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Cannabinoid signaling and liver therapeutics

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Summary

Over the last decade, the endocannabinoid system has emerged as a pivotal mediator of acute and chronic liver injury, with the description of the role of CB1 and CB2 receptors and their endogenous lipidic ligands in various aspects of liver pathophysiology. A large number of studies have demonstrated that CB1 receptor antagonists represent an important therapeutic target, owing to beneficial effects on lipid metabolism and in light of its antifibrogenic properties. Unfortunately, the brain-penetrant CB1 antagonist rimonabant, initially approved for the management of overweight and related cardiometabolic risks, was withdrawn because of an alarming rate of mood adverse effects. However, the efficacy of peripherally-restricted CB1 antagonists with limited brain penetrance has now been validated in preclinical models of NAFLD, and beneficial effects on fibrosis and its complications are anticipated. CB2 receptor is currently considered as a promising anti-inflammatory and antifibrogenic target, although clinical development of CB2 agonists is still awaited. In this review, we highlight the latest advances on the impact of the endocannabinoid system on the key steps of chronic liver disease progression and discuss the therapeutic potential of molecules targeting cannabinoid receptors.

Introduction

The endocannabinoid system, consisting of cannabinoid receptors, endogenous cannabinoid ligands and their biosynthetic and degradative enzymes, has recently emerged as an ubiquitous system with key functions in a variety of physiological settings. Identification of the system was initiated two decades ago with the characterization of two G protein-coupled receptors, CB1 and CB2 that show high affinity for Δ^9-tetrahydrocannabinol, the main psychoactive constituent of *Cannabis sativa*. CB1 receptor drives the psychoactive properties of marijuana, and as such is highly expressed in the central nervous system, albeit also present and functional in a wide range of cells and tissues, particularly in those regulating energy balance [1]. In contrast, CB2 receptor displays a more restricted distribution, predominating in immune cells, and has been identified as a major mediator of anti-inflammatory reactions [2]. In addition to phytocannabinoids, CB receptors bind to endogenous lipidic ligands, known as endocannabinoids, among which arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG) are the most thoroughly studied. Anandamide exhibits higher affinity for CB1 over CB2 receptors, and 2-AG binds to CB1 and CB2 with similar affinities. Endocannabinoid synthesis occurs on demand from distinct cell membrane phopholipid precursors and predominantly results in paracrine effects. Clearance of anandamide follows cellular uptake by a specific transporter, prior to catabolism by fatty acid amide hydrolase (FAAH), whereas 2-AG is catabolized by monoacylglycerol lipase (MAGL) [1].

CB1 antagonism attracted considerable interest, owing to the role of CB1 receptors in the pathogenesis of obesity, via combined central orexigenic effects, lipogenic effects in adipose tissue, and reduction of energy expenditure [3]. Unfortunately, approval of the CB1 antagonist rimonabant for the management of overweight and associated co-morbidities was followed by withdrawal of the drug, because of the alarming incidence of anxiety, sleeping disorders and depression, and halted development programs of other brain penetrant CB1 antagonists. Research efforts now concentrate on the development of peripherally-restricted CB1 receptor antagonists and of CB2 agonists, devoid of mood regulatory properties.

In the liver, anandamide and 2-AG are present at substantial levels, and are degraded locally, as indicated by the high expression of FAAH and MAGL. However, under physiological conditions, the endocannabinoid system is silent, since CB1 and CB2 receptors are faintly expressed. In contrast, induction of CB receptors and/or increased levels of endocannabinoids are common features of liver injuries of diverse origins [1]. In particular, CB1 receptors are upregulated in hepatocytes, hepatic myofibroblasts and endothelial cells, whereas CB2 receptors are induced in Kupffer cells and hepatic myofibroblasts, but are not expressed by hepatocytes. Endocannabinoid levels are increased with varying patterns depending on the nature of the liver insult, with anandamide being produced mainly by Kupffer cells, and 2-AG by hepatic stellate cells and hepatocytes ([1], see Figs. 1 and 2). In keeping with these data, a large body of evidence indicates that

