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Endocannabinoids signaling: Molecular mechanisms of liver regulation and diseases

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1. ABSTRACT

The endocannabinoid system (ECS) includes endocannabinoids (eCBs), cannabinoid (CB) receptors and the enzymes that are responsible for endocannabinoid production and metabolism. The ECS has been reported to be present in both brain and peripheral tissues. Recent studies have indicated that eCBs and their receptors are involved in the development of various liver diseases. They were found to be altered in response to many danger factors. It is generally accepted that eCB may exert a protective action via CB2 receptors in different liver diseases. However, eCBs have also been demonstrated to have pathogenic role via their CB1 receptors. Although the therapeutic potential of CB1 receptor blockade in liver diseases is limited by its neuropsychiatric side effects, many studies have been conducted to search for novel, peripherally restricted CB1 antagonists or CB2 agonists, which may minimize their neuropsychiatric side effects in clinical use. This review summarizes the current understanding of the ECS in liver diseases and provides evidence for the potential to develop new therapeutic strategies for the treatment of these liver diseases.

2. INTRODUCTION

Cannabis has been used as a medical herb for thousands of years in China, India and the Middle East, mainly to treat malaria, constipation and rheumatism (1). Currently, a major family of cannabis components, CBs has been identified as a main bioactive compound from Marijuana, which contains more than 60 components. Over the last 20 years, scientific research on the therapeutic potential of cannabis has been exploded and, in particular, with the discovery of eCBs the pathogenic role and pathophysiology of CBs have been extensively studied. By PubMed search for scientific journal articles published, it was found that there are more than two scientific publications published per day over the last 20 years. The ECS has been implicated in the development of different systemic and organ diseases. Recently, evidence is accumulating that eCBs and their receptors are importantly involved in the development of various liver injury and chronic liver diseases induced by different pathogenic factors such as alcohol, autoimmune diseases, bile duct disorders, exposure to toxin, hepatitis and parasites infection (2-8). This review attempted to focus on the role of the ECS in liver injury, inflammation and related fibrotic alterations and provide novel insights

into the molecular mechanisms by which the ECS works in various pathogenic processes, which may help identify new therapeutic targets for treatment of liver diseases.

3. ENDOCANNABINOIDS AND MAJOR RECEPTORS IN LIVER

ECBs are a class of new lipid mediators composed of amides, esters and long chain unsaturated fatty acids. In 1992, Raphael *et al* first isolated eCBs from a porcine brain and then demonstrated the existence of cannabinoid receptors in a variety of mammalian cells or tissues (9). At present, the majority of researches focuses on anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) as two main eCBs as well as their downstream metabolites. These main eCBs were reported to have important regulatory role in various cell functions or cellular activities. In particular, both eCBs can be produced in several types of liver cells including hepatocytes, hepatic stellate cells (HSCs), and liver vascular endothelial cells and therefore they participate in the functional regulation of these hepatic cells (10-12). Among endocannabinoid (CB) receptors, CB1 and CB2 are well studied and both belong to rhodopsin family of 7 transmembrane receptors. In these receptors, seven transmembrane helices interact to form a central core that binds to the ligands (13). Early studies have reported that the CB1 receptors are widely distributed in the central and enteric nervous system (14), while the CB2 receptors are mainly found in the peripheral nervous system as well as in the immune system such as spleen and macrophages (15). Recent studies have shown that the CB1 receptors are also expressed in the liver, in particular, in hepatocytes, HSCs, liver vascular endothelial cells and hepatic bile duct cells. Although the expression of CB2 receptors in normal liver tissues was very low, it was significantly increased in a variety of hepatic cells during fatty liver, hepatic fibrosis and hepatocellular carcinoma (16). There is accumulating evidence that increased production of eCBs participates in the pathological processes of liver injury and diseases through CB1, CB2 receptors or both together. In addition to CB1 and CB2 receptors, recent studies revealed that some CB and non-CB ligands could bind with the protein of GPR55 (17-19), which might act as a novel “type-3 (CB3)” cannabinoid receptor (20). In addition, AEA, but not 2-AG, could activate the non-selective cationic channel type-1 vanilloid receptor (transient receptor potential vanilloid 1, TRPV1), which usually was activated by capsaicin and noxious stimuli-like heat and protons (21). Nuclear receptors like the peroxisome proliferator-activated receptors (PPARs), activated under physiological and pathological conditions, are the new targets for eCBs (22). Some studies have found that eCBs can induce HSC necrosis (23) and they are significantly increased in tissue of cirrhotic and fibrotic liver (5, 24, 25). The liver has now been considered as an important target organ of eCBs, which is implicated in the development of hepatic cirrhosis and other liver diseases.

4. ENDOCANNABINOID RECEPTORS IN ACUTE LIVER INJURY

4.1. Liver ischemia and reperfusion injury

When ischemia tissues restore blood flow or when reflow in tissue or organ occurs, tissue damages are often exacerbated. This phenomenon is called ischemia-reperfusion (I/R) injury or clinically referred to as reperfusion syndrome. Many diseases or pathological processes such as delayed neuronal necrosis, irreversible shock, myocardial infarction, acute organ function failure and development of organ transplant rejection are associated with ischemia-reperfusion. Among the mechanisms producing I/R injury, oxidative stress is a main factor. I/R injury of liver tissue is considered as a lethal complication of liver surgery. It has been reported that eCBs can lead to vascular power weakening and hypothermia, both of which can reduce the blood supply contributing to I/R injury. eCBs can also promote the energy storage and reduce energy consumption, which may have protective role in I/R injury under certain conditions (26, 27).

The level of AEA and 2-AG is increased in mice with I/R and is closely related to the degree of tissue damage (27). I/R can promote the expression of CB1 receptors in liver cells surrounding hepatic sinusoid of rats, but treatment with CB1 antagonist, SR141716 markedly reduced the liver tissue necrosis, ALT levels and tissue damage caused by oxidative stress (7). CB2 agonist JWH - 133 was found to decrease neutrophil infiltration and lipid peroxidation during I/R in mice. Compared with wild counterparts, liver tissue injuries were exacerbated in $CB2^{-/-}$ mice with I/R procedures (26). Another selective CB2 receptors agonist HU-308 caused similar biological effects, namely, inhibition of liver cell apoptosis induced by ischemia-reperfusion and reduction of the expression of adhesion molecules, ICAM - 1 and VCAM 1, in hepatic sinus endothelial cells (27). It has been suggested that the activation of CB2 receptors protects liver from I/R injury, but CB1 receptors may mediate the effects of liver injury under this pathological condition.

4.2. Hepatocyte regeneration in response to injury

The ability of tissue regeneration ensures the important function of liver in mammalians. Liver cell regeneration is regulated by growth factors, cytokines and hormones. It has been reported that the CB1 receptor expression increased 40 hours after liver resection, accompanied by liver regeneration as shown by recovery of liver volume. Compared with wild-type mice, the liver volume was not increased apparently in CB1 receptor KO mice. 6 days after liver resection, however, the volume of liver between two groups of mice was almost same. This indicates that the CB1 receptor deletion can only postpone, but not block the liver cell regeneration. In the same study, the liver

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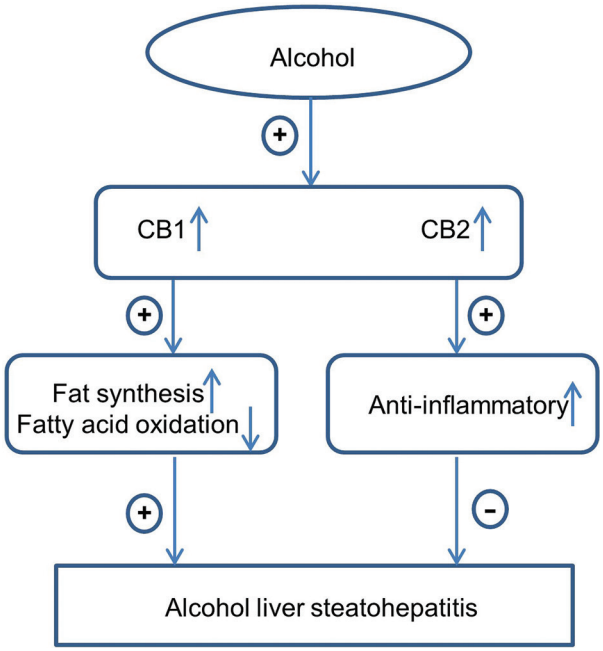

