The interplay of these phenomena culminates in the induction of mitochondrial dysfunction, lipotoxicity, and lipid accumulation within the cytoplasm of hepatocytes. At the second stage, the development of a full-fledged inflammatory process accompanied by increased production of proinflammatory cytokines and activation of Kupffer cells—resident liver macrophages—is initiated. This contributes to the maintenance of the vicious circle of inflammation and apoptosis of hepatocytes. Consequently, the proinflammatory microenvironment contributes to the activation of Ito cells, manifesting as an increased production of extracellular matrix proteins. This, in turn, results in the replacement of functional liver tissue by connective tissue. FFA—free fatty acids; TG—triglycerides; ROS—reactive oxygen species. Created in BioRender.com

2 A Key Role of PPAR Receptors in the Hepatoprotective Effect of OEA

It is well-known that members of the PPARs family function as transcription factors that are induced by ligands [34]. To date, three PPAR isoforms have been identified: PPAR-α, PPAR-β/δ, and PPAR-γ [35]. The distribution of PPARs isoforms in tissues is diverse: PPAR-α is abundantly expressed in metabolically active tissues, PPAR-β/δ is expressed ubiquitously, and PPAR-γ is predominantly found in adipose tissue and immune cells [36,37]. The multiple functions of PPARs are determined by transcriptional activity; receptors in their activated form are able to modulate the expression of a large number of target genes. PPAR target genes include enzymes of cholesterol metabolism, fat synthesis and breakdown, homeostasis enzymes, as

well as genes involved in the development of obesity and inflammation [38]. It should be noted that the regulation of gene expression by PPARs can be both positive and negative, manifested in the ability to inhibit gene expression [39].

Among all the above-mentioned subtypes of PPARs, the PPAR-α receptor contributes most importantly to the regulation of metabolic pathways in the liver. These metabolic pathways include: triglyceride synthesis and cleavage; lipoprotein and apoprotein metabolism; gluconeogenesis; bile acid metabolism; microsomal, peroxisomal, and mitochondrial fatty acids (FA) oxidation; FA binding and activation; FA elongation and desaturation and other related pathways [40]. Key regulatory enzymes that are targets of PPAR-α include FA beta-oxidation enzymes such as acyl-Coenzyme A (CoA) dehydrogenase and acyl-CoA oxidase 1 (ACOX1) [41]. PPAR-α activation enhances FA beta-oxidation, subsequent adenosine triphosphate (ATP) production, and ketogenesis, indicating a dominant role of PPAR-α in the control of FA oxidation and energy production under nutrient-deficient conditions [42].

To date, there are numerous studies showing that PPAR-α activation helps in liver damage. It has been demonstrated that prolonged PPAR-α activation can ameliorate the course of NAFLD by reducing lipotoxicity [43,44], oxidative stress, and ROS generation [40]. PPAR-α signaling has been shown to reduce the severity of hyperlipidemia and fatty liver degeneration by preventing mitochondrial and ER stress [45]. In animal studies, PPAR-α agonists stopped the development of liver fibrosis [46,47]. Gene expression of hepatic PPAR-α negatively correlates with the severity of NASH and fibrosis in humans [48], confirming the critical importance of hepatic PPAR-α for lipid homeostasis [49].

PPAR-β/δ also plays a critical role in liver metabolism, where it is mainly expressed in hepatocytes, Kupffer cells, sinusoidal endothelial cells, and human stellate cells (HSCs) [50]. Although the functions of PPAR-α and PPAR-β/δ in the liver appear to be similar, PPAR-β/δ cannot compensate for all the functions of PPAR-α, as shown in PPAR-α knockout experiments [51]. In addition, PPAR-β/δ also plays an important role in the modulation of inflammation. Ligands that bind to PPAR-β/δ induce the initiation of anti-inflammatory signals in liver-resident macrophages, and Kupffer cells [52]. However, the more detailed mechanism of the anti-inflammatory role of PPAR-β/δ is not yet fully understood.

The primary localization and functionality of PPAR-γ is exclusively concentrated in adipose tissue [53]. However, in individuals with NAFLD, PPAR-γ expression levels in the liver are significantly elevated [54], suggesting that PPAR-γ also has intrahepatic functions. PPAR-γ regulates several target genes in adipocytes that are responsible for lipid uptake and storage, production of inflammatory cytokines, and secretion of adipokines that increase insulin sensitivity [55]. In the liver, PPAR-γ has also been shown to stimulate free fatty acid uptake through the expression of fatty acid synthase (FASN) and is involved in activating the conversion of pyruvate to fatty acids in hepatocytes [56]. PPAR-α and PPAR-γ regulate lipid metabolism in opposite ways, but due to their localization in different tissues, PPAR-γ, although promoting fat accumulation in the liver, has a beneficial effect on NAFLD by reducing insulin resistance [38].

