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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CB1 antagonist rimonabant, initially approved for the management of overweight and related cardiometabolic risks, was withdrawn because of an alarming rate of mood adverse effects.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.
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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 monoacyglycerol 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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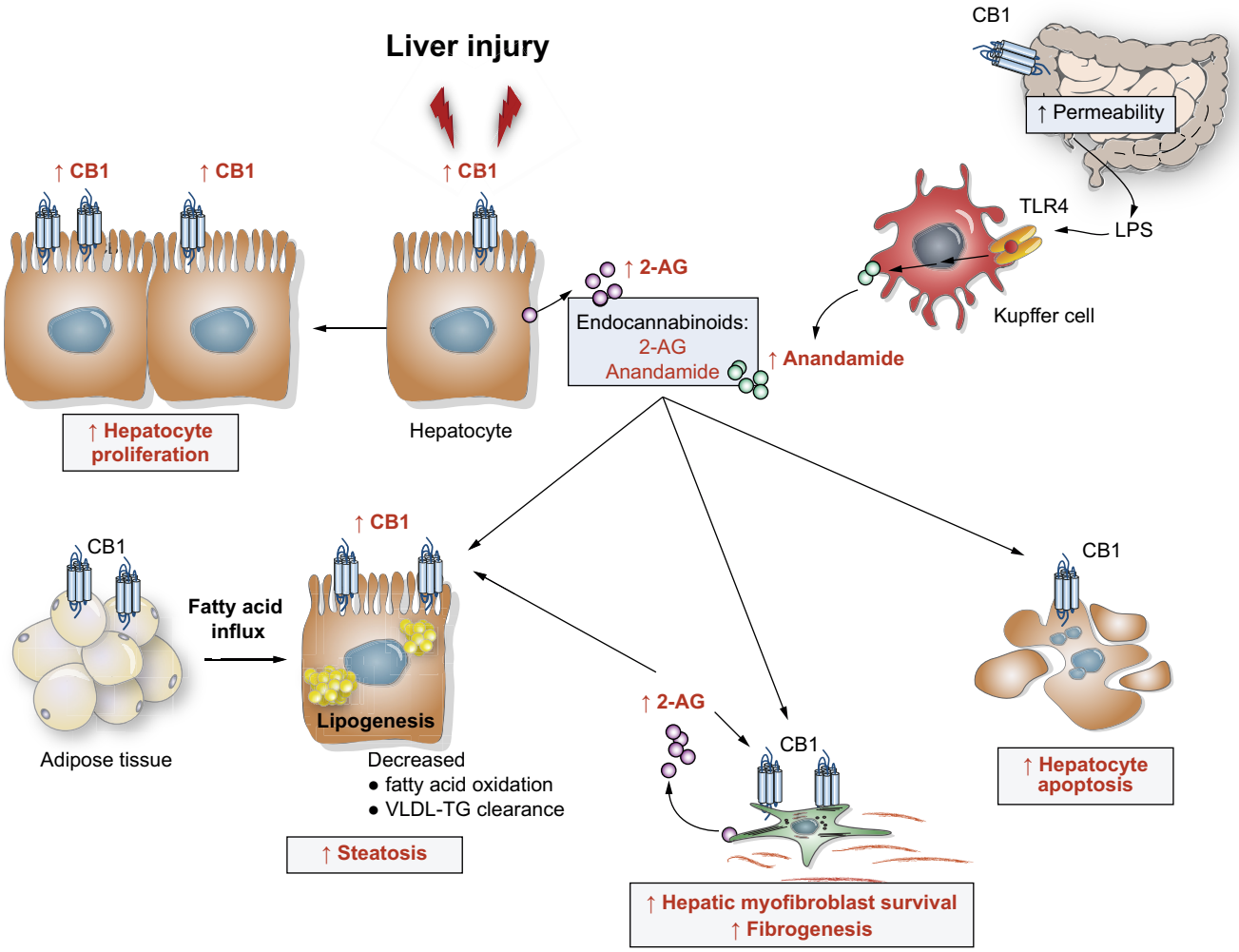

Fig. 1. Cellular targets of CB1-mediated effects during liver injury. CB1 receptors expressed in hepatocytes and hepatic myofibroblasts contribute to high fat diet and alcohol-induced steatosis, liver regeneration, and fibrogenesis. Steatogenic properties of CB1 result from hepatocyte activation of lipogenesis, 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).

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