Figure 1. Endocannabinoid receptors in alcoholic liver steatohepatitis. CB2 receptor agonists and CB1 receptor antagonist may provide potential targets for the treatment of alcoholic liver injury.

tissues of wild-type mice were found to have higher level of AEA at the early stage, which quickly returned to normal 6 days after resection. This phenomenon was not observed in the CB1 receptor KO mice or in SR141716 treated mice. It appears that AEA can activate the CB1 receptor and at the same time induce its synthesis by itself. Mechanistic studies showed that 40 hours after hepatectomy, cyclin decreased in the liver of CB1 $^{-/-}$ mice, but not in wild type mice, suggesting that CB1 activation during liver resection promotes the regeneration of liver cells by increasing cell proliferation (16). Other studies have demonstrated that CB2 receptor gene transcription increased in wild type mice in 24 to 72 hours after liver resection, and such changes were obviously delayed in CB2$^{-/-}$ mice, indicating that CB2 receptors may also promote liver regeneration during liver resection (28). In animals with acute liver injury induced by carbon tetrachloride, the CB2 receptor expression in liver tissue of mice increased significantly with enhanced liver cell proliferation. However, this liver cell proliferation was found delayed if CB2 gene was deleted (29). This also implies that the activation of CB2 receptors can promote the regeneration of liver cells. In some other studies, however, the activation of CB2 receptors was only found to reduce liver tissue damage in animals with multiple acute hepatic injuries, but it is not involved in liver regeneration (26, 29-31). Further studies may be needed to further clarify under which condition eCBs are involved in liver cell regeneration and how eCBs work to lead to cell proliferation and growth in the liver.

5. ENDOCANNABINOID RECEPTORS IN CHRONIC LIVER DISEASES

5.1. Alcoholic fatty liver diseases

Chronic alcoholism can lead to liver fatty degeneration and fatty liver, which further develop into liver cirrhosis and liver cancer. Alcohol can promote the synthesis of liver cell fat and reduce the oxidation of fatty acids (32, 33). High fat diet or alcohol induced hepatic steatosis and increased eCBs levels (2), suggesting that eCBs may play an important role in the pathogenesis of alcoholic fatty liver. In this regard, Jeong WI, *et al.* demonstrated that when mice were exposed to alcohol, the expression of CB1 receptors and 2-AG levels increased significantly. Gene knockout of CB1 receptors or the use of CB1 receptor antagonist, SR141716 was found to reduce liver fatty degeneration more significantly compared to control mice under the same condition of alcohol intake and with similar blood alcohol concentration. In addition, the expression of lipogenic enzymes increased in hepatocytes when co-culturing HSCs isolated from alcohol-fed mice with hepatocytes from normal mice. However, hepatocytes from CB1$^{-/-}$ mice were co-cultured with normal HSCs, there was no change in the expression of lipogenic enzymes and HSCs produced much less paracrines. It has been assumed that 2-AG secreted by HSCs may activate CB1 receptors, further promoting fat synthesis and inhibiting fatty acid oxidation in the liver cells (12).

Alcohol can promote Kupffer cell polarization transfer to the M1 phenotype, a proinflammatory phenotype, which can upregulate cytokines, chemokines and their cognate receptors, finally inducing alcoholic steatohepatitis (34). Some studies have found that *in vivo* activation of CB2 receptors can prevent Kupffer cells to transform to their M1 phenotype. However, some *in vitro* studies showed that the activation of CB2 receptors induced the polarization of Kupffer cells, leading to their transformtion to M2 phenotype and inhibition of inflammatory response. CB2 receptor agonist JWH-133 can inhibit inflammatory reaction induced by lipopolysaccharide (LPS) through the inhibition of NF-kappa B pathway in Kupffer cells. In addition, the fatty liver deformation significantly increased in CB2$^{-/-}$ mice with alcohol. In CB2$^{-/-}$ mice exposed to alcohol treated with JWH-133, however, there is no obvious fatty degeneration in liver cells (35). Since hepatocytes do not express CB2 receptors (36, 37), the anti-inflammatory effects mediated by CB2 activation are mainly derived from Kupffer cells. Targeting CB2 receptors by its agonists may provide a potential useful strategy for the treatment of alcoholic liver injury (Figure 1).

5.2. Non-alcoholic fatty liver diseases

The metabolic syndrome is referred to as insulin resistance with central obesity, hyperlipidemia, fatty degeneration of the liver, and other metabolic disorders.

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The high fat diet is an important factor or tool to induce the metabolic syndrome. There are reports that AEA increased significantly in liver tissue in mice with high-fat diet (38). Compared to mice fed with normal chow, the expression of CB1 receptors in liver tissue from mice on the high-fat di*et al*so increased significantly. In CB1 gene knockout (KO) mice, 3 or 14 weeks of high-fat diet failed to induce hepatocyte fatty degeneration and had no effects to increase their body weight and blood triglycerides and insulin levels compared to their WT littermates. In addition, CB1 agonist, HU–210 induced obvious glucose intolerance and insulin resistance in WT mice, but not in CB1 KO mice. CB1 antagonist SR141716 reversed the effects of HU-210. It has been suggested that high-fat diet induces nonalcoholic fatty hepatitis and activated CB1 receptor in liver tissue, which may contribute at least to some of metabolic changes observed in the metabolic syndrome. In addition, there is evidence that CB1 receptor activation participates in the liver steatosis and related hormonal and metabolic changes. It appears that CB1 receptor antagonist may be possibly used for the treatment of the metabolic syndrome (39). As mentioned above, the expression of CB2 receptors was significantly increased in liver tissues of patients with non alcoholic fatty liver (40). In animal experiments, it was found that CB2 receptor gene KO mice on the high fat diet had increased insulin sensitivity, but reduced hepatic steatosis, lowered blood triglyceride concentrations and suppressed inflammatory factor production compared to WT mice on the same diet. However, in obese mice receiving CB2 receptor agonist, jwh-133, the insulin resistance and liver tissue triglyceride aggregation increased significantly, and the production of inflammatory cytokines was also enhanced. These results suggest that the activation of CB2 receptors may promote insulin resistance and other metabolic changes during high fat diet (36).

5.3. Autoimmune hepatitis

Autoimmune hepatitis is a liver disease with probable autoimmune etiology, and the target of the autoimmune attack is hepatocyte in autoimmune hepatitis (41). The occurrence and development of this autoimmune disease is favored by the breakdown of immune-regulatory mechanisms (41). Some studies have demonstrated that, in a mouse model of concanavalin A (ConA)-induced antoimmune hepatitis, the endocannabinoid system is involved in the modulation of this disease, and the administration of anandamide can decrease serum ALT and AST levels, liver injury and inflammatory cytokines (e.g. TNF-a, interleukin-9 and interleukin-12) in this mouse model (31, 42). In addition, CB1 receptor antagonist AM251 and CB2 receptor antagonist AM630 can negate the anandamide-mediated decrease in the level of serum AST (42).

5.4. Chronic viral hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common reasons for chronic viral hepatitis. Worldwide, there are about 350 to 400 million people chronically infected with HBV and about 180 million people with HCV (42). The endocannabinoid system is involved in liver disease progression, including chronic hepatitis C (43, 44), and HCV-transfected hepatocytes increased the expression of CB1 *in vitro* (45). In addition, Some studies showed that patients with chronic hepatitis C and daily cannabis consumption have more severe fibrosis than non- or occasional consumers (5, 46, 47). AEA and 2-AG are increased in plasma of patients with chronic hepatitis C, and increased AEA and 2-AG can suppress inflammatory cytokines production and aggravate liver fibrosis via direct HSC activation, which reveal immunosuppressive and profibrogenic effects (48). Taken together, the endocannabinoid system can be a future therapeutic target in chronic hepatitis C.