Currently, many potential endogenous ligands for PPAR-α have been described, including the aforementioned group of NAE, as well as FAs themselves and some of their derivatives, such as eicosanoids [57]. Also, these receptors can be activated by pharmacological agents used in the therapy of diabetes mellitus [58] and atherosclerosis [59], which indicates the important role of PPAR-α in the normalization of metabolic processes closely related to liver function. The anti-inflammatory properties of PPAR-α agonists are due to their ability to limit cytokine expression in the liver through different transcriptional mechanisms and targets [60]. Thus, the presence of multidirectional transcriptional activity for this receptor makes its agonists, including OEA, promising pharmacological targets for complex therapy of NAFLD.

Recent studies have shown that fenofibrate, a PPAR-α agonist, lowers lipid levels in an mTOR-independent manner by activating autophagy and transcription factors [61]. Unfortunately, fenofibrate has minimal activity in lowering blood glucose and regulating insulin sensitivity [62]. Pemafibrate, a newer and more specific PPAR-α modulator, has shown better efficacy than its predecessor both in preclinical models of NAFLD and in humans with diabetes and dyslipidemia [63]. However, all PPAR-α agonists show greater therapeutic benefit when combined with PPAR-γ agonists than when used alone [64]. At the same time, some researchers believe that pan-PPAR agonism appears to be necessary to achieve significant results on histologic endpoints in NAFLD treatment [65]. Therefore, OEA with activity against both PPAR-α and PPAR-γ, as shown in our previous work [66], is a promising candidate for the treatment of NAFLD.

The selective PPAR-β/δ agonist Seladelpar demonstrated improved insulin sensitivity in steatohepatitis in patients with NASH [67]. However, clinical trials of Seladelpar were prematurely terminated due to alarming findings of portal inflammation as well as hepatitis and localized biliary abnormalities at the end of treatment in patients with NASH [68].

The PPAR-α potential as a target for the treatment and prevention of NAFLD is clear due to its functional placement at the interface of lipid metabolism, energy balance, and inflammation. In the following, this review will discuss the various mechanisms, mainly PPAR-α-dependent, that enable OEA may reduce hepatocellular damage and ameliorate the progression of NAFLD.

3 OEA Reduces the Inflammatory Response in the Liver and Total Oxidative Stress

It is generally accepted that the inflammatory response and the emergence of general oxidative stress play a key role in the pathophysiology of acute liver injury [69]. In the process of liver injury, immune system cells produce a variety of proinflammatory cytokines, which contribute to further activation of immune cells, the development of a vicious circle of inflammation, hepatocyte damage, and eventually remodeling of the extracellular matrix and fibrosis development. At last, because overexpression of proinflammatory markers increases insulin resistance, it is critical to the pathophysiology of NAFLD.

It has been proven that exogenous administration of OEA through agonism with PPAR-α, is able to suppress the production of pro-inflammatory factors in the liver. In this instance, the drop in cytokine production was also accompanied by a rise in PPAR-α expression and a decrease in nuclear factor NF-κB and the other pro-inflammatory factor activator protein 1 (AP-1). Mechanisms by which PPAR-α can inhibit the transcriptional activity of these factors have also been described [70] thereby suppressing the production of pro-inflammatory cytokines [71]. That is, by reducing the expression level of NF-κB, a key mediator of the inflammatory response, the production of inflammatory factors such as TNFα, IL-1β, and IL-6 is ultimately suppressed. In a study by Payahoo et al., it was demonstrated that OEA treatment leads to a reduction in inflammation in obese patients by decreasing serum IL-6 and TNFα concentrations [72]. In a study by Yang et al., OEA inhibited lipopolysaccharide (LPS)-induced activation of NF-κB, AP-1, and signal transducer and activator of transcription 3 (STAT-3) [73]. In the same study, OEA significantly reduced the expression of TNFα, IL-1β, and IL-6 in the liver, brain, and spleen of mice treated with LPS. In a study by Tutunchi et al., a significant decrease in the expression levels of NF-κB and IL-6 was observed in obese and NASH patients after OEA supplementation with a simultaneous increase in the level of the anti-inflammatory cytokine IL-10. In a randomized clinical trial, treatment with OEA along with calorie restriction reduced systemic inflammatory factors in obese patients with NAFLD [74]. In the study by Hu et al., OEA markedly reduced the mRNA expression of pro-inflammatory factors including TNFα, IL-6, MCP1, and RANTES. In addition, OEA decreased IL-1β expression in the liver and plasma [75]. Also, in the same study, it was shown that the targeted inhibition of the inflammasome NLRP3 may underlie the anti-inflammatory action of OEA. In a mouse model of liver inflammation induced by LPS/D-Gal, OEA protected against acute liver injury through

inhibition of NLRP3 inflammasome components. Given the fact that NLRP3 can be activated in response to increased expression of pro-inflammatory factors [76], and its activation is also a contributing factor to the pathogenesis of NAFLD [77], the effect of OEA on this signaling pathway may also depend on PPAR-α.

In the pathogenesis of NAFLD, inflammation is intimately connected with the development of oxidative stress the production of free radicals, and the activation of lipid peroxidation. OEA works as an antioxidant by interacting with PPAR-α, it can activate several links of the antioxidant defense system at once.

