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Endocannabinoids and Liver Disease. III. Endocannabinoid effects on immune cells: implications for inflammatory liver diseases

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Abstract

Recent studies have implicated dysregulation of the endocannabinoid system in various liver diseases and their complications (e.g., hepatitis, fibrosis, cirrhosis, cirrhotic cardiomyopathy, and ischemia-reper-fusion), and demonstrated that its modulation by either cannabinoid 2 (CB_2) receptor agonists or CB_1 antagonists may be of significant therapeutic benefits. This review is aimed to focus on the triggers and sources of endocannabinoids during liver inflammation and on the novel role of CB_2 receptors in the interplay between the activated endothelium and various inflammatory cells (leukocytes, lymphocytes, etc.), which play pivotal role in the early development and progression of inflammatory and other liver diseases.

Keywords

ischemia-reperfusion; endocannabinoids; cannabinoid 2 receptor; inflammation; endothelium

ENDOCANNABINOIDS ARE ENDOGENOUS lipid mediators produced by most cell types in the brain and various peripheral tissues, which exert broad range of biological effects similar to those of cannabis. Arachidonoyl ethanolamide or anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the two most widely studied endocannabinoids, which exert their effects via two G protein-coupled cannabinoid receptors: the CB_1 and the CB_2 receptors. 2-AG binds to both CB_1 and CB_2 receptors, whereas AEA shows higher affinity for CB_1 than CB_2 receptors. In addition, AEA may also bind to vanilloid VR_1 ($TRPV_1$) receptors. The tissue concentration of endocannabinoids is determined by their synthesis (involving phospholipase D-dependent, diacylglycerol lipase-dependent, and other pathways), their cellular uptake, and their degradation by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipases (5, 19).

The CB_1 receptor is predominantly expressed in brain and to a much less extent in various peripheral tissues such as vasculature, heart (18), and liver (19). The CB_2 receptor was previously considered to be expressed primarily in immune and hematopoietic cells; however, more recent studies have also identified CB_2 receptors in brain, myocardium (18), human vascular smooth muscle (23), activated hepatic stellate cells (10,14), and endothelial cells of

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various origins (22,24) (reviewed in Refs. 19 and 21). Interestingly, it appears that in various pathological states the expression of CB_2 receptor can be significantly upregulated (19). CB_1/CB_2 receptor signaling is complex and may involve $G_{i/o}$-dependent inhibition of adenylyl cyclase, activation of mitogen-activated protein kinases, protein kinase A and C, and cyclooxygenase-2 pathways, just to name a few (19). Increasing recent evidence also supports the possible existence of additional yet unidentified cannabinoid receptors (19).

Dysregulation of the endocannabinoid system (ECS) has been implicated in virtually all diseases affecting humans, and its pharmacological modulation holds tremendous promise in the treatment of pain, cancer, and metabolic, cardiovascular, and various inflammatory disorders (11,19). Numerous recent studies have linked dysregulation of the ECS to a number of liver diseases including hepatitis (8), nonalcoholic fatty liver disease (16), hepatic ischemia-reperfusion (I/R) injury (3,24), and liver fibrosis and cirrhosis (10,14,15,27) and its hemo-dynamic consequences (1,2,17,25). In aggregate these studies have suggested that modulation of the ECS by either CB_1 antagonists or CB_2 receptor agonists may be of significant therapeutic benefit (15,19). This synopsis will focus on sources and triggers of endocannabinoids during liver inflammatory disorders (in both leukocytes and parenchymal cells) and on the novel role of CB_2 receptors in the interplay between inflammatory cells and the activated endothelium, which plays a crucial role in the early development and progression of inflammatory liver diseases (9) (Fig. 1).

ECS in Leukocytes

Cannabinoid receptors are expressed in virtually all human peripheral blood immune cells with the following rank order of mRNA levels for CB_1: B lymphocytes > natural killer (NK) cells ≥ polymorphonuclear neutrophils (PMNs) ≥ CD8 lymphocytes > monocytes > CD4 lymphocytes, and for CB_2:B cells > NK cells > monocytes > PMNs > T cells (overviewed in Ref. 12). The data available on the protein levels of these receptors in immune cells should only be considered with great caution owing to the recognized problem with the specificity of most available CB_1 and CB_2 antibodies (12,23). Importantly, the CB receptor expression in immune cells may be modulated by various inflammatory [e.g., bacterial lipopolysaccharide (LPS)] and other stimuli resulting in activation of these cells, and may therefore largely be influenced by the experimental conditions (12). Paradoxically, inflammatory stimuli also trigger increased production of endocannabinoids (AEA and 2-AG) in immune cells (e.g., macrophages, peripheral-blood mononu-clear cells, and dendritic cells) via activation of various bio-synthetic pathways and by reducing expression of FAAH, the enzyme responsible for the degradation of AEA (overviewed in Refs. 5 and 11).