5.5. Liver fibrosis and cirrhosis

Liver fibrosis, namely, deposition of collagen fibers in liver tissue, is the end-stage of chronic progressive liver disease caused by various injury factors. The center mechanism leading to liver fibrosis is mainly associated with the resting state of HSCs, where these cells are activated and differentiate into fibroblast and secretory myofibroblasts. These activated HSC or myofibroblasts can secrete lots of extracellular matrix (ECM) proteins, resulting in the imbalance of generation and degradation of ECM. This promotes the occurrence and development of liver fibrosis (49). So far, there are no effective treatments to cure liver fibrosis. In terms of the potential of the ECS as a therapeutic target for liver fibrosis, some studies showed that AEA can induce necrosis of HSCs (23), and other studies found that AEA inhibited HSCs growth in a concentration-dependent manner. Furthermore, a high concentration of AEA (20 μmol/L) was shown to trigger marked necrosis, but not apoptosis in the liver (50). Some reports have shown that the level of AEA and 2-AG increased in liver tissue and peripheral blood of patients or animal models with liver cirrhosis (23-25). Studies in patients with hepatitis C have also shown that smoking marijuana can promote liver fibrosis (5). There is agreement that eCBs promote liver fibrosis in different chronic liver diseases.

Liver fibrosis is a common outcome of chronic liver diseases and leads to liver cirrhosis and hepatocellular carcinoma. Liver fibrosis stands for a kind of pathological change in liver, which is a key stage for the development of liver cirrhosis. With respect to the changes of CB receptors and their actions during liver cirrhosis, there are reports showing that the expression if this type of CB receptors increased significantly in liver tissues of patients with liver cirrhosis. In animal models with liver fibrosis induced by carbon tetrachloride, bile duct ligation and thioacetamide (TAA), the expression of CB1 receptors was also found increased. This increased expression of CB1 receptors may exert action in liver cirrhosis through increase in TGF-beta and alpha 1-SMA

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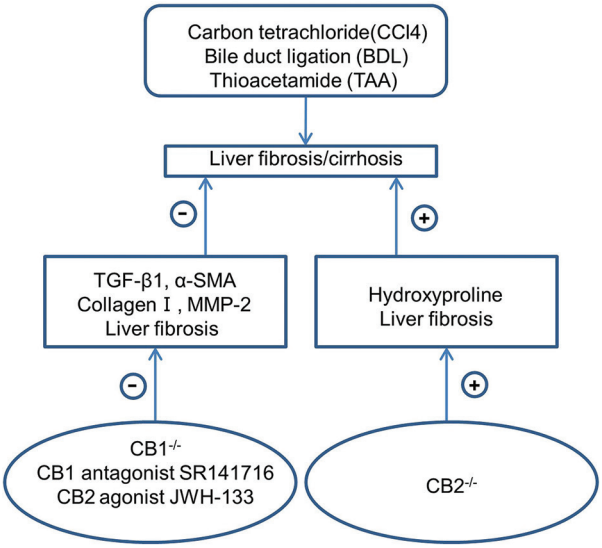

Figure 2. Endocannabinoid receptors in liver fibrosis/cirrhosis. CB1 antagonists are potential targets for liver fibrosis. Activation of CB2 receptors may inhibit the development of liver fibrosis.

production as knocking out of CB1 gene or giving CB1 antagonists SR141716 prevented TGF-beta and alpha 1-SMA production in mice. In these mice with CB1 gene deletion or receiving CB1 antagonists, the degree of liver fibrosis was also significantly reduced (10). In addition, CB1 antagonist, SR141716 was also demonstrated to improve ascites and sodium imbalances in rats with liver cirrhosis induced by carbon tetrachloride (3), and silencing CB1 receptor gene or administrating antagonists CB1 receptors also prevented liver fibrosis in mice with bile duct ligation (3, 51). We found that the fibrotic activation of HSCs on *Schistosoma J.* infection was associated with NADPH oxidase-mediated redox regulation of CB1 expression, which may be a triggering mechanism for schistosomiasis-associated liver fibrosis (SSLF). This NADPH oxidase activation may be attributable to the formation lipid raft redox signaling platforms in HSCs (4). All these findings strongly suggest that CB1 receptor activation is a fibrotic mechanism and that CB1 receptor antagonists could be potential candidates of medication for prevention and treatment of liver cirrhosis.

It has been well known that in the liver, IL-22 displays hepatoprotective effects and stimulates hepatic regeneration (52), while IL-17 is profibrogenic either due to enhanced inflammation or to direct activation of myofibroblast profibrogenic function (53, 54). This profibrogenic effect of IL-17 and the antifibrogenic properties of IL-22 have also been reported in liver under pathological conditions (55). Interestingly, CB2 receptor activation was found to decrease liver fibrosis by selective reduction of IL-17 production via a STAT5-dependent pathway and strong suppression of the proinflammatory effects of IL-17 on its target cells (56). Although CB2 receptors are not expressed in normal liver tissues, they are increased in liver with cirrhosis and fibrosis. This increased CB2 receptor expression may modulate fibrogenesis during liver cirrhosis induced by carbon tetrachloride because CB2 receptor gene knockout increased the degree of fibrosis progression (29). Indeed, the expressions of TGF-β1 and collagen type I as well as the content of collagen fibers were shown to be significantly reduced when rats with liver fibrosis received CB2 receptor agonist, JWH – 133, while the expression and activity of MMP-2 were increased (57). This anti-fibrotic action of CB2 receptors was also confirmed in other organs when they are stimulated by fibrogenic factors (58, 59). All these findings suggest that the activation of CB2 receptors may be protective from liver fibrosis under different pathological conditions (Figure 2).

6. ENDOCANNABINOID RECEPTORS IN CIRRHOTIC COMPLICATIONS

6.1. Hepatic encephalopathy

Hepatic encephalopathy is one of the most serious complications of hepatic cirrhosis and the most common cause of death in patients with liver dysfunction or cirrhosis at the end stage. This central nervous system (CNS) dysfunction syndrome is a metabolic disorder with features of disturbance in consciousness, behavior disorders, and even coma (60). It has been reported that injection of liver fibrogenic reagent, TAA markedly increased the level of eCBs, 2-AG and CB2 expression in the mouse brain. Mouse CNS symptoms were improved after treatment of experimental mice with 2-AG, but enhanced by SR141716. In CB2 receptor gene knockout mice, the CNS protective effects of 2-AG disappeared. Mechanistically, it has been demonstrated that CB2 receptor-mediated neural protective effects at the end stage of cirrhosis are attributed to the activation of AMP-associated protein kinase, which regulates energy balance to control the cognitive function of brain and the apoptosis of neurons (61). In addition, the improvement of cognitive and other CNS symptoms in hepatic encephalopathy by CB2 receptor agonists was also observed in liver cirrhotic mouse models with bile duct ligation, which is associated with activation of 5-HT1A receptor function and inhibition of the inflammatory response, but this protective effect has nothing to do with the improvement of liver function (62). It is clear that CB2 receptors in the CNS are importantly involved in the counteraction on hepatic encephalopathy (49) (Figure 3).

6.2. Cirrhotic cardiomyopathy

There is evidence that eCBs can increase mesenteric vascular diameter, blood flow and cardiac output in rats suffering from liver cirrhosis induced by bile duct ligation (63). In these rats, CB1 receptor antagonist AM251 was found to recover the slow reaction of

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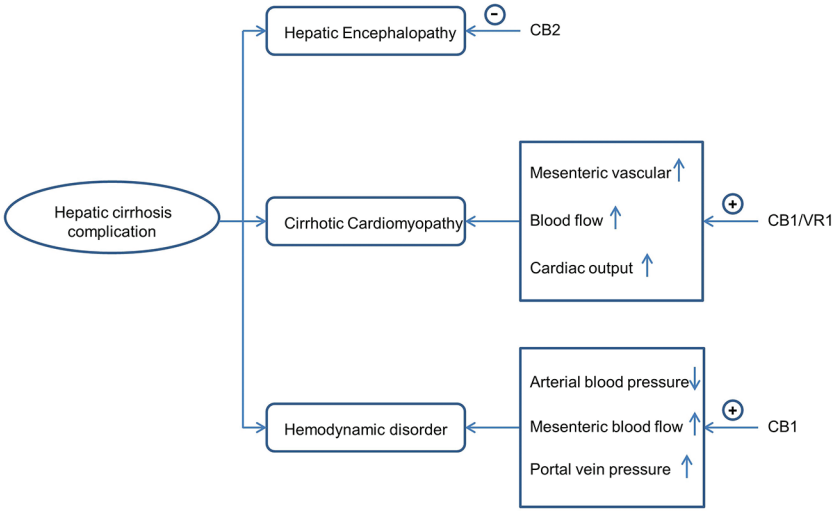