OEA, by enhancing PPAR-α signaling, inhibited LPS-induced oxidative stress; this effect was accompanied by a decrease in ROS production in obese humans [78]. Moreover, Giudetti et al., in an animal model of high-fat diet (HFD)-induced liver injury, demonstrated that OEA concurrently boosted the activity of antioxidant enzymes such as glutathione peroxidase (GSH-Px), catalase, and superoxide dismutase (SOD) in addition to lowering the formation of ROS [79]. A 12-week administration of OEA to subjects with obesity-associated NAFLD resulted in a decrease in markers of lipid peroxidation, such as malondialdehyde MDA and oxidized low-density lipoprotein (ox-LDL), in serum. Concurrently, the study observed an increase in total antioxidant capacity (TAC) and superoxide dismutase (SOD) serum levels [78]. OEA also reduced the hepatic MDA levels while boosting the activities of glutathione peroxidase (GSH-PX) and SOD in a mouse model of acute liver damage caused by LPS/D-Gal. This effect was accompanied by normalization of the levels of antioxidant factors Nrf-2 and HO-1, which were reduced during inflammation, indicating that OEA has several mechanisms for antioxidant activity (Fig. 2) [75].

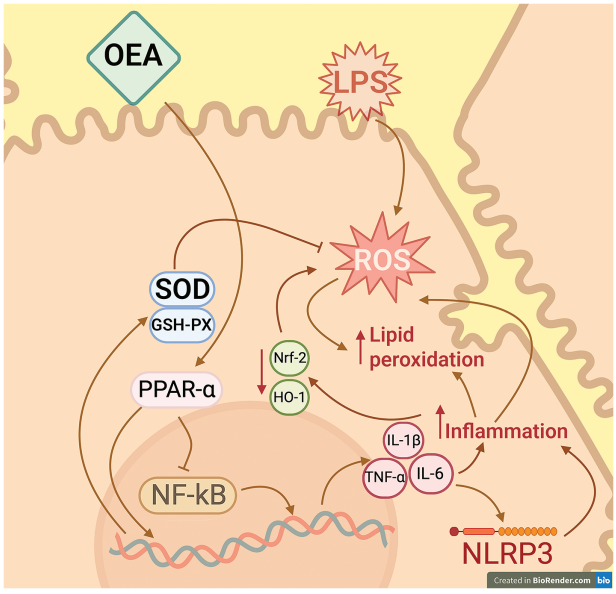

Figure 2: Effect of OEA on the development of inflammation and oxidative stress in hepatocytes. OEA has been shown to act as an agonist for the peroxisome proliferator-activated receptor alpha (PPAR-α). Activation of this receptor results in its function as a transcription regulator, capable of inducing or repressing the transcription of target genes. Notably, through a process known as transrepression, PPAR-α functions to impede the nuclear factor NF-κB, a pivotal component in inflammatory responses that plays a crucial role in the transcription of inflammatory cytokine genes. In the absence of OEA, when liver cells are exposed to LPS as an inflammation-inducing agent, NF-κB-dependent pathways are activated, which promotes inflammation and, consequently, oxidative stress. OEA has been shown to mitigate these effects by inhibiting the NF-κB pathway and by activating the transcription of antioxidant defense system enzymes, a process that is dependent on the activation of PPAR-α. SOD—superoxide dismutase; GSH-PX—glutathione peroxidase, NF-κB—nuclear factor κB; LPS—lipopolysaccharide; ROS—reactive oxygen species; NRF2—nuclear factor erythroid 2-related factor 2; HO-1—heme-oxygenase 1. Created in BioRender.com

4 OEA Prevents Hepatocyte Apoptosis and Also Regulates the Activity of Some Types of Non-Parenchymal Liver Cells

Reduced activity of antioxidant systems caused by the development of inflammation usually leads to irreversible damage to critical cellular structures and, as a consequence, to cell death [80]. The pathogenesis of NAFLD, in addition to the above factors, is based on excessive intake of FA into the liver and overload of hepatocytes with FA exceeding their enzymatic capacity. As a result, unmetabolized (unoxidized) FAs accumulate in hepatocytes, lipotoxicity, fatty degeneration, and subsequent apoptosis.

During the development of liver inflammation and oxidative stress, various signaling molecules activate resident liver macrophages (Kupffer cells) [81]. These cells acquire a pro-inflammatory phenotype (M1) and secondarily produce more and more pro-inflammatory cytokines such as TNFα and IL-6 [82], which promotes a vicious cycle of inflammation and further damage to hepatocytes [83]. In addition, being one of the main sources of ROS, activated macrophages contribute to the oxidative stress that develops in NAFLD [84,85]. Thus, the combination of increased ROS production, loss of antioxidant activity, activation of liver macrophages, and, as a consequence, increased lipid peroxidation (LPO) leads to the initiation of the apoptosis program in hepatocytes [86].

OEA administration can prevent cell damage by reducing the activity of apoptosis signaling pathways and inhibiting the expression of pro-apoptotic markers. A study by Hu et al. showed that OEA significantly reduced the levels of hepatocyte damage indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH), as well as the synthesis of Bax, Bcl-2 and cleaved caspase-3. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining also confirmed OEA-mediated attenuation of hepatocyte apoptosis. Moreover, these processes occurred against the background of a significant increase in PPAR-α expression in the liver [75]. Hu et al. also revealed a pattern of increased activated Kupffer cells, which was accompanied by an increased hepatic expression of proinflammatory factors such as TNFα, IL-6, MCP1, and RANTES. OEA therapy against the background of increased hepatic levels of PPAR-α decreased both the number of activated Kupffer cells and the expression of proinflammatory cytokines.