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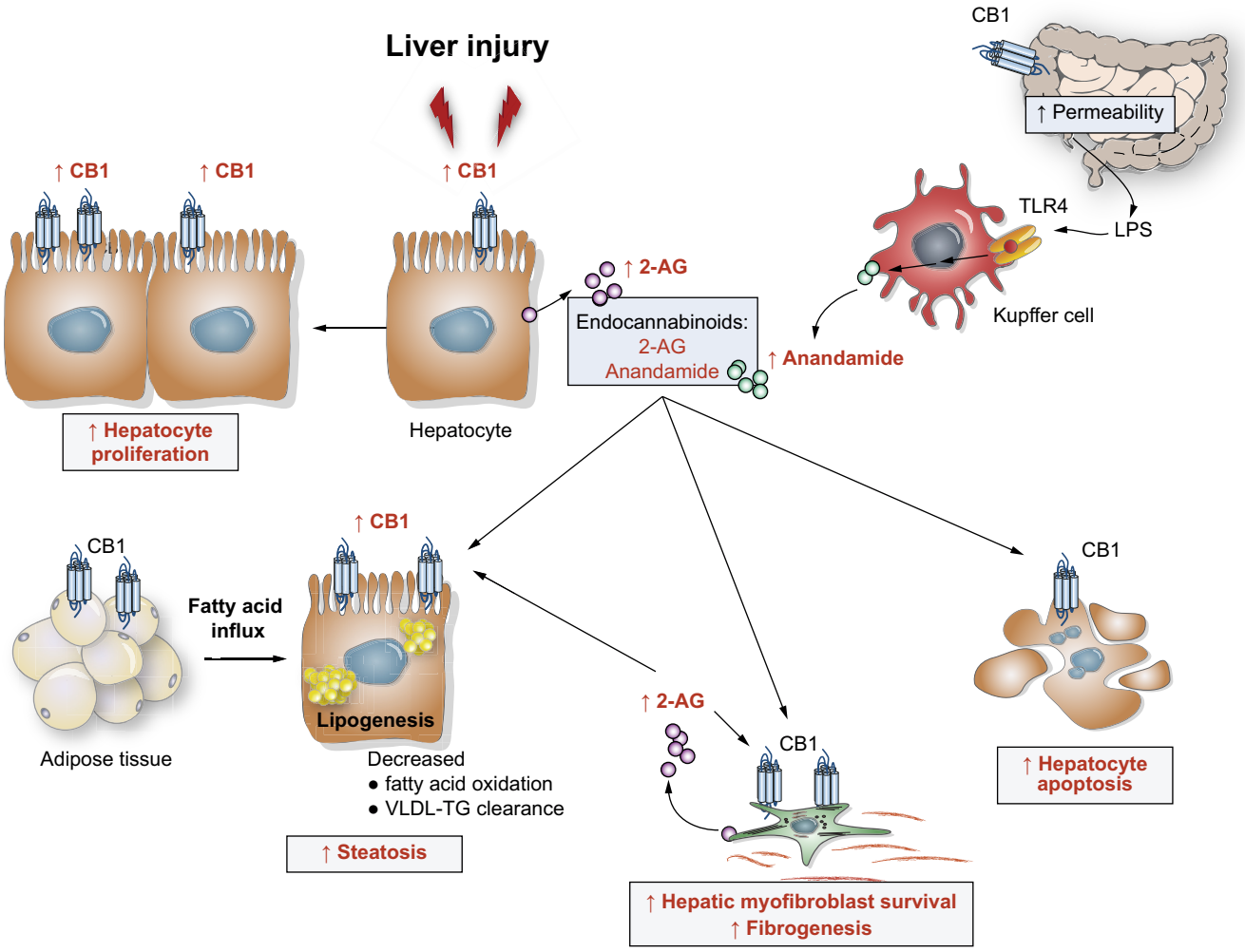

Fig. 1. Cellular targets of CB1-mediated effects during liver injury. CB1 receptors expressed in hepatocytes and hepatic myofibroblasts contribute to high fat diet and alcohol-induced steatosis, liver regeneration, and fibrogenesis. Steatogenic properties of CB1 result from hepatocyte activation of lipogenesis, reduction of fatty acid oxidation, and decreased release of TG-rich VLDL, combined to CB1-dependent release of free fatty acids from the adipose tissue. While anandamide binding to CB1 receptors drives metabolic steatosis, 2-AG is the endogenous ligand promoting alcoholic steatosis. CB1 also activates hepatocyte proliferation and promotes fibrogenesis by enhancing hepatic myofibroblast survival.

dysregulation of CB receptor-mediated pathways is the major determinant in several key aspects of liver pathogenesis. In this review, we summarize the latest findings regarding the impact of cannabinoid signaling in acute and chronic liver injury, and discuss the possible future clinical development of molecules targeting cannabinoid receptors.

