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EDITORIAL

Role of cannabinoids in chronic liver diseases

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Abstract

Cannabinoids are a group of compounds acting primarily *via* CB1 and CB2 receptors. The expression of cannabinoid receptors in normal liver is low or absent. However, many reports have proven up-regulation of the expression of CB1 and CB2 receptors in hepatic myofibroblasts and vascular endothelial cells, as well as increased concentration of endocannabinoids in liver in the course of chronic progressive liver diseases. It has been shown that CB1 receptor signalling exerts profibrogenic and proinflammatory effects in liver tissue, primarily due to the stimulation of hepatic stellate cells, whereas the activation of CB2 receptors inhibits or even reverses liver fibrogenesis. Similarly, CB1 receptor stimulation contributes to progression of liver steatosis. In end-stage liver disease, the endocannabinoid system has been shown to contribute to hepatic encephalopathy and vascular effects, such as portal hypertension, splanchnic vasodilatation, relative peripheral hypotension and probably cirrhotic cardiomyopathy. So far, available evidence is based on cellular cultures or animal models. Clinical data on the effects of cannabinoids in chronic liver diseases are limited. However, recent studies have shown the contribution of cannabis smoking to the progression of liver fibrosis and steatosis. Moreover, controlling CB1 or CB2 signalling appears to be an attractive target in managing liver diseases.

Key words: Hepatic fibrosis; Endocannabinoids; Endocannabinoid receptors; CB1; CB2

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INTRODUCTION

Hepatic fibrosis is a dynamic process resulting from liver tissue injury. Previously, it was believed that hepatic fibrosis is irreversible. However, current knowledge allows us to consider fibrosis as an active, potentially reversible process originating from wound-healing responses to chronic liver injury of various etiology. The continuous influence of injuring stimuli leads to an imbalance between the accumulation and degradation of extracellular matrix (ECM) components, which include mainly deposits of fibrillar collagens, proteoglycans and glycoproteins. The major sources of ECM elements are hepatic stellate cells (HSCs), which physiologically constitute about 5%-8% of liver cells. In the course of chronic liver injury, HSCs are activated and transformed from fat-storing cells (Ito cells) to myofibroblast-like cells. Along with this transformation, they undergo morphological and functional changes into contractile, smooth muscle α-actin-positive cells expressing profibrogenic and proinflammatory properties[1,2]. Among mediators activating HSCs, transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) are of special concern. PDGF stimulates proliferation and migration of HSCs, whereas TGF-β, which is the most potent profibrogenic cytokine, acting through its receptor, induces downstream signalling involving Smad family mediators. Thus, it regulates transcription of TGF-β target genes. The results of the above-mentioned signalling are complex; these include increased synthesis of fibrillar collagens, especially collagen type 1, and other ECM components, reduced expression of matrix metalloproteinase, along with augmented production of tissue inhibitor of metalloproteinase-1 (TIMP-1). So far, the perfect non-invasive biomarkers of hepatic fibrosis are under investigation include TGF-β, ECM components and TIMPs[3-5]. The overproduction of ECM components and imbalanced processes of synthesis-degradation eventually lead to progressive liver fibrosis[2]. Thus, reduction of fibrosis

can be obtained by either reduced liver myofibroblast activity, resulting from inhibition of ECM components synthesis, or enhanced degradation of ECM. The clinical data demonstrated that even advanced liver fibrosis can be inhibited and reversed[6]. However, the compounds with antifibrotic activities, potentially useful in clinical practice, are still under investigation.