The same study demonstrated the ability of OEA to suppress the expression of F4/80, which is a well-known marker of activated macrophages. These results suggest that OEA via PPAR-α can modulate immune cell activity in the liver, reducing inflammation and hepatocyte damage. In addition, OEA administration leads to the polarization of macrophages towards an anti-inflammatory M2 phenotype. Studies on BV2 microglia culture showed that OEA shifts the balance towards the M2 phenotype in LPS-induced inflammation, accompanied by downregulation of M1 phenotype markers (Iba-1, CD16, CD32) and upregulation of M2 phenotype markers (CD206, Arg, YM1) [87].

In an animal model of middle cerebral artery occlusion, similar changes in M1- and M2-specific markers were observed with OEA therapy; however, PPAR-α knockout mice did not show similar effects, suggesting a PPAR-α-dependent polarization mechanism [87]. Furthermore, in the THP-1 macrophage cell line, OEA supplementation promoted the expression of M2 phenotype macrophage markers (CD206 and TGFβ), while the expression of M1 markers (iNOS) was reduced. At the same time, blocking PPAR-α significantly reduced the expression of M2 markers [88].

Ito cells, or hepatic stellate cells, are also crucial for the pathophysiology of NASH and subsequent liver fibrosis. In the normal state, Ito cells function as antigen-presenting cells in the liver and are also responsible for storing vitamin A [89]. In chronic liver inflammation, these cells are activated, accompanied by enhanced production of extracellular matrix proteins, which underlies the pathogenesis of fibrotic liver injury. The

profibrotic functions of activated Ito cells are based on the TGF-B1/Smad pathway, which is triggered by proinflammatory factors [90,91].

OEA, like other PPAR-α agonists in liver fibrosis models, can inhibit Smad protein phosphorylation and reduce TGFβ1 transcription, thereby inhibiting the proinflammatory JNK p38 and MAPK pathways. Numerous studies have shown that by preventing the activation of hepatic stellate cells, PPAR-α activation can reduce liver fibrosis associated with NAFLD [92,93]. In a study by Chen et al., OEA slowed the progression of liver fibrosis in mouse models by inhibiting collagen matrix, α-SMA (alpha-smooth muscle actin), and hepatic stellate cell activation, as well as genes involved in extracellular matrix remodeling and inflammation, including TIMP1, MMP2, and MMP9. *In vitro* studies showed that OEA inhibited the TGFβ1 pathway by suppressing phosphorylation of factor Smad2/3, α-SMA expression, and inhibiting the transformation of stellate cells into myofibroblasts. In addition, OEA administration did not induce antifibrotic effects in PPAR-α mutant animals, indicating that PPAR-α activation is the mechanism underlying all the above-mentioned actions of OEA *in vivo* and *in vitro* [94]. In the same study, the antifibrotic effect of OEA was accompanied by a decrease in serum levels of ALT, AST, and hepatic triglycerides (TGs), indicating an overall improvement in the metabolic profile and a reduction in hepatocyte damage.

In combination with anti-inflammatory activity, these effects of OEA allow us to speak about its effectiveness in complex therapy both at the initial stages of NAFLD and at the progression of the disease and the beginning of fibrotic processes.

5 Hepatoprotective Effects of OEA Caused by Regulation of Lipid Metabolism in the Liver

Numerous experimental studies confirm that OEA, via its association with PPAR-α, impacts multiple hepatic lipid metabolic pathways [95] that are crucial in the development of NAFLD [96]. A study by Drover et al. showed that the expression of PPAR receptors, including PPAR-α, was significantly increased in CD36-null mice [97]. Perhaps the regulation of the uptake of FAs by liver cells is also associated with the activation of PPAR, and exogenous activation of PPAR promotes the reduction of FA transport into hepatocytes and influences the pathogenesis of the development of NAFLD [40].

The ability of OEA to activate lipolysis in the liver by enhancing the expression of beta-oxidation enzymes has been repeatedly demonstrated in experimental studies in animal models. A study by Li et al. demonstrated that OEA in an HFD rat model stimulated β-lipid oxidation and simultaneously inhibited *de novo* lipogenesis [98]. OEA treatment markedly boosted PPAR-α and carnitine palmitoyltransferase I (CPT-1) mRNA levels and decreased sterol regulatory element binding protein 1c (SREBP-1c) and stearoyl-CoA desaturase-1 (SCD-1) expression, indicating that OEA may alter fatty acid metabolism in rats on a normal diet as well as in rats on an HFD [99]. A study of SCD-1 enzyme activity in the liver showed that OEA, by inhibiting SCD-1 activity, reduced the desaturation index in an HFD model. Cells derived from PPAR-α null mice did not exhibit the lipolytic effects of OEA, confirming the critical role of OEA in FAs metabolism by activating PPAR-α [100].