CB1-mediated signaling during liver disease

CB1 receptors contribute to the pathogenesis of alcohol-induced liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), liver regeneration, fibrogenesis, and cardiovascular alterations associated with cirrhosis. These effects are mediated by CB1 receptors expressed in hepatocytes, hepatic myofibroblasts, and endothelial cells, and extrahepatic CB1 receptors, in particular originating from the adipose tissue and the intestine (Fig. 1).

Non-alcoholic fatty liver disease

CB1-mediated endocannabinoid tone is enhanced in experimental diet-induced or genetical models of NAFLD, and is characterized by upregulation of adipose tissue and hepatocyte CB1 receptors and increased liver synthesis of anandamide. The pathogenic role of CB1 receptors in NAFLD is supported by the resistance to steatosis of obese mice bearing a global or hepatocyte-specific CB1 deletion, or of rodents administered rimonabant or AM6545, a CB1 antagonist with limited brain penetrance [4–6]. Studies in cultured hepatocytes and liver slices further indicate that the steatogenic properties of CB1 arise from combined hepatocyte activation of SREBP1c-mediated lipogenesis, reduction of fatty acid oxidation via inhibition of AMP kinase, and decreased release of TG-rich VLDL [4,5,7]. In addition, the adipose tissue may largely contribute to the steatogenic process via CB1-induced release of free fatty acids by adipocytes [3,8] (Fig. 1).

