

## The Regulation of Lipid Metabolism by Targeting Opioid Receptors in Nonalcoholic Fatty Liver Disease

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### ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a well-known hepatic disease without a history of alcohol abuse, which displays a dysfunction of the normal processes of lipid synthesis and elimination in hepatocytes. The chronic endoplasmic reticulum (ER) stress caused by lipid accumulation in hepatocytes interferes with normal cellular function. In addition, inflammation has been thought to be associated with the formation of nonalcoholic steatohepatitis (NASH) and promotes the progression to hepatic fibrosis and liver cirrhosis. Opioid receptors seem to be involved in the regulation of lipid and energy metabolism. Furthermore, the pathogenesis of NAFLD can be improved by the modulation of opioid receptors to attenuate hepatic

lipid abnormalities. Thus, the identification of potential compounds by targeting opioid receptors in the improvement of NAFLD is promising.

**Key words:** Endoplasmic reticulum; Hepatic steatosis; Inflammation; Lipid metabolism; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Opioid receptor

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### INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has attracted much attention in the recent years. The clinical diagnosis and evaluation of NAFLD can be diagnosed based on physical examination, illness history, ultrasound examination and hepatic imaging<sup>[1]</sup>. NAFLD begins as lipid accumulation in the liver (hepatic steatosis), and inflammation can induce the pathogenesis of non-alcoholic steatohepatitis (NASH) that can progress to different degrees of hepatic fibrosis and hepatocellular carcinoma<sup>[2]</sup>. The pathogenesis of hepatic steatosis is related to lifestyles, dietary habits and environmental factors<sup>[3]</sup>. Additionally, genetic factors and polymorphisms also contribute to the formation of hepatic steatosis<sup>[4]</sup>. Moreover, the dysfunction of lipid metabolism in the liver is associated with NAFLD because the increased accumulation of fatty deposition in the liver can initiate a series of inflammatory responses and pathologic changes. Interestingly, opioid receptors and peptides have been thought to play a critical role in the regulation of endocrine metabolism and glucose homeostasis in the past studies<sup>[5-7]</sup>. However, the effect and mechanism of opioid receptors on the improvement of NAFLD are still unclear. Thus, the review aims to summarize how NAFLD is prevented from further progression by targeting opioid receptors to modulate the lipid metabolism.

## THE ROLE OF LIPID METABOLISM WITH INFLAMMATION IN NON-ALCOHOLIC FATTY LIVER DISEASE

Lipids consist of many molecules such as phospholipids, fatty acids, cholesterol, and triglycerides. Hepatic lipid metabolism contains fatty acid synthesis, lipoprotein synthesis and lipid oxidation<sup>[8]</sup>, which is controlled at the genomic levels by multiple regulatory proteins, metabolic enzymes, transcription factors and coregulators, such as fatty acid transport protein (FATP), carbohydrate responsive element binding protein (ChREBP), sterol regulatory element binding protein (SREBP), acetyl-CoA carboxylase (ACC), lipoprotein lipase (LPL), liver X receptor (LXR), farnesoid X receptor (FXR), and peroxisome proliferator-activated receptor (PPAR)<sup>[9]</sup>. The impairment of lipid metabolism leads to excessive lipid accumulation and triggers inflammatory responses. Some studies have shown that inflammation is involved in many metabolic diseases, including diabetes, hypertension, and NAFLD<sup>[10,11]</sup>. Inflammation disturbs cellular metabolism and function via the endoplasmic reticulum (ER) stress or oxidative stress, which induces metabolic diseases by interfering with normal glucose and lipid metabolism<sup>[12,13]</sup>. Inflammatory cytokines can attenuate the sensitivity of metabolic tissues or organs for metabolic hormones by disrupting the signal transduction of glucose and lipid metabolism<sup>[14]</sup>. Take type 2 diabetes for example, higher levels of inflammatory cytokines [e.g., Interleukin-1 beta (IL-1 $\beta$ ), Interleukin-6 (IL-6), Interleukin-18 (IL-18), C-reactive protein (CRP)], tumor necrosis factor (TNF)- $\alpha$  and low levels of adiponectin are closely associated with the induction of insulin resistance<sup>[15]</sup>. Additionally, the impairment of lipid metabolism via inflammatory response has been reported in NAFLD, and lipotoxicity-induced hepatic injury is characterized by the presence of inflammatory cells in NASH<sup>[16]</sup>. For the exploration of hepatic lipid metabolism, many animal models have been adopted for the investigation of NAFLD or NASH, including three main types of animal models: (1) Genetic animal models [e.g., SREBP-1c transgenic mice, ob/ob mice, db/db mice and phosphatase and tensin homologue deleted on chromosome 10 (PTEN) null mice]; (2) Nutritional/dietary animal models [e.g., methionine and choline deficiency (MCD) diet, high fat diet (HFD), fructose diet and atherogenic diet]; (3) Combined animal models of genetic modification and dietary factors [e.g., db/db mice fed with MCD diet and PPAR- $\alpha$  null mice fed with MCD diet]<sup>[17]</sup>. Although no animal model can completely exhibit hepatic pathophysiology of NAFLD or NASH in humans, the researchers can select the suitable animal model for their studies according to their experimental design. In summary, the dysfunction of hepatic lipid metabolism with inflammation has a great influence on the development of NAFLD.