Figure 3. Endocannabinoid receptors in cirrhotic complications. CB2 receptor activation may improve hepatic encephalopathy, but CB1 and TRPV1 may mediate cirrhotic complications due to their action to induce a hyperdynamic circulatory syndrome, mesenteric congestion, and sodium retention.

myocardium to adrenaline, to narrow mesenteric artery, and to reduce the superior mesenteric artery blood flow, but to increase cardiac output. However, the capsaicin receptor, the transient receptor potential vanilloid receptor 1 (TRPV1) antagonist capsazepine reduced the cardiac output, decreased the mesenteric artery diameter and blood flow, and increased the systemic vascular resistance despite that the CB2 antagonist, AM630 had no effects (64). It is possible that via CB1 and TRPV1 receptor-mediated mechanism, eCBs are involved in high power cycle of the heart and in mesenteric congestion process during liver cirrhosis (65) (Figure 3).

6.3. Portal hypertension

In liver cirrhosis, hepatic lobular reconstruction and regenerative nodule formation will result in portal hypertension, which increases the blood volume and resistance of portal vein. The dilatation of small blood vessels within the liver leads to higher power cycle of the heart, hypotension and mesenteric congestion, which further aggravates the portal hypertension. Studies have confirmed that CBs like THC, AEA and 2-AG can cause long periods of bradycardia (66-68). This effect can be blocked by CB1 antagonists (24). At the same time, CB1 antagonists can also reduce portal vein and mesenteric blood flow (65, 67-69), and their effect may be associated with the anti-fibrotic effect during chronic liver injury (69). The level of AEA isolated from macrophages and platelets of peripheral blood in patients or animals with liver cirrhosis is higher than that in normal humans or animals. It has been reported that after receiving transfusion of isolated macrophages or platelets, which were treated with SR141716 to block CB1 receptors, rats had increased arterial blood pressure, lower mesenteric blood flow and decreased portal venous pressure compared to those without cell transfusion. The mechanism is assumed to be associated with the upregulation of CB1 receptors in vascular endothelial cells during liver cirrhosis, which enhanced the sensitivity to vasodilatory factors or paracrine AEA secreted by macrophages or platelets adhesive on the endothelium. AEA binds to CB1 receptors on endothelial cells and activates the downstream signal transduction pathways, enhancing diastolic vascular reactivity (68) (also see Figure 3).

6.4. Hepatorenal syndrome

Acute kidney injury (AKI) is a common complication of patients with advanced cirrhosis. Approximately 20% of hospitalized cirrhotic patients may develop renal dysfunction or renal insufficiency, which is related to poor prognosis in patients with liver cirrhosis (70-72). Hepatorenal syndrome (HRS) is characterized by functional prerenal AKI, which is not responsive to volume expansion. It has been reported that HRS is a unique cause of renal failure in patients with liver cirrhosis (73-75). This syndrome includes two types: a rapidly progressive type 1 and a more prolonged type-2 (70). A functional eCB system has been found in the kidney and it can be activated during kidney injury (76-78). There is evidence that the activation of CB2 receptors, which are mainly expressed in immune cells, renal endothelial and certain parenchymal cells, can protect against tissue damage in various experimental models such as I/R injury (26, 79, 80). The ECS through CB2 receptors protects the kidney from chemotherapeutic drug cisplatin by attenuation of local inflammation and oxidative stress (76). In contrast, activation of CB1 receptors may participate in the development of renal diseases associated with enhanced inflammation and cell death (77). It has been well known that the HRS is mainly associated with

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infections and hypovolemia (72, 81), which initiates a cascade of hemodynamic disturbances that aggravate vasodilation and further damage renal function (82, 83). Some studies reported that eCBs participate in peripheral vasodilation of experimental cirrhosis, which may cause HRS (24, 84). The hypotensive effects of AEA may be associated with CB1 and non-CB1 receptor-mediated vasodilation due to hyperpolarization (85) and TRPV1 activity (86). Another possible mechanism by which eCBs contribute to HRS may be associated with their effects on sodium balance and retention to form ascites. It has been reported that CB1 receptor antagonist, rimonabant reduced sodium retentions and delayed decompensation in preascitic experimental cirrhosis, which is likely to be attributed to improvement in systemic and renal hemodynamics (3). In some other studies, although the plasma level of endogenously produced AEA was found elevated in patients with liver cirrhosis, this increase in AEA was neither correlated with the degree of hepatic and kidney dysfunction nor with the extent of hemodynamic disturbance (87). More studies are needed to further confirm the role of eCBs in the initiation or modulation of HRS during liver cirrhosis.

7. ENDOCANNABINOID RECEPTORS IN OTHER LIVER DISEASES

Liver cancer is the second most prevalent cancer worldwide, including hepatocellular carcinoma (HCC) and cholangiocarcinoma. HCC is the most predominant liver cancer, which accounts for four out of five liver tumors. Some studies reported that CB1R is significantly overexpressed in both mouse and human HCC (88, 89), and blockade or genetic ablation of CB1R can suppress the growth of HCC, which reveals the tumor-promoting function of the endocannabinoid/CB1R system acting through hepatic CB1R (88). The expression of CB1 and CB2 receptors in cancerous tissue is higher than in the non-malignant liver tissue, and well-differentiated hepatocellular tumors showed a higher expression and poorly differentiated tumors exhibited low CB1 immunoreactivity (89). The synthetic cannabinoid WIN 55,212-2 (WIN) can induce apoptosis in a HCC cell line by modulating CB1 and CB2 receptors (90). These findings suggest that modulation of CB receptors may have a role in the treatment of HCC. In addition, cholangiocarcinoma has limited treatment options and poor prognosis. Some reports have demonstrated that cannabinoids, including AEA and 2-AG, were involved in cholangiocarcinoma growth *in vitro* and *in vivo* (91). AEA showed antiproliferative actions; however, 2-AG showed growth-promoting effects on cholangiocarcinoma growth through different mechanisms (91-93).

8. CLINICAL PERSPECTIVE

Despite some reports on the use of eCBs in the treatment of liver diseases, clinical studies or trials are still very limited. In the North America, a randomized controlled clinical trial demonstrated that CB1 receptor antagonist, rimonabant (SR141716) treatment in patients with overweight and obesity remarkably reduced the patients' body weight and waist circumference and thereby improved their cardiovascular adverse effects (94). In the European Union, rimonabant has even been approved for the treatment of obesity and nonalcoholic fatty liver in 2006. In the process of clinical application of this medication, however, the main problem is the high dosage required, which may lead to the increased incidence rate of dose dependency and possible adverse reactions. In addition, rimonabant was also found to produce spiritual aspects such as depression and anxiety in patients (40). It was also reported to increase the risk of suicide, which resulted in a withdrawal of rimonabant for clinical use in the European Union in January 2009 (95). In recent years, efforts have been made to develop the second generation of CB1 receptor antagonists such as Taranabant and Bromine, which will improve its selectivity and lower the dosage to be used for patients. It is anticipated that these new antagonists or agonists of CB receptors will be developed for clinical use in the future, which are more efficient and without mental side effects.