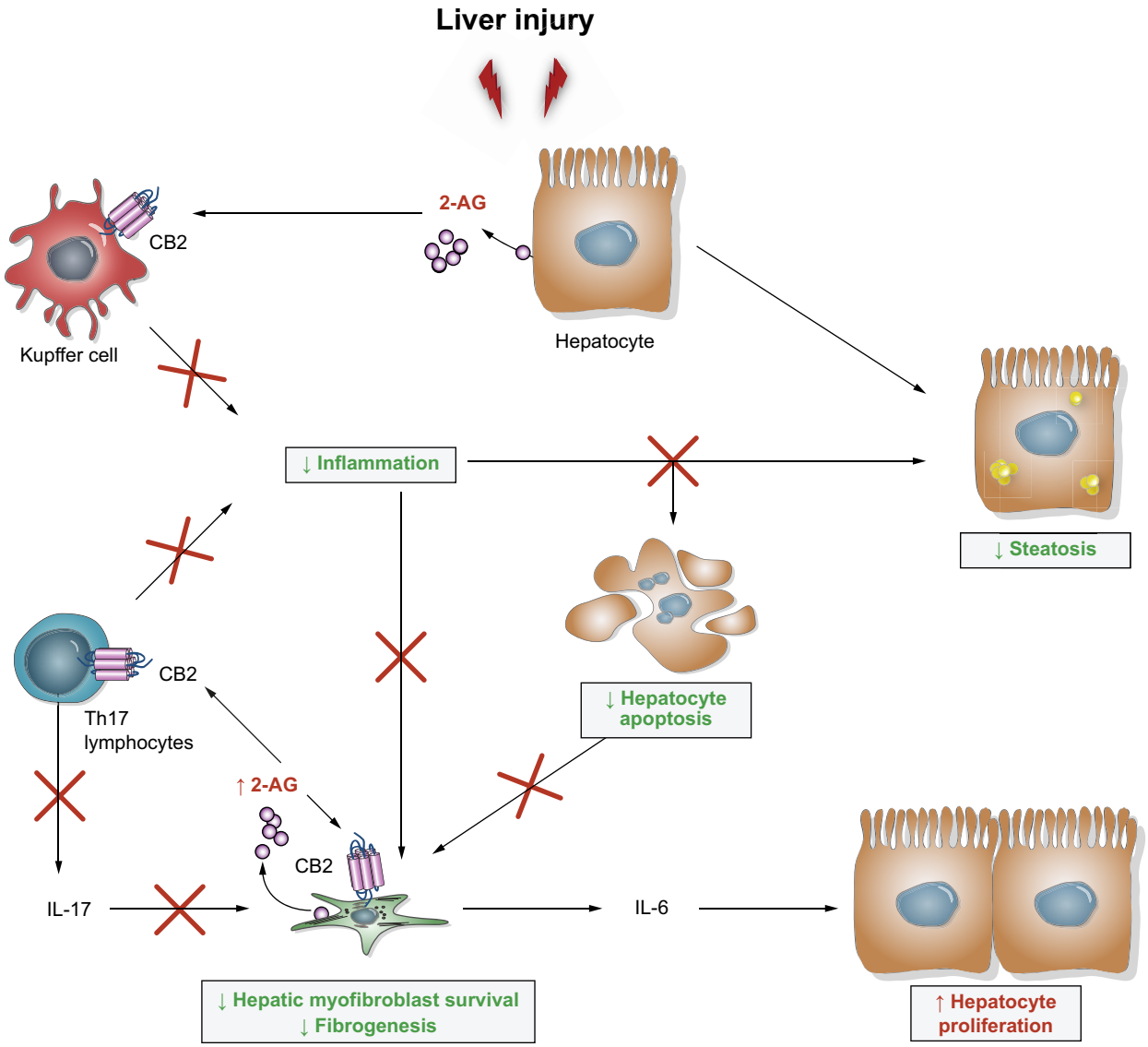

Fig. 2. Hepatic cellular targets of CB2-mediated protective effects. CB2 receptors expressed in immune cells (Kupffer cells, Th17 lymphocytes) and hepatic myofibroblasts display anti-inflammatory properties and protect against alcohol-induced steatosis, hepatocyte apoptosis, and fibrogenesis. Antifibrogenic properties result from (i) direct CB2-mediated effects on hepatic myofibroblasts and (ii) indirect hepatoprotective effects on hepatocytes, anti-inflammatory properties on Kupffer cell and downregulation of the production of the profibrogenic cytokine IL17 by Th17 lymphocytes.

Pharmacological or genetic inactivation of CB1 receptors is also associated with a decrease in serum transaminase levels in obese rodents [5,6]. These observations suggest that besides their steatogenic properties, hepatocyte CB1 receptors might also adversely affect hepatocyte survival. Whether reduced hepatocyte survival may be a consequence of CB1-mediated activation of endoplasmic reticulum stress [5] remains to be investigated.

A potential impact of CB1 receptors on the inflammatory response associated with NASH has been suggested by experiments in obese rats, showing that rimonabant reduces liver inflammation [5,6]. The underlying mechanism remains to be delineated but in hepatocytes, CB1 receptors could contribute to the acute phase response, via activation of CREBH, a liver-specific transcription factor that upregulates acute phase response genes [9]. In addition, extrahepatic sources of CB1 receptors could participate in Kupffer cell activation by LPS. Indeed, activation of CB1 receptors in the intestine increases gut permeability and LPS release in obese mice [10]. In addition, fat CB1 receptors reduce the production of adiponectin, an adipokine which reduces hepatic inflammation [5,6]. In keeping with these data, administration of rimonabant to obese mice reduces gut permeability and endotoxemia, restores adiponectin levels, and improves the hepatic inflammatory response [5,6,10].

Alcohol-induced liver disease

The pathogenic role of CB1 shares striking similarities in ALD and NAFLD, in keeping with common pathological features of liver injury. Mice fed an alcohol-enriched diet display enhanced production of 2-AG by hepatic stellate cells, resulting in paracrine induction of CB1 receptors in hepatocytes [11]. As demonstrated in experimental models of NAFLD, administration of rimonabant

or genetic ablation of CB1 receptors promotes resistance to alcohol-induced steatosis, following combined reduction of lipogenesis and enhanced fatty acid oxidation [11].