## THE EFFECT OF OPIOID RECEPTOR ON LIPID AND ENERGY METABOLISM

Opioid receptors belong to inhibitory G protein-coupled receptors. In general, opioid receptors are classified into three subtypes, including mu ( $\mu$ )-opioid receptors (MOR), kappa ( $\kappa$ )-opioid receptors (KOR) and delta ( $\delta$ )-opioid receptors (DOR)<sup>[18]</sup>. In addition, the endogenous opioid peptides contain dynorphins, enkephalins, endorphins, endomorphins and nociceptin. The regulation of opioid receptors with opioid agonists or antagonists can affect many cellular and neuronal signal transductions. Many studies have reported that opioid receptors have beneficial effects on the regulation of glucose metabolism<sup>[19,20]</sup>. However, the regulation of opioid receptors on lipid

and energy metabolism remains obscure. Cholesterol contributes to opioid receptor signaling via two mechanisms: maintaining the entirety of lipid raft microdomains and directly facilitating opioid receptor signaling<sup>[21]</sup>. On one hand, the activation of central opioid receptors by selective agonists can stimulate appetite<sup>[22]</sup>. Interestingly, the stimulation of hypothalamic MOR promotes the preference of HFD<sup>[23]</sup>, and HFD also induces fat accumulation via the higher expression of MOR in the brain suggesting decreased release of endogenous  $\mu$ -opioid peptides<sup>[24,25]</sup>. In addition, galanin-induced feeding of HFD is specifically modulated by MOR signaling pathway in sated condition, whereas that is mediated by KOR in starvation<sup>[26]</sup>. On the other hand, endogenous opioid peptides namely enkephalin and  $\beta$ -endorphin are thought to modulate energy consumption and body weight via targeting MOR and DOR<sup>[27,28]</sup>. Obesity with increased adiposity and impaired glucose tolerance is resistant in MOR deficient (MOR $^{-/-}$ ) mice fed with HFD, which is associated with the activation of metabolic enzymes involved in fatty acid oxidation in skeletal muscle<sup>[29]</sup>. The long term administration of opioid receptor antagonists can suppress appetite and body weight gain in genetic obese animal models or obese humans<sup>[30,31]</sup>. The inhibition of opioid receptors by opioid antagonists can improve HFD-induced dyslipidemia<sup>[32]</sup>. Moreover, the antagonism of opioid receptors can also reduce fat accumulation by the stimulation of lipid utilization and the inhibition of energy intake<sup>[33,34]</sup>. Thus, the involvement of opioid receptors plays a critical role in lipid and energy metabolism.

## THE REGULATION OF OPIOID RECEPTORS IN NON-ALCOHOLIC FATTY LIVER DISEASE

So far, the role of opioid receptors in the improvement of NAFLD has not been clarified. According to the previous report, the hepatic expressions of MOR and DOR but not KOR were present in the rat indicating the distribution difference of opioid receptor subtypes<sup>[35]</sup>. Some studies have shown that opioid receptors can be potential drug targets in the improvement of liver diseases<sup>[36,37]</sup>. Opioid signal transduction is upregulated in patients with inflammatory liver disease, and some opioid-like compounds exert immunomodulatory activities to attenuate inflammation<sup>[38]</sup>. In obese patients with NAFLD, the increased expression of opioid receptors within gastric mucosa is related to the induction of inflammatory cytokines suggesting the effect of opioid receptors on the pathogenesis of NAFLD<sup>[39]</sup>. The activation of MOR with peripheral MOR agonist can prevent acute hepatic inflammation and cell death induced by hepatotoxin<sup>[40]</sup>. The overexpression of KOR in lateral hypothalamic area (LHA) can induce hepatic steatosis via parasympathetic nervous system to regulate lipid metabolism, but silencing of KOR expression can abolish hepatic steatosis<sup>[41]</sup>. The attenuation of KOR expression can decrease hepatic triglyceride synthesis in mice fed with high-energy diet (HED)<sup>[42]</sup>. In addition, melanin-concentrating hormone (MCH) increases lipid accumulation by the activation of MCH receptors through the parasympathetic nervous system, which promotes the formation of hepatic steatosis<sup>[43]</sup>. Mice lacking DOR by genetic disruption can decrease hepatic lipid content through the higher expression of adipose triglyceride lipase (ATGL) and increase thermogenesis in brown adipose tissue (BAT) involved in the activation of uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor gamma coactivator-1  $\alpha$  (PGC1 $\alpha$ ), and fibroblast growth factor 21 (FGF21)<sup>[44,45]</sup>. The higher expression of DOR in hepatocellular carcinoma (HCC) is associated with the tumor progression, which can be attenuated by the silencing of DOR<sup>[46]</sup>.

Taken together, the blockade of opioid receptors by genetic silencing or chemical antagonists provides beneficial effects for the impairment of lipid metabolism in NAFLD.

## CONCLUSION

In conclusion, the regulation of lipid metabolism by targeting opioid receptors can improve NAFLD and attenuate the progression to NASH and hepatic fibrosis. Therefore, the development of compounds for targeting opioid receptors will be beneficial for the clinical patients with NAFLD.

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