CANNABINOIDS AND ENDOCANNABINOID SYSTEM IN PHYSIOLOGY AND PATHOLOGY

Cannabinoids are a group of compounds acting primarily *via* CB1 and CB2 receptors. The first cannabinoid discovered, in 1964, was a plant-derived Δ^9-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa*[7]. Following this finding was the discovery and determination of receptors for cannabinoids in nervous tissue. The first results were obtained by Matsuda *et al*[8] and presented the effects of cloning cDNA of G protein-coupled receptor found in neural cells, recognized then as CB1 receptor. However, this receptor was shown to be responsible primarily for psychoactive and neuronal effects of cannabinoids, which did not explain the other effects exerted by THC. Hence, the research for other receptors led to the discovery of CB2 receptor, expressed in macrophages of the spleen[9]. The presence of cannabinoid receptors in mammalian tissues prompted the research for its endogenous ligands and resulted in isolation of anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG)[10,11]. So far, among several endogenous discovered ligands for cannabinoid receptors, AEA and 2-AG are the best characterized. The interesting feature of endocannabinoid mediators is that they are not stored in cells, instead, they are synthesized from lipid precursors in cellular membranes and released in response to specific stimuli[12].

The endocannabinoid system is comprised of at least two types of receptors for THC (CB1 and CB2), endogenous lipid compounds acting as ligands, and molecules regulating the synthesis and degradation of endocannabinoids. The expression of CB1 receptors was initially associated with the nervous system, as they were shown to control perception, cognitive, motor and behavioral functions. Nevertheless, the CB1 receptors are present peripherally in endothelial cells, adipocytes, gut and liver cells[13-16]. It has been shown that cannabinoid CB1 signalling regulates intake of high-energy-containing food and alcohol, energy homeostasis and hepatic lipogenesis. As to CB2 receptors, they are largely expressed in several lines of peripheral blood immune cells, tonsils, spleen and testis[17]. Moreover, their presence at low levels has been confirmed in various other tissues and cells, like hepatic myofibroblasts[18].

The imbalance in endocannabinoid system signaling is observed in various pathological conditions, including nervous system disorders, metabolic disturbances, impaired immunological responses (both allergy and hypersensivity), cardiovascular and gastrointestinal diseases, and carcinogenesis[19].

CANNABINOIDS IN HEPATIC FIBROSIS

The expression of cannabinoid receptors in normal liver is very low, partially because they are not expressed in hepatocytes. However, many studies have demonstrated the up-regulation of the expression of CB1 and CB2 receptors in hepatic myofibroblasts and vascular endothelial cells, as well as increased concentration of endocannabinoids, especially AEA, in liver in the course of chronic progressive liver diseases[18,20,21]. Teixeira-Clerc *et al*[20] have provided evidence for the involvement of CB1 receptor in regulation of hepatic fibrosis and the profibrogenic effect of CB1 signaling. Increased expression of CB1 receptors has been observed in human cirrhotic liver samples, primarily in HSCs during their transformation into myofibroblasts during the course of chronic liver injury. Moreover, the effect of CB1 inactivation was demonstrated in three experimental models of liver injury induced by CCl_4, thioacetamide or biliary cholestasis. The favorable antifibrogenic results were obtained either by pharmacological inactivation with rimonabant (SR141716), a selective antagonist of CB1 receptor, and *via* genetic inactivation in homozygous CB1-deficient mice. Decreased progression of fibrosis was accompanied by reduced hepatic TGF-β expression, and growth inhibition and increased apoptosis of myofibroblasts. These effects seemed to result from reduced phosphorylation of protein kinase B (PKB/Akt) and extracellular signal-regulated kinase (ERK), thus affecting the pathways responsible for cell proliferation and survival.

Although CB1 receptor is believed to have profibrogenic effects, studies on the CB2 receptor have proven its antifibrogenic activity in liver, as CB2 knockout mice developed augmented cirrhosis when exposed to CCl_4, compared to wild type[18]. It has been demonstrated in human cirrhotic liver samples that the expression of CB2 receptor is limited primarily to the cells positive for smooth muscle α-actin located within fibrotic septa; however, it is also detected in non-parenchymal cells, inflammatory cells and bile duct epithelial cells adjacent to fibrotic septa. The supporting results were obtained in separate research on cultured human hepatic myofibroblasts and activated rat HSCs, which were shown to express CB2 receptor. The final effects of the stimulation of CB2 receptor with THC or selective agonist JWH-015 are dose-dependent and expressed as growth inhibition or apoptosis. Interestingly, these two endpoints result from two distinct pathways, the induction of cyclooxygenase-2 (COX-2) in growth inhibition and intracellular oxidative stress for apoptosis, as they are diminished by the selective COX-2 inhibitor and two potent antioxidants, respectively.