A study by Pan et al. showed that OEA inhibited triacylglycerol synthesis and secretion, apolipoprotein B (apoB) secretion, as well as microsomal triglyceride transfer protein (MTP) expression and activity in human hepatoma cell cultures Huh-7 and HepG2. Through PPAR-α-dependent processes, OEA also decreased lipoprotein secretion, glycerolipid production, and MTP expression in hepatocyte culture. Moreover, PPAR-α-deficient hepatocytes did not respond to exogenous OEA, suggesting a role for this receptor also in lipoprotein metabolism [100]. Taking into account the above-mentioned lipolytic activity of PPAR-α, we can conclude that OEA promotes the FAs redirection to a beta-oxidation pathway by inhibiting lipoprotein assembly in the liver.

OEA treatment has previously been shown to enhance ketone body production in rats [101]. Misto et al. then detailed the mechanism of OEA-mediated enhancement of fasting-induced hepatic ketogenesis by activating PPAR-α. Their findings indicate that histamine is secreted by extrahepatic mast cells in response to fasting. Histamine enters the liver via the portal vein, where it interacts with PPAR-α to activate G-protein coupled H1 receptors, cause local endogenous OEA production, and stimulate the transcription of ketogenesis enzymes genes including Acat-1 and Hmgcs-2. In the meantime, starvation-induced ketogenesis has been significantly reduced due to interfering genetic or pharmaceutical modifications such as mast cell eradication, the ablation of histamine or OEA synthesizing enzymes, and the H1 blockade. These results imply that endogenous histamine activates the H1 receptor and PPAR-α to promote OEA production in the liver [102]. Further Lin et al. showed that alimentary-induced obesity disrupts this mechanism and fasting does not cause histamine release and cannot trigger biosynthesis of hepatic OEA (Fig. 3) [103].

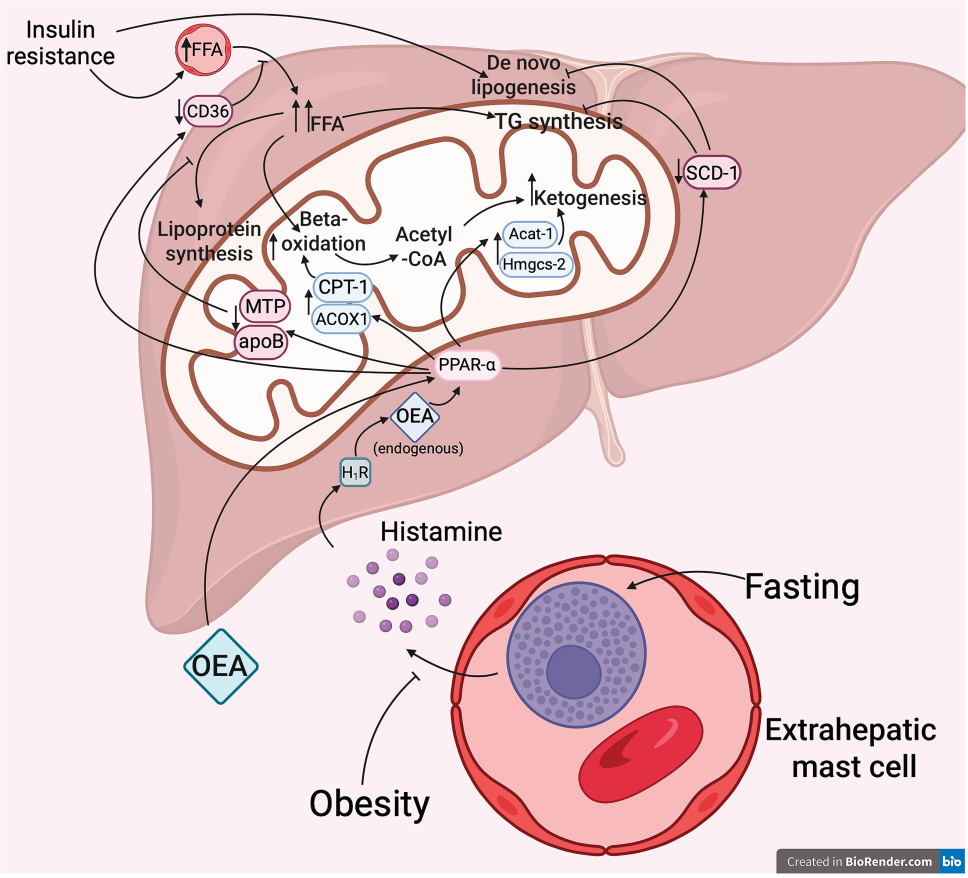

Figure 3: Effects of OEA on lipid metabolism in the liver. Fasting has been demonstrated to promote the release of histamine by extrahepatic mast cells. This, in turn, has been shown to interact with histamine 1 receptors (H1R) in the liver, thereby promoting the formation of endogenous OEA. The subsequent formation of endogenous OEA, in turn, activates the transcription of key enzymes involved in fatty acid beta-oxidation and ketogenesis, a process that is dependent on the presence of a specific mechanism that involves PPAR-α. Concurrently, the activation of PPAR-α results in a reduction in hepatic lipogenesis and a limitation of free fatty acid flux. Consequently, the exogenous administration of OEA may serve as a preventative measure against mitochondrial overload in conditions of insulin resistance and obesity, particularly when the endogenous production of OEA is impaired. ACOX1—acyl-Coenzyme A oxidase I; CPT-I—carnitine palmitoyltransferase I; Acat-1—acetyl-CoA acetyltransferase I; Hmgcs-2—hydroxymethylglutaryl-CoA synthase-2; SCD-1—stearoyl-CoA desaturase-1; MTP—microsomal triglyceride transfer protein; apoB—apolipoprotein B; FFA—free fatty acids; TG—triglycerides. Created in BioRender.com