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10. REFERENCES

1. H. Bernadette: Cannabinoid therapeutics: high hopes for the future. *Drug Discov Today*, 10(7), 459-62 (2005) DOI: 10.1016/S1359-6446(05)03417-3
2. B. S. Basavarajappa, M. Saito, T. B. Cooper and B. L. Hungund: Stimulation of cannabinoid receptor agonist 2-arachidonylglycerol by chronic ethanol and its modulation by specific neuromodulators in cerebellar granule neurons. *Biochim Biophys Acta*, 1535(1), 78-86 (2000) DOI: 10.1016/S0925-4439(00)00085-5
3. M. Domenicali, P. Caraceni, F. Giannone, A. M. Pertosa, A. Principe, A. Zambruni, F. Trevisani, T. Croci and M. Bernardi: Cannabinoid type 1 receptor antagonism delays ascites formation in rats with cirrhosis. *Gastroenterology*, 137(1), 341-9 (2009) DOI: 10.1053/j.gastro.2009.01.004
4. M. Wang, J. M. Abais, N. Meng, Y. Zhang,

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J. K. Ritter, P. L. Li and W. X. Tang: Upregulation of cannabinoid receptor-1 and fibrotic activation of mouse hepatic stellate cells during Schistosoma J. infection: role of NADPH oxidase. *Free Radic Biol Med*, 71, 109-20 (2014
DOI: 10.1016/j.freeradbiomed.2014.03.015

5. C. Hezode, F. Roudot-Thoraval, S. Nguyen, P. Grenard, B. Julien, E. S. Zafrani, J. M. Pawlotsky, D. Dhumeaux, S. Lotersztajn and A. Mallat: Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology*, 42(1), 63-71 (2005)
DOI: 10.1002/hep.20733

6. A. Mallat and S. Lotersztajn: Endocannabinoids and liver disease. I. Endocannabinoids and their receptors in the liver. *Am J Physiol Gastrointest Liver Physiol*, 294(1), G9-G12 (2008)
DOI: 10.1152/ajpgi.00467.2007

7. P. Caraceni, A. M. Pertosa, F. Giannone, M. Domenicali, I. Grattagliano, A. Principe, C. Mastroleo, M. G. Perrelli, J. Cutrin, F. Trevisani, T. Croci and M. Bernardi: Antagonism of the cannabinoid CB-1 receptor protects rat liver against ischaemia-reperfusion injury complicated by endotoxaemia. *Gut*, 58(8), 1135-43 (2009)
DOI: 10.1136/gut.2007.147652

8. A. J. Sanchez Lopez, L. Roman-Vega, E. Ramil Tojeiro, A. Giuffrida and A. Garcia-Merino: Regulation of cannabinoid receptor gene expression and endocannabinoid levels in lymphocyte subsets by interferon-beta: a longitudinal study in multiple sclerosis patients. *Clin Exp Immunol*, 179(1), 119-27 (2015)
DOI: 10.1111/cei.12443

9. W. A. Devane, L. Hanus, A. Breuer, R. G. Pertwee, L. A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger and R. Mechoulam: Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, 258(5090), 1946-9 (1992)
DOI: 10.1126/science.1470919

10. F. Teixeira-Clerc, B. Julien, P. Grenard, J. Tran Van Nhieu, V. Deveaux, L. Li, V. Serriere-Lanneau, C. Ledent, A. Mallat and S. Lotersztajn: CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. *Nat Med*, 12(6), 671-6 (2006)
DOI: 10.1038/nm1421

11. N. E. Buckley, S. Hansson, G. Harta and E. Mezey: Expression of the CB1 and CB2 receptor messenger RNAs during embryonic development in the rat. *Neuroscience*, 82(4), 1131-49 (1998)
DOI: 10.1016/S0306-4522(97)00348-5

12. W. I. Jeong, D. Osei-Hyiaman, O. Park, J. Liu, S. Batkai, P. Mukhopadhyay, N. Horiguchi, J. Harvey-White, G. Marsicano, B. Lutz, B. Gao and G. Kunos: Paracrine activation of hepatic CB1 receptors by stellate cell-derived endocannabinoids mediates alcoholic fatty liver. *Cell Metab*, 7(3), 227-35 (2008)
DOI: 10.1016/j.cmet.2007.12.007

13. V. Di Marzo, M. Bifulco and L. De Petrocellis: The endocannabinoid system and its therapeutic exploitation. *Nat Rev Drug Discov*, 3(9), 771-84 (2004)
DOI: 10.1038/nrd1495

14. R. N. Kumar, W. A. Chambers and R. G. Pertwee: Pharmacological actions and therapeutic uses of cannabis and cannabinoids. *Anaesthesia*, 56(11), 1059-68 (2001)
DOI: 10.1046/j.1365-2044.2001.02269.x

15. R. G. Pertwee: Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther*, 74(2), 129-80 (1997)
DOI: 10.1016/S0163-7258(97)82001-3

16. B. Mukhopadhyay, R. Cinar, S. Yin, J. Liu, J. Tam, G. Godlewski, J. Harvey-White, I. Mordi, B. F. Cravatt, S. Lotersztajn, B. Gao, Q. Yuan, K. Schuebel, D. Goldman and G. Kunos: Hyperactivation of anandamide synthesis and regulation of cell-cycle progression via cannabinoid type 1 (CB1) receptors in the regenerating liver. *Proc Natl Acad Sci U S A*, 108(15), 6323-8 (2011)
DOI: 10.1073/pnas.1017689108

17. R. G. Pertwee: GPR55: a new member of the cannabinoid receptor clan? *Br J Pharmacol*, 152(7), 984-6 (2007)
DOI: 10.1038/sj.bjp.0707464

18. E. Ryberg, N. Larsson, S. Sjogren, S. Hjorth, N. O. Hermansson, J. Leonova, T. Elebring, K. Nilsson, T. Drmota and P. J. Greasley: The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol*, 152(7), 1092-101 (2007)
DOI: 10.1038/sj.bjp.0707460

© 1996-2016

19. J. E. Lauckner, J. B. Jensen, H. Y. Chen, H. C. Lu, B. Hille and K. Mackie: GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. *Proc Natl Acad Sci U S A*, 105(7), 2699-704 (2008
DOI: 10.1073/pnas.0711278105

20. A. Moriconi, I. Cerbara, M. Maccarrone and A. Topai: GPR55: Current knowledge and future perspectives of a purported "Type-3" cannabinoid receptor. *Curr Med Chem*, 17(14), 1411-29 (2010)

21. V. Di Marzo and L. De Petrocellis: Endocannabinoids as regulators of transient receptor potential (TRP) channels: A further opportunity to develop new endocannabinoid-based therapeutic drugs. *Curr Med Chem*, 17(14), 1430-49 (2010)
DOI: 10.2174/092986710790980078

22. M. Pistis and M. Melis: From surface to nuclear receptors: the endocannabinoid family extends its assets. *Curr Med Chem*, 17(14), 1450-67 (2010)
DOI: 10.2174/092986710790980014

23. S. V. Siegmund, H. Uchinami, Y. Osawa, D. A. Brenner and R. F. Schwabe: Anandamide induces necrosis in primary hepatic stellate cells. *Hepatology*, 41(5), 1085-95 (2005)
DOI: 10.1002/hep.20667

24. S. Batkai, Z. Jarai, J. A. Wagner, S. K. Goparaju, K. Varga, J. Liu, L. Wang, F. Mirshahi, A. D. Khanolkar, A. Makriyannis, R. Urbaschek, N. Garcia, Jr., A. J. Sanyal and G. Kunos: Endocannabinoids acting at vascular CB1 receptors mediate the vasodilated state in advanced liver cirrhosis. *Nat Med*, 7(7), 827-32 (2001)
DOI: 10.1038/89953

25. S. V. Siegmund, T. Qian, S. de Minicis, J. Harvey-White, G. Kunos, K. Y. Vinod, B. Hungund and R. F. Schwabe: The endocannabinoid 2-arachidonoyl glycerol induces death of hepatic stellate cells via mitochondrial reactive oxygen species. *FASEB J*, 21(11), 2798-806 (2007)
DOI: 10.1096/fj.06-7717com

26. S. Batkai, D. Osei-Hyiaman, H. Pan, O. El-Assal, M. Rajesh, P. Mukhopadhyay, F. Hong, J. Harvey-White, A. Jafri, G. Hasko, J. W. Huffman, B. Gao, G. Kunos and P. Pacher: Cannabinoid-2 receptor mediates protection against hepatic ischemia/reperfusion injury. *FASEB J*, 21(8), 1788-800 (2007)
DOI: 10.1096/fj.06-7451com

27. M. Rajesh, H. Pan, P. Mukhopadhyay, S. Batkai, D. Osei-Hyiaman, G. Hasko, L. Liaudet, B. Gao and P. Pacher: Cannabinoid-2 receptor agonist HU-308 protects against hepatic ischemia/reperfusion injury by attenuating oxidative stress, inflammatory response, and apoptosis. *J Leukoc Biol*, 82(6), 1382-9 (2007)
DOI: 10.1189/jlb.0307180