Additionally, apart from receptor-dependent mechanisms of endocannabinoid actions on HSCs, the direct mechanism exerted by AEA leading to cell death have been observed in the research of Siegmund *et al*[22]. Stimulation of cultured human HSCs with AEA induces cell death in the necrotic pathway. This event is preceded by reactive oxygen species (ROS) formation and an increase in intracellular Ca^{2+} in HSCs. The pharmacologi-

cal inactivation of CB1, CB2 and vanilloid receptor-1 (VR1) does not prevent AEA-triggered cell death, which appears to be mediated by membrane cholesterol. Furthermore, the distinction between cholesterol content in the cellular membrane of HSCs and hepatocytes results in selective elimination of HSCs that are richer in cholesterol[22]. The conclusion of their analysis is that AEA exerts a potential antifibrogenic effect by inhibition of HSC proliferation and induction of necrotic death. The elevated levels of circulating AEA in cirrhotic patients might reflect the regulatory antifibrotic response to progression of fibrosis[22,23]. However, due to disadvantageous properties, such as triggering a local inflammatory response to necrosis and tissue damage, as well as systemic vasodilatation, the usefulness of AEA in the treatment of liver fibrosis is limited.

CANNABINOIDS IN LIVER STEATOSIS

Metabolic syndrome, leading to liver steatosis, has emerged as an important and frequent cause of chronic liver injury, ranging from simple steatosis to steatohepatitis, which is accompanied by inflammatory reaction and progressive fibrosis of liver tissue. The involvement of the endocannabinoid system in the pathogenesis of fatty liver disease has been shown recently. Since endocannabinoids are essential in regulation of energy balance, food intake and lipogenesis, impairment of this homeostasis results in various metabolic disturbances. Apart from central control of energy homeostasis *via* CB1 receptors localized in the brain, endocannabinoids seem to exert, as well CB1-receptor-dependent, peripheral effects on lipid metabolism in adipocytes, liver tissue and skeletal muscle[14]. This could be partially explained by increased expression of lipogenic transcription factor and activation of downstream enzymes, which result in increased fatty acid synthesis. Moreover, fat-rich diet has been shown to contribute to enhanced hepatic expression of CB1 in liver tissue and increased levels of endocannabinoids, thus increasing the metabolic imbalance[15].

ROLE OF ENDOCANNABINOID SYSTEM IN CONDITIONS ACCOMPANYING END-STAGE LIVER DISEASE

The role of the endocannabinoid system in liver diseases is complex. It has been particularly examined in end-stage liver disease and shown to contribute to hepatic encephalopathy and vascular effects such as portal hypertension, splanchnic vasodilatation, relative peripheral hypotension and probably cirrhotic cardiomyopathy.

There is limited, but reliable data on the neuroprotective role of the endocannabinoid system in hepatic encephalopathy. It has been demonstrated in a murine model that during fulminant hepatic failure, the levels of 2-AG in the brain are elevated, probably as a response to liver damage. The administration of CB2 endogenous ligand 2-AG, an antagonist of CB1 receptor, SR141716A, or an agonist of CB2 receptor, HU308, accomplished a marked improvement in neurological score. Hence, influencing the endocannabinoid system with exogenous cannabinoid derivates specific for the CB2 or CB1 receptor might have a beneficial therapeutic effect on neurological dysfunction in liver diseases[24]. Further research has indicated the impact of CB2 signaling on the activity of cerebral AMP-activated protein kinase (AMPK) in conditions of liver failure. It has been shown in wild type mice that administration of THC leads to increased activity of AMPK in the brain and neurological improvement, possibly *via* stimulation of CB2 receptors, as this effect is absent in CB2 knock-out mice[25].