Taken together, the results of these studies suggest that impaired mobilization of endogenous OEA in the liver caused by a high-fat diet may contribute to the development of NAFLD due to impaired lipid utilization. In this case, administration of exogenous OEA may contribute to the correction of these metabolic disorders.

6 Other Potential Mechanisms of Hepato-Protective Effect of OEA, Which May Be Mediated by Interaction with PPAR Receptors

6.1 OEA Regulates PCSK9 Protein Expression, Contributing to the Reduction of Cholesterol and LDL Levels

The low-density lipoprotein (LDL) receptor is naturally inhibited by the proprotein convertase subtilisin/kexin type 9 (PCSK9). Whether it is secreted or cellular, mature PCSK9 inhibits low-density lipoprotein receptor (LDLr) recycling by binding to its domain and promoting further degradation, much like a chaperone. Therefore, by decreasing LDL synthesis and resulting in hypercholesterolemia, overexpression of PCSK9 strongly contributes to the pathogenesis of NAFLD [104]. Moreover, insulin can stimulate PCSK9 transcription [105], supporting the link between liver pathology and problems with the metabolism of glucose and cholesterol. Conversely, a defect in PCSK9 decreases plasma cholesterol levels and offers protection against heart disease. Therefore, combination illnesses that do not react well to conventional therapy can be treated with drugs that inhibit the synthesis, processing, or binding of PCSK9 to LDL.

It has been demonstrated that PPAR-α agonists, which lower cholesterol, decrease PCSK9 mRNA and protein in the liver of mice. Fibrate, a traditional PPAR-α activator, affects the expression of many genes, which reduces macrophage activation [106], inhibits the growth of vascular smooth muscle cells [107], and speeds up the macrophages' clearance of lipids [108]. By modifying the activity of its promoter, fibrates have been shown in numerous studies to be capable of controlling transcription factors including PPAR-α and sterol regulatory element-binding proteins (SREBP-1/2) [109,110]. Therefore, by binding to the appropriate locations on the PCSK9 gene promoter, PPAR-α activation suppresses PCSK9 gene expression.

Additionally, the study by Kourimate et al. showed that furin and PC5/6A, which are in charge of PCSK9's proteolytic inactivation in a PPAR-α-dependent way, are positively regulated by fibrates. Therefore, posttranslational downregulation of PCSK9 also takes place [109]. Additionally, by triggering vascular endothelial lipoprotein lipase, which includes furin and PC5/6A, PPAR-α activation can lower the amount of lipids in plasma [111]. As per Jin et al., cleavage and inhibition of endothelial synthase triggered by furin and PC5/6A results in elevated amounts of antiatherogenic high-density lipoproteins (HDL-C) [112].

OEA may also help LDLr levels return to normal via a PPAR-dependent mechanism. By upregulating LDLr expression, activation of PPAR-α would improve cellular absorption of cholesterol and hence lower plasma cholesterol levels. Accordingly, exogenous OEA-mediated regulation of PPAR-α may have a complex impact on cholesterol metabolism and help lower hypercholesterolemia. It's also critical to emphasize that fibrates do not have the same anorexigenic effects as OEA because they concurrently boost the expression of the lipolysis and lipogenesis enzymes [113]. For NAFLD linked to obesity and hypercholesterolemia, OEA is a more attractive therapeutic target.

6.2 OEA Stimulates GLP-1 Secretion, Contributing to the Reduction of Insulin Resistance

Several subtypes of PPARs are known to be involved in the regulation of glucose metabolism. The most studied modulators of carbohydrate metabolism are considered to be thiazolidinediones, which are pharmacological activators of PPAR-γ and are used for the treatment of type 2 diabetes mellitus (T2DM), helping to reduce insulin resistance [114].

In several studies, activation of PPAR-γ by drugs from the thiazolidinedione group led to a reduction in the intensity of inflammation in NAFLD [115,116], as well as improved insulin sensitivity in the liver [117].

However, studies conducted in mouse models of insulin resistance have shown that PPAR-α activation also improves glucose homeostasis by decreasing endogenous glucose production, reducing lipid content in adipose and non-adipose tissues, and increasing insulin sensitivity [118,119], its overexpression in mouse models of obesity improved insulin sensitivity [120].

In addition to its known agonism with PPAR-α, OEA also has the ability to bind to G-protein-coupled receptor 119 (GPR119), which is found in intestinal L-cells and pancreatic β-cells [121]. Activation of GPR119 is also a promising strategy in the therapy of NAFLD [122].