28. A. A. Izzo and D. G. Deutsch: Unique pathway for anandamide synthesis and liver regeneration. *Proc Natl Acad Sci U S A*, 108(16), 6339-40 (2011)
DOI: 10.1073/pnas.1103566108

29. B. Julien, P. Grenard, F. Teixeira-Clerc, J. T. Van Nhieu, L. Li, M. Karsak, A. Zimmer, A. Mallat and S. Lotersztajn: Antifibrogenic role of the cannabinoid receptor CB2 in the liver. *Gastroenterology*, 128(3), 742-55 (2005)
DOI: 10.1053/j.gastro.2004.12.050

30. Y. Avraham, O. Zolotarev, N. C. Grigoriadis, T. Poutahidis, I. Magen, L. Vorobiav, A. Zimmer, Y. Ilan, R. Mechoulam and E. M. Berry: Cannabinoids and capsaicin improve liver function following thioacetamide-induced acute injury in mice. *Am J Gastroenterol*, 103(12), 3047-56 (2008)
DOI: 10.1111/j.1572-0241.2008.02155.x

31. V. L. Hegde, S. Hegde, B. F. Cravatt, L. J. Hofseth, M. Nagarkatti and P. S. Nagarkatti: Attenuation of experimental autoimmune hepatitis by exogenous and endogenous cannabinoids: involvement of regulatory T cells. *Mol Pharmacol*, 74(1), 20-33 (2008)
DOI: 10.1124/mol.108.047035

32. C. S. Lieber and R. Schmid: The effect of ethanol on fatty acid metabolism; stimulation of hepatic fatty acid synthesis *in vitro*. *J Clin Invest*, 40, 394-9 (1961)
DOI: 10.1172/JCI104266

33. M. You, M. Fischer, M. A. Deeg and D. W. Crabb: Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). *J Biol Chem*, 277(32), 29342-7 (2002)
DOI: 10.1074/jbc.M202411200

34. P. Mandrekar and G. Szabo: Signalling

© 1996-2016

pathways in alcohol-induced liver inflammation. *J Hepatol*, 50(6), 1258-66 (2009)
DOI: 10.1016/j.jhep.2009.03.007

35. A. Mallat, F. Teixeira-Clerc, V. Deveaux, S. Manin and S. Lotersztajn: The endocannabinoid system as a key mediator during liver diseases: new insights and therapeutic openings. *Br J Pharmacol*, 163(7), 1432-40 (2011)
DOI: 10.1111/j.1476-5381.2011.01397.x

36. V. Deveaux, T. Cadoudal, Y. Ichigotani, F. Teixeira-Clerc, A. Louvet, S. Manin, J. T. Nhieu, M. P. Belot, A. Zimmer, P. Even, P. D. Cani, C. Knauf, R. Burcelin, A. Bertola, Y. Le Marchand-Brustel, P. Gual, A. Mallat and S. Lotersztajn: Cannabinoid CB2 receptor potentiates obesity-associated inflammation, insulin resistance and hepatic steatosis. *PLoS One*, 4(6), e5844 (2009)
DOI: 10.1371/journal.pone.0005844

37. F. Teixeira-Clerc, M. P. Belot, S. Manin, V. Deveaux, T. Cadoudal, M. N. Chobert, A. Louvet, A. Zimmer, T. Tordjmann, A. Mallat and S. Lotersztajn: Beneficial paracrine effects of cannabinoid receptor 2 on liver injury and regeneration. *Hepatology*, 52(3), 1046-59 (2010)
DOI: 10.1002/hep.23779

38. D. Osei-Hyiaman, M. DePetrillo, P. Pacher, J. Liu, S. Radaeva, S. Batkai, J. Harvey-White, K. Mackie, L. Offertaler, L. Wang and G. Kunos: Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest*, 115(5), 1298-305 (2005)
DOI: 10.1172/JCI200523057

39. D. Osei-Hyiaman, J. Liu, L. Zhou, G. Godlewski, J. Harvey-White, W. I. Jeong, S. Batkai, G. Marsicano, B. Lutz, C. Buettner and G. Kunos: Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *J Clin Invest*, 118(9), 3160-9 (2008)
DOI: 10.1172/JCI34827

40. T. Yoshino, K. Nisijima, K. Shioda, K. Yui and S. Katoh: Perospirone, a novel atypical antipsychotic drug, potentiates fluoxetine-induced increases in dopamine levels via multireceptor actions in the rat medial prefrontal cortex. *Neurosci Lett*, 364(1), 16-21 (2004)
DOI: 10.1016/j.neulet.2004.03.079

41. R. Liberal, C. R. Grant, M. S. Longhi, G. Mieli-Vergani and D. Vergani: Regulatory T cells: Mechanisms of suppression and impairment in autoimmune liver disease. *IUBMB Life*, 67(2), 88-97 (2015)
DOI: 10.1002/iub.1349

42. P. P. Basu, M. M. Aloysius, N. J. Shah and R. S. Brown, Jr.: Review article: the endocannabinoid system in liver disease, a potential therapeutic targ*et aliment Pharmacol Ther*, 39(8), 790-801 (2014)
DOI: 10.1111/apt.12673

43. L. Zhou, L. Ding, P. Yin, X. Lu, X. Wang, J. Niu, P. Gao and G. Xu: Serum metabolic profiling study of hepatocellular carcinoma infected with hepatitis B or hepatitis C virus by using liquid chromatography-mass spectrometry. *J Proteome Res*, 11(11), 5433-42 (2012)
DOI: 10.1111/apt.12673

44. A. Mallat, F. Teixeira-Clerc and S. Lotersztajn: Cannabinoid signaling and liver therapeutics. *J Hepatol*, 59(4), 891-6 (2013)
DOI: 10.1016/j.jhep.2013.03.032

45. D. van der Poorten, M. Shahidi, E. Tay, J. Sesha, K. Tran, D. McLeod, J. S. Milliken, V. Ho, L. W. Hebbard, M. W. Douglas and J. George: Hepatitis C virus induces the cannabinoid receptor 1. *PLoS One*, 5(9) (2010)
DOI: 10.1371/journal.pone.0012841

46. J. H. Ishida, M. G. Peters, C. Jin, K. Louie, V. Tan, P. Bacchetti and N. A. Terrault: Influence of cannabis use on severity of hepatitis C disease. *Clin Gastroenterol Hepatol*, 6(1), 69-75 (2008)
DOI: 10.1016/j.cgh.2007.10.021

47. C. Hezode, E. S. Zafrani, F. Roudot-Thoraval, C. Costentin, A. Hessami, M. Bouvier-Alias, F. Medkour, J. M. Pawlostky, S. Lotersztajn and A. Mallat: Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology*, 134(2), 432-9 (2008)
DOI: 10.1053/j.gastro.2007.11.039

48. E. Patsenker, P. Sachse, A. Chicca, M. S. Gachet, V. Schneider, J. Mattsson, C. Lanz, M. Worni, A. de Gottardi, M. Semmo, J. Hampe, C. Schafmayer, R. Brenneisen, J. Gertsch, F. Stickel and N. Semmo: Elevated levels

© 1996-2016

of endocannabinoids in chronic hepatitis C may modulate cellular immune response and hepatic stellate cell activation. *Int J Mol Sci*, 16(4), 7057-76 (2015)
DOI: 10.3390/ijms16047057

49. S. Lotersztajn, F. Teixeira-Clerc, B. Julien, V. Deveaux, Y. Ichigotani, S. Manin, J. Tran-Van-Nhieu, M. Karsak, A. Zimmer and A. Mallat: CB2 receptors as new therapeutic targets for liver diseases. *Br J Pharmacol*, 153(2), 286-9 (2008)
DOI: 10.1038/sj.bjp.0707511

50. Q. Yang, H. Y. Liu, Y. W. Zhang, W. J. Wu and W. X. Tang: Anandamide induces cell death through lipid rafts in hepatic stellate cells. *J Gastroenterol Hepatol*, 25(5), 991-1001 (2010)
DOI: 10.1111/j.1440-1746.2009.06122.x