Numerous hemodynamic vascular effects contributing to the poor prognosis of disease outcome accompany end-stage liver disease. The cirrhotic rebuilding of hepatic tissue results in increased resistance in portal circulation and eventually in elevated portal pressure. Additionally, the arterial vasodilatation in splanchnic and systemic circulations contributes to hyperdynamic state, arterial hypotension and increased blood inflow from mesenteric arteries, which augments the unfavorable effect of portal hypertension. There are many reports linking these vascular effects with the improper activity of the endocannabinoid system, particularly with stimulation of CB1 receptor in vascular endothelial cells with endogenous cannabinoids. The cirrhotic state is often accompanied by the endotoxemia caused by release of bacterial lipopolysaccharide (LPS) synthesized by the intestinal flora into the systemic circulation, while its hepatic elimination is insufficient[26]. The effects of blood LPS on systemic circulation correspond to the hemodynamic changes observed in cirrhosis[27]. Batkai *et al*[21] have provided evidence that explains the association between the endocannabinoid system and its influence on circulatory changes in cirrhosis. It was demonstrated in an animal model of cirrhosis complicated by hemodynamic alterations, that treatment with CB1 receptor antagonist (SR141716A) sufficiently improved hemodynamic state, which manifested in elevation of arterial pressure and reduction of mesenteric blood flow and portal pressure. It was shown that the intravenous injection of the monocyte fraction isolated from the blood of both cirrhotic rats and a patient with cirrhosis, was able to induce hypotension. This was reversible by treatment with SR141716A, whereas the injection of monocytes from controls did not exert such an effect. Moreover, the examination of monocytes from cirrhotic and control individuals and animals demonstrated increased levels of AEA in the monocytes in cirrhotic state, which may have reflected the stimulation of endocannabinoid synthesis by bacterial LPS shown in previous studies[21]. Additionally, upregulation of CB1 receptors in hepatic arterial endothelial cells isolated from cirrhotic livers was observed, thus, indicating its increased sensitivity to vasodilatory stimuli, such as endocannabinoids secreted by the monocytes and platelets adhering to endothelium[21].

Vascular effects exerted by endocannabinoids are divergent and complex. It is postulated that endocannabinoids might contribute to potency disorders in cirrhosis, as was observed in animal models. AEA was shown to

augment the relaxation of samples of corpus cavernosum from biliary cirrhotic rats, probably through CB1 and VR1 signalling[28].

Recently, the role of endocannabinoid signaling in the development of cardiomyopathy during liver cirrhosis has been investigated. It is characterized by decreased β-adrenergic responsiveness, impaired cardiac conduction and insufficient heart muscle contraction to excitation stimuli, whereas cardiac output remains increased compared to baseline. Gaskari *et al*[29] have confirmed in an animal model the role of CB1 signaling in the pathogenesis of cirrhotic cardiomyopathy. It has been shown that, when the cardiac muscle probes from cirrhotic rats are pre-incubated with the CB1 antagonist, AM251, their contractility is similar to the controls[29]. The significance of CB1 signaling has been demonstrated *in vivo* in cirrhotic rats presenting late symptoms of decreased cardiac contractility, hypotension and tachycardia. These symptoms were ameliorated in cirrhotic rats, by the bolus injection of AM251, whereas its administration in controls had no effect. Hence, the authors concluded that the above-mentioned cardiac effects might have resulted from increased concentration of AEA in cardiac tissue in liver cirrhosis, as the cardiac expression of CB1 receptors was similar in cirrhotic and non-cirrhotic control rats[30]. These observations are consistent with the study of Bonz *et al*[31] assessed the influence of AEA on the contractility of human heart atrial muscle upon electrical stimulation. The inotropic negative effect exerted by AEA and other examined CB1 agonists was predictably abolished by pre-incubation with CB1 antagonist ation[31]. Thus, blocking the CB1 signaling might have advantageous therapeutic effects on various clinical aspects of cirrhotic cardiomyopathy and other related conditions.