Other GPR119 agonists have been shown to increase the release of glucagon-like peptide-1 (GLP-1) [123,124]. GLP-1 regulates glucose metabolism by significantly increasing insulin sensitivity and glucose uptake in insulin-dependent tissues [125]. It has been suggested that GLP-1, in addition to enhancing glucose uptake, may also reduce insulin resistance [126]. Thus, GLP-1 agonists are a promising pharmacological target in the comprehensive therapy of NAFLD [127].

Thus, OEA can potentially modulate glucose homeostasis by interacting with several receptor targets at once.

6.3 OEA through PPAR-α Activation Can Enhance the Expression of Thermogenesis Proteins UCP1 and UCP2

Activation of uncoupling proteins (UCP) family thermogenesis proteins is another strategy to reduce inflammation and modulate immune cells in liver injury. UCP1-deficient mice exhibited succinate receptor 1 (SUCNR1)-dependent activation of stellate cells and macrophages in the liver, which promoted inflammation [128]. It has been shown that one aspect of the anorexigenic action of OEA may be the enhancement of thermogenesis in adipose tissue, including through UCP1 activation [129].

Treatment of OEA in obese and NAFLD patients resulted in a marked increase in the expression levels of PPAR-α, UCP1, and UCP2 genes in peripheral blood mononuclear cells (PBMCs) in a triple-blind placebo-controlled randomized clinical trial [130]. In addition, when comparing the OEA group with the placebo group, a decrease in anthropometric parameters, energy, and carbohydrate intake, and glycemic parameters other than hemoglobin A1c concentration was observed. When taking OEA, there was also a significant decrease in TG, ALT, AST, and serum ALT/AST index, as well as an increase in HDL levels. In animal models of alimentary-induced obesity, OEA administration led to an increase in the level of hepatic PPAR-α and UCP2 [131], and even in the adipose tissue of rats without obesity [101]. In addition, lipolysis enzymes were activated, but not in PPAR-α null animals.

Thus, OEA promotes the expression of PPAR-α, UCP1, and UCP2 genes in PBMCs during the treatment of NAFLD, which is reflected in increased energy expenditure, decreased *de novo* fat synthesis, inflammation, and overall weight loss.

6.4 OEA Reduces Hepatic Lipid Accumulation and Apoptosis through Enhanced Adiponectin Production

An important aspect of the pathogenesis of nonalcoholic fatty liver disease is adipokine regulation. The most common adipokine that has been shown to directly reduce inflammation and insulin resistance while also controlling hepatic lipid and glucose metabolism is adiponectin [132]. Adiponectin expression is directly proportional to HDL levels and inversely linked with cardiovascular risk factors [133,134].

According to certain theories, adiponectin may both promote FAs beta-oxidation and prevent *de novo* lipogenesis, which would result in the metabolic consequences listed above [135]. Furthermore, upregulation

of adiponectin receptor expression in adipose tissue can result from agonist-induced activation of PPAR-α. On the other hand, serum adiponectin rises in response to PPAR-γ activation [136]. Reduced inflammation and enhanced insulin sensitivity accompanied both outcomes. Consequently, medication for metabolic diseases targeted at raising adiponectin levels may be essential to reducing NAFLD progression [137,138].

Apart from its metabolic functions, adiponectin possesses a range of anti-apoptotic properties. Adiponectin inhibited diabetic apoptosis in an animal model of diabetes *in vivo* and *in vitro* using a cardiomyocyte cell culture H9c2 by suppressing the TLR4/NF-κB signaling pathway [139]. Adiponectin reduced ER-stress-driven apoptosis in adipose tissue in a mouse model of tunicamycin-induced ER stress; this effect was mediated through interaction with the PPAR-α receptor. Adiponectin treatment was associated with an increase in the anti-apoptotic protein Bcl-2 and a decrease in the proapoptotic markers Bax, Chop, GRP78, ATF2, cleaved caspase 3/9, and Apaf-1 [140]. Lastly, another possible mechanism of OEA's hypocholesterolemic action may be adiponectin, which has antiatherosclerotic activity of its own. Experimental evidence has demonstrated its capacity to inhibit monocyte adhesion to endothelial cells by decreasing TNF-α-induced endothelial adhesion molecules. Additionally, it has been shown to inhibit macrophage conversion into foam cells and prevent endothelial cell activation [141]. Moreover, adiponectin caused endothelial cells to produce more nitric oxide (NO) and lower C-reactive protein (CRP) [142]. Additionally, it suppressed the generation of ROS and cell proliferation brought on by low-density lipoprotein (LDL) oxidase during the development of atherosclerotic plaque [143].

Thus, OEA, being an agonist of PPAR-α, upregulating adiponectin, may have a complex effect on several pathogenetic factors in the development of NAFLD.