51. Y. Y. Yang, H. C. Lin, Y. T. Huang, T. Y. Lee, M. C. Hou, Y. W. Wang, F. Y. Lee and S. D. Lee: Effect of chronic CB1 cannabinoid receptor antagonism on livers of rats with biliary cirrhosis. *Clin Sci (Lond)*, 112(10), 533-42 (2007)
DOI: 10.1042/CS20060260

52. W. W. Xing, M. J. Zou, S. Liu, T. Xu, J. Gao, J. X. Wang and D. G. Xu: Hepatoprotective effects of IL-22 on fulminant hepatic failure induced by d-galactosamine and lipopolysaccharide in mice. *Cytokine*, 56(2), 174-9 (2011)
DOI: 10.1016/j.cyto.2011.07.022

53. D. M. Cortez, M. D. Feldman, S. Mummidi, A. J. Valente, B. Steffensen, M. Vincenti, J. L. Barnes and B. Chandrasekar: IL-17 stimulates MMP-1 expression in primary human cardiac fibroblasts via p38 MAPK- and ERK1/2-dependent C/EBP-beta, NF-kappaB, and AP-1 activation. *Am J Physiol Heart Circ Physiol*, 293(6), H3356-65 (2007)
DOI: 10.1016/j.cyto.2011.07.022

54. W. Feng, W. Li, W. Liu, F. Wang, Y. Li and W. Yan: IL-17 induces myocardial fibrosis and enhances RANKL/OPG and MMP/TIMP signaling in isoproterenol-induced heart failure. *Exp Mol Pathol*, 87(3), 212-8 (2009)
DOI: 10.1016/j.yexmp.2009.06.001

55. X. Kong, D. Feng, H. Wang, F. Hong, A. Bertola, F. S. Wang and B. Gao: Interleukin-22 induces hepatic stellate cell senescence and restricts liver fibrosis in mice. *Hepatology*, 56(3), 1150-9 (2012)
DOI: 10.1002/hep.25744

56. A. Guillot, N. Hamdaoui, A. Bizy, K. Zoltani, R. Souktani, E. S. Zafrani, A. Mallat, S. Lotersztajn and F. Lafdil: Cannabinoid receptor 2 counteracts interleukin-17-induced immune and fibrogenic responses in mouse liver. *Hepatology*, 59(1), 296-306 (2014)
DOI: 10.1002/hep.26598

57. J. Munoz-Luque, J. Ros, G. Fernandez-Varo, S. Tugues, M. Morales-Ruiz, C. E. Alvarez, S. L. Friedman, V. Arroyo and W. Jimenez: Regression of fibrosis after chronic stimulation of cannabinoid CB2 receptor in cirrhotic rats. *J Pharmacol Exp Ther*, 324(2), 475-83 (2008)
DOI: 10.1124/jpet.107.131896

58. N. Defer, J. Wan, R. Souktani, B. Escoubet, M. Perier, P. Caramelle, S. Manin, V. Deveaux, M. C. Bourin, A. Zimmer, S. Lotersztajn, F. Pecker and C. Pavoine: The cannabinoid receptor type 2 promotes cardiac myocyte and fibroblast survival and protects against ischemia/reperfusion-induced cardiomyopathy. *FASEB J*, 23(7), 2120-30 (2009)
DOI: 10.1096/fj.09-129478

59. A. Servettaz, N. Kavian, C. Nicco, V. Deveaux, C. Chereau, A. Wang, A. Zimmer, S. Lotersztajn, B. Weill and F. Batteux: Targeting the cannabinoid pathway limits the development of fibrosis and autoimmunity in a mouse model of systemic sclerosis. *Am J Pathol*, 177(1), 187-96 (2010)
DOI: 10.2353/ajpath.2010.090763

60. I. Magen, Y. Avraham, E. Berry and R. Mechoulam: Endocannabinoids in liver disease and hepatic encephalopathy. *Curr Pharm Des*, 14(23), 2362-9 (2008)
DOI: 10.2174/138161208785740063

61. Y. Dagon, Y. Avraham, Y. Ilan, R. Mechoulam and E. M. Berry: Cannabinoids ameliorate cerebral dysfunction following liver failure via AMP-activated protein kinase. *FASEB J*, 21(10), 2431-41 (2007)
DOI: 10.1096/fj.06-7705com

62. Y. Avraham, E. Israeli, E. Gabbay, A. Okun, O. Zolotarev, I. Silberman, V. Ganzburg, Y. Dagon, I. Magen, L. Vorobia, O. Pappo, R. Mechoulam, Y. Ilan and E. M. Berry: Endocannabinoids affect neurological and cognitive function in thioacetamide-induced hepatic encephalopathy in mice. *Neurobiol Dis*, 21(1), 237-45 (2006)

© 1996-2016

DOI: 10.1016/j.nbd.2005.07.008

63. L. Moezi, S. A. Gaskari, H. Liu, S. K. Baik, A. R. Dehpour and S. S. Lee: Anandamide mediates hyperdynamic circulation in cirrhotic rats via CB(1) and VR(1) receptors. *Br J Pharmacol*, 149(7), 898-908 (2006)
DOI: 10.1038/sj.bjp.0706928

64. S. A. Gaskari, H. Liu, L. Moezi, Y. Li, S. K. Baik and S. S. Lee: Role of endocannabinoids in the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. *Br J Pharmacol*, 146(3), 315-23 (2005)
DOI: 10.1038/sj.bjp.0706331

65. M. S. Mandell and M. Y. Tsou: Cardiovascular dysfunction in patients with end-stage liver disease. *J Chin Med Assoc*, 71(7), 331-5 (2008)
DOI: 10.1016/S1726-4901(08)70134-5

66. N. L. Benowitz and R. T. Jones: Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clin Pharmacol Ther*, 18(3), 287-97 (1975)
DOI: 10.1002/cpt1975183287

67. K. Varga, K. Lake, B. R. Martin and G. Kunos: Novel antagonist implicates the CB1 cannabinoid receptor in the hypotensive action of anandamide. *Eur J Pharmacol*, 278(3), 279-83 (1995)
DOI: 10.1016/0014-2999(95)00181-J

68. Z. Jarai, J. A. Wagner, S. K. Goparaju, L. Wang, R. K. Razdan, T. Sugiura, A. M. Zimmer, T. I. Bonner, A. Zimmer and G. Kunos: Cardiovascular effects of 2-arachidonoyl glycerol in anesthetized mice. *Hypertension*, 35(2), 679-84 (2000)
DOI: 10.1161/01.HYP.35.2.679

69. Y. Y. Yang, H. C. Lin, Y. T. Huang, T. Y. Lee, M. C. Hou, Y. W. Wang, F. Y. Lee and S. D. Lee: Role of Ca2+-dependent potassium channels in *in vitro* anandamide-mediated mesenteric vasorelaxation in rats with biliary cirrhosis. *Liver Int*, 27(8), 1045-55 (2007)
DOI: 10.1111/j.1478-3231.2007.01551.x

70. L. M. Risor, F. Bendtsen and S. Moller: Immunologic, hemodynamic, and adrenal incompetence in cirrhosis: impact on renal dysfunction. *Hepatol Int*, 9(1), 17-27 (2015)
DOI: 10.1007/s12072-014-9581-1

71. J. M. Belcher, G. Garcia-Tsao, A. J. Sanyal, H. Bhogal, J. K. Lim, N. Ansari, S. G. Coca and C. R. Parikh: Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology*, 57(2), 753-62 (2013)
DOI: 10.1002/hep.25735

72. P. Angeli, A. Sanyal, S. Moller, C. Alessandria, A. Gadano, R. Kim, S. K. Sarin and M. Bernardi: Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: report from the International Club of Ascites. *Liver Int*, 33(1), 16-23 (2013)
DOI: 10.1111/j.1478-3231.2012.02807.x

73. E. Sola and P. Gines: Challenges and Management of Liver Cirrhosis: Pathophysiology of Renal Dysfunction in Cirrhosis. *Dig Dis*, 33(4), 534-8 (2015)
DOI: 10.1159/000375344