CLINICAL ASPECTS

There are limited clinical data on the effects of cannabinoids in chronic liver diseases. According to clinical research of Hezode *et al*[32], daily cannabis smoking appears to be an independent factor of fibrosis progression in chronic hepatitis C (CHC) patients. The research was performed on a group of 270 CHC patients, divided into non-cannabis users (52.2%), occasional cannabis users (14.8%) and daily cannabis users (33.0%). The collected data on epidemiological, demographic, metabolic and virological aspects, and history of cannabis, alcohol and tobacco abuse, allowed them to specify the factors for fibrosis progression. This study confirmed the well-recognized independent fibrosis predictors such as necroinflammatory activity ⩾ A2 (METAVIR score), age > 40 years at the time of exposure, steatosis and serious alcohol abuse, but also rated the daily cannabis use as a distinct factor that influenced alone the progression of liver fibrosis. This could result from profibrogenic activity of CB1 signaling, thus implying the beneficial therapeutic potential of CB1 antagonists.

Moreover, it has been proven that regular daily cannabis use has a significant impact on the severity of steatosis, which may eventually contribute to fibrosis progression in the course of CHC[33]. It has been shown that high fat dietary supply increases the hepatic levels of AEA, expression of CB1 receptor and augments fatty acid synthesis, thus contributing to obesity and other metabolic disorders proceeding to liver steatosis[15,34]. The mechanisms, in which endocannabinoids lead to obesity-associated fatty liver, or even steatohepatitis, are CB1-receptor-dependent and include increase in fatty acids intake, induction of lipolysis in adipocytes, stimulation of hepatic lipogenesis and downregulation of adiponectin in adipose tissue. Interestingly, CB1-knockout mice are resistant to obesity induced by high-energy-containing food intake[35]. Similarly, the pharmacological inactivation of CB1 with rimonabant (SR141716) results in reduction of obesity and hepatic steatosis in rodents[36,37].

ENDOCANNABINOID SYSTEM AS A THERAPEUTIC TARGET

The beneficial effect of the regulation of endocannabinoid signaling is postulated in management of various pathological conditions, including obesity and metabolic syndrome; addiction to alcohol, tobacco and opiates; Alzheimer's disease, Parkinson's disease, schizophrenia, memory loss, chronic pain, liver fibrosis, and numerous inflammatory conditions and allergies[38].

Due to their regulatory functions in chronic hepatic disorders, especially fibrosis, influencing the endocannabinoid receptors seems to be an advantageous therapeutic target. It seems that treatment with CB1 antagonist, CB2 agonist or both, may offer clinical benefits, resulting in at least deceleration of disease progression. It has also been shown that blocking CB1 signaling is favorable in maintaining the proper blood pressure in hypotensive cirrhotic rats[21,39]. Moreover, in clinical studies, rimonabant has exerted additional beneficial actions influencing the profile of blood lipids and glycemia control in obesity, metabolic syndrome and type 2 diabetes mellitus. It also had an impact on lifestyle modification, for instance, cigarette smoking cessation rates were significantly higher during treatment with rimonabant[40]. Interestingly, Wang *et al*[41] have suggested a possible link between CB1 signaling and ethanol preference in immature mice, and this effect was diminished after administration of rimonabant. This observation might be particularly useful in patients with alcoholic liver disease who persist in drinking.

CONCLUSION

The role of the endocannabinoid system in hepatic physiology and pathologic conditions has been studied recently. Unquestionably, influencing endocannabinoid signaling may have a beneficial effect on delaying or even reversing hepatic fibrosis. It is particularly important due to the lack of antifibrotic drugs with established advantageous profiles of activity, despite years of investigations into this subject. Thus, further research may provide the valuable means of management in hepatic fibrosis in the future.

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