7 Bioavailability and Side Effects of OEA

In vivo, studies of the beneficial effects of OEAs have focused primarily on intraperitoneal or subcutaneous administration of the drug. However, oral administration is considered to be the most convenient route of administration for the patient, which involves additional metabolic events that should be discussed in this review. The main disadvantage of fatty acid ethanolamides as a class of therapeutic agents is their poor metabolic stability *in vivo* due to their rapid hydrolysis by a number of hydrolytic enzymes such as fatty acid amide hydrolase (FAAH), N-acylethanolamic acid amidase (NAAA), and monoacylglycerol lipase (MAGL) [144]. Therefore, it is necessary to take these metabolic characteristics into account when calculating the dosage of the drug. It has also been found that significant hypophagic effects with oral administration of OEA occur only at the highest doses (100 and 200 mg/kg) [145–147]. In a study of the bioavailability of oral OEA, it was found that the drug is actively degraded along the gastrointestinal tract, resulting in only 0.48% of the administered OEA dose being converted unchanged into tissues. The ratio of intact OEA to hydrolyzed OEA decreases along the gastrointestinal tract, indicating that OEA is gradually catabolized [147].

In a randomized, double-blind, placebo-controlled study in humans, OEA at doses of 300 and 600 mg/day also showed significant anti-inflammatory efficacy, but side effects such as nausea, vomiting, dyspepsia, and headache were noted. It should be noted, however, that no statistically significant differences in reported adverse events were found between the different groups (treatment and placebo) [148].

In general, to expand the use of OEA in medical practice, it is necessary to search for new approaches, one of which may be to reduce the degradation of OEA through the possible development of FAAH inhibitors. On the other hand, an alternative strategy may be the development of OEA analogues that are more stable for enzymatic inactivation.

8 Conclusion

It is well known that the PPAR-α receptor regulates the expression of many genes that are crucial in the pathogenesis of nonalcoholic fatty liver disease. One of the main mechanisms responsible for the hepatoprotective effect of OEA is probably an agonistic action on the PPAR-α receptor. Thus, OEA may be used for the treatment of NAFLD due to the growing evidence supporting its efficacy in this disease, especially if NAFLD is accompanied by obesity, hypercholesterolemia, and insulin resistance. Alo, the possibility that the effect of OEA on lipid and carbohydrate metabolism is mediated by other target receptors cannot be excluded (Fig. 4), but a thorough investigation of these pathways is still needed.

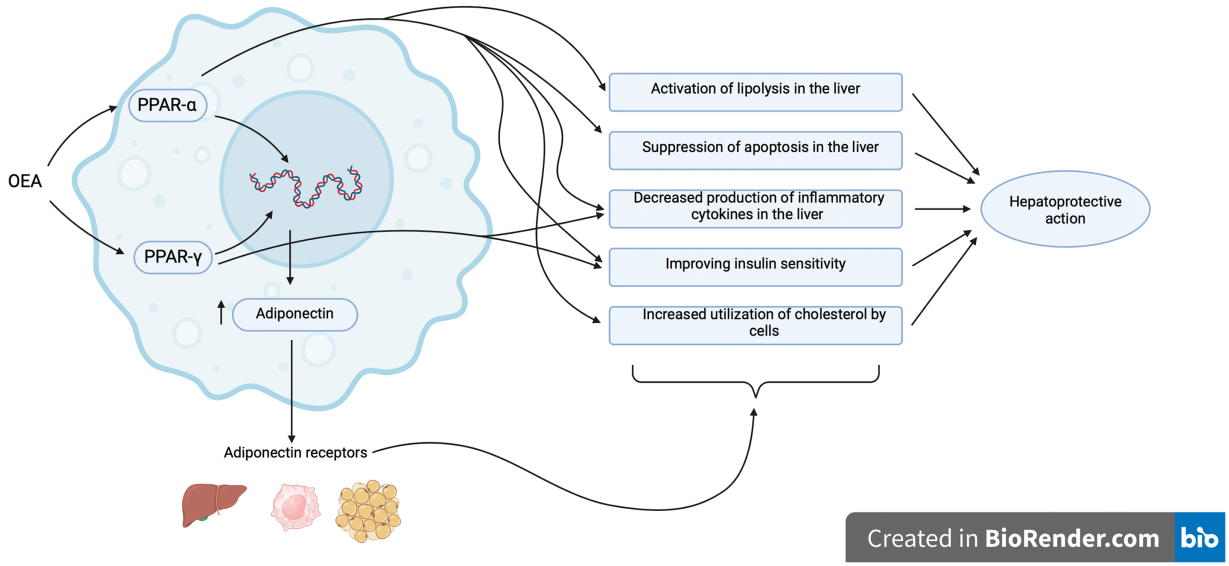

Figure 4: General scheme of receptor-mediated actions of OEA through which its hepatoprotective effect may be realized. Peroxisome proliferator-activated receptors alpha (PPAR-α) and gamma (PPAR-γ) are nuclear receptors that regulate the transcription of a wide range of target genes. The greatest contribution to the realization of the effects of OEA is made by the PPAR-α type, which is expressed to the greatest extent in the liver. However, it is noteworthy that both the PPAR-γ and G-protein-coupled receptor 119 (GPR119) may also contribute significantly to the complex hepatoprotective effect of OEA due to their ability to regulate carbohydrate metabolism. Created in BioRender.com

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