74. A. Cardenas and P. Gines: Acute-on-chronic liver failure: the kidneys. *Curr Opin Crit Care*, 17(2), 184-9 (2011)
DOI: 10.1097/MCC.0b013e328344b3da

75. J. M. Belcher, C. R. Parikh and G. Garcia-Tsao: Acute kidney injury in patients with cirrhosis: perils and promise. *Clin Gastroenterol Hepatol*, 11(12), 1550-8 (2013)
DOI: 10.1016/j.cgh.2013.03.018

76. P. Mukhopadhyay, M. Rajesh, H. Pan, V. Patel, B. Mukhopadhyay, S. Batkai, B. Gao, G. Hasko and P. Pacher: Cannabinoid-2 receptor limits inflammation, oxidative/nitrosative stress, and cell death in nephropathy. *Free Radic Biol Med*, 48(3), 457-67 (2010)
DOI: 10.1016/j.freeradbiomed.2009.11.022

77. P. Mukhopadhyay, H. Pan, M. Rajesh, S. Batkai, V. Patel, J. Harvey-White, B. Mukhopadhyay, G. Hasko, B. Gao, K. Mackie and P. Pacher: CB1 cannabinoid receptors promote oxidative/nitrosative stress, inflammation and cell death in a murine nephropathy model. *Br J Pharmacol*, 160(3), 657-68 (2010)
DOI: 10.1111/j.1476-5381.2010.00769.x

78. D. G. Deutsch, M. S. Goligorsky, P. C. Schmid, R. J. Krebsbach, H. H. Schmid, S. K. Das, S. K. Dey, G. Arreaza, C. Thorup, G. Stefano and L. C. Moore: Production and physiological actions of anandamide in the vasculature of the rat kidney. *J Clin Invest*, 100(6), 1538-46 (1997)
DOI: 10.1172/JCI119677

© 1996-2016

79. F. Montecucco, S. Lenglet, V. Braunersreuther, F. Burger, G. Pelli, M. Bertolotto, F. Mach and S. Steffens: CB(2) cannabinoid receptor activation is cardioprotective in a mouse model of ischemia/reperfusion. *J Mol Cell Cardiol*, 46(5), 612-20 (2009)
DOI: 10.1016/j.yjmcc.2008.12.014

80. M. Zhang, M. W. Adler, M. E. Abood, D. Ganea, J. Jallo and R. F. Tuma: CB2 receptor activation attenuates microcirculatory dysfunction during cerebral ischemic/reperfusion injury. *Microvasc Res*, 78(1), 86-94 (2009)
DOI: 10.1016/j.mvr.2009.03.005

81. A. Krag, F. Bendtsen, A. K. Burroughs and S. Moller: The cardiorenal link in advanced cirrhosis. *Med Hypotheses*, 79(1), 53-5 (2012)
DOI: 10.1016/j.mehy.2012.03.032

82. E. Kakazu, Y. Kondo and T. Shimosegawa: The Relationship between Renal Dysfunction and Abnormalities of the Immune System in Patients with Decompensated Cirrhosis. *ISRN Gastroenterol*, 2012, 123826 (2012)
DOI: 10.5402/2012/123826

83. P. Tandon and G. Garcia-Tsao: Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin Liver Dis*, 28(1), 26-42 (2008)
DOI: 10.1055/s-2008-1040319

84. J. Ros, J. Claria, J. To-Figueras, A. Planaguma, P. Cejudo-Martin, G. Fernandez-Varo, R. Martin-Ruiz, V. Arroyo, F. Rivera, J. Rodes and W. Jimenez: Endogenous cannabinoids: a new system involved in the homeostasis of arterial pressure in experimental cirrhosis in the rat. *Gastroenterology*, 122(1), 85-93 (2002)
DOI: 10.1053/gast.2002.30305

85. M. D. Randall and D. A. Kendall: Anandamide and endothelium-derived hyperpolarizing factor act via a common vasorelaxant mechanism in rat mesentery. *Eur J Pharmacol*, 346(1), 51-3 (1998)
DOI: 10.1016/S0014-2999(98)00003-X

86. P. M. Zygmunt, J. Petersson, D. A. Andersson, H. Chuang, M. Sorgard, V. Di Marzo, D. Julius and E. D. Hogestatt: Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature*, 400(6743), 452-7 (1999)
DOI: 10.1038/22761

87. C. M. Fernandez-Rodriguez, J. Romero, T. J. Petros, H. Bradshaw, J. M. Gasalla, M. L. Gutierrez, J. L. Lledo, C. Santander, T. P. Fernandez, E. Tomas, G. Cacho and J. M. Walker: Circulating endogenous cannabinoid anandamide and portal, systemic and renal hemodynamics in cirrhosis. *Liver Int*, 24(5), 477-83 (2004)
DOI: 10.1111/j.1478-3231.2004.0945.x

88. B. Mukhopadhyay, K. Schuebel, P. Mukhopadhyay, R. Cinar, G. Godlewski, K. Xiong, K. Mackie, M. Lizak, Q. Yuan, D. Goldman and G. Kunos: Cannabinoid receptor 1 promotes hepatocellular carcinoma initiation and progression through multiple mechanisms. *Hepatology*, 61(5), 1615-26 (2015)
DOI: 10.1002/hep.27686

89. X. Xu, Y. Liu, S. Huang, G. Liu, C. Xie, J. Zhou, W. Fan, Q. Li, Q. Wang, D. Zhong and X. Miao: Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma. *Cancer Genet Cytogenet*, 171(1), 31-8 (2006)
DOI: 10.1016/j.cancergencyto.2006.06.014

90. M. Giuliano, O. Pellerito, P. Portanova, G. Calvaruso, A. Santulli, A. De Blasio, R. Vento and G. Tesoriere: Apoptosis induced in HepG2 cells by the synthetic cannabinoid WIN: involvement of the transcription factor PPARgamma. *Biochimie*, 91(4), 457-65 (2009)
DOI: 10.1016/j.biochi.2008.11.003

91. S. DeMorrow, S. Glaser, H. Francis, J. Venter, B. Vaculin, S. Vaculin and G. Alpini: Opposing actions of endocannabinoids on cholangiocarcinoma growth: recruitment of Fas and Fas ligand to lipid rafts. *J Biol Chem*, 282(17), 13098-113 (2007)
DOI: 10.1074/jbc.M608238200

92. S. DeMorrow, H. Francis, E. Gaudio, J. Venter, A. Franchitto, S. Kopriva, P. Onori, R. Mancinelli, G. Frampton, M. Coufal, B. Mitchell, B. Vaculin and G. Alpini: The endocannabinoid anandamide inhibits cholangiocarcinoma growth via activation of the noncanonical Wnt signaling pathway. *Am J Physiol Gastrointest Liver Physiol*, 295(6), G1150-8 (2008)
DOI: 10.1152/ajpgi.90455.2008

93. G. Frampton, M. Coufal, H. Li, J. Ramirez and S. DeMorrow: Opposing actions of

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endocannabinoids on cholangiocarcinoma growth is via the differential activation of Notch signaling. *Exp Cell Res*, 316(9), 1465-78 (2010)
DOI: 10.1016/j.yexcr.2010.03.017

94. F. X. Pi-Sunyer, L. J. Aronne, H. M. Heshmati, J. Devin and J. Rosenstock: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA*, 295(7), 761-75 (2006)
DOI: 10.1001/jama.295.7.761

95. K. Strojek, W. M. Bebakar, D. T. Khutsoane, M. Pesic, A. Smahelova, H. F. Thomsen and S. Kalra: Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. *Curr Med Res Opin*, 25(12), 2887-94 (2009)
DOI: 10.1185/03007990903354674

Abbreviations: ECS: endocannabinoid system, eCBs: endocannabinoids, CB: cannabinoid, AEA: anandamide, 2-AG: 2-Arachidonoylglycerol, HSCs: hepatic stellate cells, I/R: ischemia-reperfusion, ECM: extracellular matrix, SSLF: schistosomiasis-associated liver fibrosis, CNS: central nervous system, AKI: Acute kidney injury, HRS: Hepatorenal syndrome

Key Words: Cannabinoid receptor 1, Cannabinoid Receptor 2, Liver Fibrosis, Liver Cirrhosis, Cirrhosis Complications, Alcoholic Fatty Liver, Review

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