Liver fibrosis

CB1 receptor expression is upregulated in hepatic myofibroblasts from cirrhotic patients, and profibrogenic effects of CB1 receptors expressed in hepatic myofibroblasts were described in mice undergoing bile duct ligation, chronic exposure to carbon tetrachloride or thioacetamide, and in a model of NASH elicited by prolonged high fat feeding [12,13]. In these models, treatment with rimonabant or genetic ablation of CB1 receptors reduces fibrogenesis compared to control animals. Antifibrogenic properties of CB1 antagonism have been ascribed to growth inhibitory and proapoptotic effects towards hepatic myofibroblasts [12]. Importantly, CB1 antagonism remains operant at advanced stages of chronic liver injury, as shown by the therapeutic effects of rimonabant in rats with full-blown cirrhosis [14].

Liver regeneration

Liver regeneration is associated with a marked induction of CB_1 receptors and increased hepatic production of anandamide [15]. Mice administered rimonabant or lacking CB1 either globally or selectively in hepatocytes, show delayed liver regeneration, as reflected by decreased mitogenic activity of hepatocytes. Reduced hepatocyte proliferation results from inhibition of cell cycle proteins involved in mitotic progression [15].

Cardiovascular alterations associated with advanced cirrhosis

Endogenous activation of CB1 receptors promote hypotension and splanchnic vasodilation associated with advanced cirrhosis, as a consequence of the enhanced production of anandamide by circulating macrophages and upregulation of CB1 receptors in endothelial cells and mesenteric arteries of cirrhotic rats [16]. Blockade of this vasodilatory tone by rimonabant improves blood pressure, peripheral vascular resistance and portal pressure, and prevents the development of ascites [16].

CB2-mediated signaling during liver diseases

CB2 receptors predominantly display protective properties during liver injury. These effects largely depend on anti-inflammatory and antifibrogenic signals generated by CB2-expressing hepatic immune cells and/or hepatic myofibroblasts, with paracrine impact on hepatocytes, which do not express CB2 [1] (Fig. 2).

Alcoholic and non-alcoholic fatty liver disease

Activation of CB2 receptors in Kupffer cells limits liver inflammation and reduce alcohol-induced liver injury [17]. Indeed, in alcohol-fed mice, endogenous or exogenous stimulation of CB2 receptors prevents the switch of Kupffer cells to a proinflammatory M1 phenotype, and enhances transition towards the anti-inflammatory M2 phenotype, via a mechanism involving activation of heme oxygenase-1 [17]. Stimulation of Kupffer cell CB2 receptors also blunts alcohol-induced fat accumulation in hepatocytes. The antisteatogenic signal ensues from the reduced paracrine release of steatogenic cytokines (i.e., TNF-α and IL1-β) by CB_2-stimulated Kupffer cells [17].

Strinkingly, CB2 receptors display steatogenic properties in HFD-fed mice that derive from indirect CB2-mediated increase in adipose tissue inflammation and insulin resistance [18]. Whether CB2 receptors display protective effects against NASH, as anticipated from their anti-inflammatory and hepatoprotective effects (see below), deserve further studies.

Hepatocyte apoptosis and liver regeneration following acute liver injury

Endogenous or exogenous activation of CB2 receptors has been described as a protective pathway in several models of acute liver injury, in which CB2 receptors undergo early induction in non-parenchymal cells [2]. Interestingly, and similar to CB2 agonists, MAGL inhibition also protects against hepatocyte apoptosis elicited by acute liver injury, by enhancing 2-AG-mediated CB2 signaling [19]. Hepatoprotective properties of 2-AG-mediated CB2 effects result from indirect reduction of oxidative/nitrosative stress in hepatocytes [19,20]. In addition, CB2 receptors expressed in hepatic myofibroblasts also contribute to liver regeneration by accelerating proliferation of hepatocytes via a paracrine interleukin-6 dependent pathway [20].

Hepatocarcinogenesis

Although CB2 receptors are not expressed by hepatocytes, their expression has been detected in human hepatocarcinoma cell lines and their activation promote growth inhibition and apoptosis of tumor cells, via an autophagy-dependent pathway [21]. In line with *in vitro* observations, the CB2 agonist JWH-015 reduces tumor growth in an orthotopic model of hepatocarcinoma xenograft [21].

Liver fibrosis

In contrast to CB1, CB2 signaling has been identified as an antifibrogenic pathway. Thus, CB_2-deficient mice show enhanced fibrosis [22], whereas administration of the CB2 agonist JWH-133 to rats with established cirrhosis improves liver fibrosis [23]. Antifibrogenic properties of CB2 receptors rely on combined direct and indirect effects on hepatic myofibroblasts. Indeed, activation of CB2 receptors in hepatic myofibroblasts reduce their density, owing to antiproliferative and apoptotic properties [22]. In addition, CB2 receptors indirectly reduce hepatic myofibroblast accumulation via (i) indirect hepatoprotective effects on hepatocyte survival [20], (ii) anti-inflammatory properties of Kupffer cell CB2 receptors [17] and (iii) downregulation of the production of the profibrogenic cytokine IL17 by Th17 lymphocytes [24] (Fig. 2).

CB1 antagonism and CB2 agonism as future approaches for the management of liver diseases

As depicted in previous sections, numerous experimental evidence supports the key role of the hepatic endocannabinoid system in the pathogenesis of liver disease, with CB1 and CB2 receptors often fulfilling opposite functions. Enhanced CB1 tone promotes liver fibrogenesis, cardiovascular alterations associated

with cirrhosis, and contributes to the pathogenesis of NAFLD and ALD. On the other hand, upregulated CB2 signaling displays hepatoprotective effects, reduces liver inflammation, and improves ALD and liver fibrogenesis. Although experimental results demonstrate deleterious, steatogenic properties of CB2 receptors at early stages of NAFLD, protective effects against NASH are expected from their anti-inflammatory and hepatoprotective effects in various experimental models.

Interestingly, available clinical studies in NAFLD and hepatitis C support the relevance of experimental findings to human liver diseases. Enhancement of hepatic and extrahepatic endocannabinoid tones has been documented in several instances, including NAFLD, chronic hepatitis C, and cirrhosis of diverse origins [1]. Regular cannabis use was identified as an independent predictor of fibrosis progression [25], indicating that the profibrogenic CB1 signal prevails on the antifibrogenic properties of CB2. The impact of endocannabinoids on NAFLD has been supported in several studies. In patients with chronic hepatitis C, daily cannabis use has been identified as an independent predictor of steatosis severity [26], and phase III trials in overweight patients have shown that the CB1 antagonist rimonabant decreases serum transaminases [27], visceral and liver fat [28]. However, side effects of rimonabant have precluded further therapeutic development of brain penetrant inverse CB1 agonists. Nevertheless, encouraging results are increasingly obtained with second generation peripherally-restricted CB1 antagonists that appear to retain meaningful therapeutic properties for the management of liver diseases. Treatment of high fat-fed mice with the neutral antagonist AM 6545 induces weight-independent improvement in fatty liver, glucose homeostasis and plasma lipid profile [5]. Similar effects have been obtained with JD 5037, an inverse CB1 receptor agonist with limited brain accessibility [29]. In addition, preliminary results from our group indicate that AM6545 displays antifibrogenic effects similar to rimonabant. Future studies should clarify whether, as recently suggested, neutral antagonist may prove safer in terms of digestive and psychological side effects.

Key Points

- The endocannabinoid system, consisting of the cannabinoid receptors, endogenous cannabinoid ligands and their biosynthetic and degradative enzymes, is a key mediator of acute and chronic liver injury
- CB1 receptors participate in the pathogenesis of ALD and NAFLD, promote liver regeneration and accelerate liver fibrogenesis
- CB2 receptors exert hepatoprotective effects, reduce alcohol-induced liver inflammation and injury, and display antifibrogenic properties
- Antagonism of CB1 receptors and CB2 receptor agonism have been identified as promising therapeutic strategies for the management of liver diseases

Conclusions

Overwhelming evidence supports the therapeutic potential of peripherally-restricted CB1 antagonists and CB2 agonists in the management of chronic liver diseases. A major interest of this approach resides in the multiple levels of action of these therapeutic strategies on various steps of chronic liver disease progression. Exciting therapeutic developments are now anticipated from the development of the second generation of neutral and inverse peripherally-restricted CB1 antagonists that show promising effects in preclinical studies. However, long-term studies are required to confirm the absence of central effects of these new molecules in both experimental models and humans. Based on the promising protective effects of CB2 receptor agonists on various steps of acute and chronic liver disease progression, the development of stable CB2 agonists is also eagerly awaited. Whether the potential of CB2 and CB1-based therapeutics can be turned to reality will be the challenge of the next few years.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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