Most earlier studies investigating various immunomodula-tory effects of the active constituent of cannabis, delta-9-tetrahydrocannabinol (THC; a ligand for both CB_1 and CB_2 receptors), and other natural or synthetic cannabinoids in mice and rats or in immune cells cultured from humans have shown suppressive effects on B, T, and NK cells and macrophages, which were most likely mediated by both CB_1 and CB_2 receptor-dependent and -independent mechanisms (11,12). More recent studies have suggested that endocannabinoids may also have important effects on immune functions by modulating T and B lymphocytes proliferation and apoptosis, macrophage-mediated killing of sensitized cells, inflammatory cytokine production, and immune cell activation by inflammatory stimuli (e.g., LPS), chemotaxis, and inflammatory cell migration, just to mention a few (11,12). However, these effects (mostly, but not always, inhibitory) were largely influenced by the endocannabinoid or synthetic agonist or antagonist, trigger and condition, and cell type used (11,12). Furthermore, cannabinoids have also been reported to modulate inducible nitric oxide (NO) synthase (iNOS) expression and NO and/or reactive oxygen species production in immune cells; however, this is a controversial issue requiring further clarification. The importance of CB_2 receptor activation in the above-

mentioned immunomodulatory effects of endocannabinoids and various cannabinergic ligands is now becoming increasingly recognized, which is also supported by multiple lines of evidence demonstrating anti-inflammatory effects of CB_2 receptor activation in a multitude of disparate diseases and pathological conditions, ranging from atherosclerosis, inflammatory pain, gastrointestinal inflammatory and neurodegenerative disorders, myocardial infarction, stroke, to hepatic I/R injury and other liver inflammatory disorders, to mention just a few (11,19); for further reading also see a recent (January 2008) special issue of *British Journal of Pharmacology* on this subject.

Endocannabinoid System in Hepatic I/R Injury

Hepatic I/R injury is a significant clinical problem involved in the liver failure associated with circulatory shock, hepatic surgery, and liver transplantation. Hepatic I/R injury is characterized by Kupffer cell activation and PMN cell infiltration and activation as well as inflammatory cytokine responses. The first step in the pathophysiology of I/R injury is the priming and recruitment of neutrophils into the liver vasculature upon reperfusion by inflammatory mediators. The second step comprises endothelial cell activation, which promotes the attachment and activation of inflammatory cells resulting in endothelial damage and dysfunction. Next, adherent inflammatory cells transmigrate through the damaged endothelium, attach to hepatocytes, and become fully activated to release oxidants and proteolytic enzymes, which in turn trigger intracellular oxidative stress and mitochondrial dysfunction in hepatocytes, eventually culminating in cell death (9). Hepatic I/R also leads to significant reduction of endothelial NO synthase activity in sinusoidal endothelial cells during I/R (20). This results in an imbalance between sinusoidal vasoconstrictors (e.g., endothelins) and vasodilators (NO) in the liver, creating a situation favoring sinusoidal vasoconstriction during reperfusion. As already mentioned above, hepatic I/R also activates Kupffer cells, which then produce proinflammatory cytokines, free radicals, oxidants, and large amounts of NO due to iNOS expression. NO promptly reacts with superoxide anion leading to formation of the reactive oxidant peroxynitrite and decreased NO bioavailability (20). These events lead to further activation of endothelial cells, neutrophils, and hepatocytes, resulting in amplified reactive oxygen and nitrogen species generation in the delayed phase of hepatic I/R aggravating the organ injury.

Studies in the heart have implicated endocannabinoids in the protective effects of ischemic preconditioning through cannabinoid receptor-dependent and -independent mechanisms; however, majority of these studies were restricted to the use of ex vivo models (e.g., isolated perfused hearts), in which the role of very important immunomodulatory effects of cannabinoids could not be evaluated (21). In contrast, other reports have suggested that endocannabinoids overproduced during various forms of I/R such as myocardial infarction or circula-tory shock may contribute to the cardiovascular depressive state associated with these pathologies (21). Overall, the role of endocannabinoids and cannabinoid receptors (especially CB_1 receptors) in cell protective mechanisms against I/R damage in the heart and brain is still elusive (overviewed in Ref. 21).

Role of CB_2 receptors in endothelial activation and endothelial/inflammatory cell interactions

In recent studies we tried to address the role of endocannabinoid system, in particular CB_2 receptors, using selective CB_2 agonists and CB_2 knockout mice in a hepatic I/R injury model (3,24). We wanted to understand the role of CB_2 receptors in endothelial cell activation and endothelial/inflammatory cell interactions, which are critical steps not only in reperfusion injury, but also in atherosclerosis and various other inflammatory disorders. This indeed turned to be very important, because the selective CB_2 cannabinoid agonists JWH133 and HU-308 decreased TNF-α-induced ICAM-1 and VCAM-1 expression in human liver sinusoidal endothelial cells (HLSECs) expressing CB_2 receptors, as well as the adhesion of human

neutrophils to HLSECs in vitro. In support of a global role for CB_2 receptors as modulators of endothelial cell activation, these receptors were also detectable in human coronary artery endothelial cells, and selective CB_2 agonists attenuated TNF-α-induced NF-κB and RhoA activation, upregulation of ICAM-1, VCAM-1, and macrophage inflammatory protein (MCP)-1, and monocyte adhesion and transmigration through monolayers of coronary endothelial cells (22). The protective effect of selective CB_2 agonists against TNF-α- and/or endotoxin-induced endothelial cell activation was also observed in intact aortas, both ex vivo and in vivo (22). In the liver, selective CB_2 receptor agonists administered prior to experimental hepatic ischemia attenuated the I/R-induced rise in serum transaminases by decreasing inflammatory cell infiltration, tissue and serum levels of proinflammatory cytokines/chemokines [TNF-α, macrophage inflammatory protein (MIP)-1α, and MIP-2], hepatic lipid peroxidation, and expression of the adhesion molecule ICAM-1. In addition, CB_2 receptor activation significantly reduced the extent of the histological damage and PMN cell infiltration 1 day following the ischemic insult. In agreement with the protective role of CB_2 receptor activation, $CB_2^{-/-}$ mice developed aggravated I/R-induced tissue damage and proinflammatory phenotype (3,24).

Triggers, sources, and roles of endocannabinoids during liver inflammation

The first evidence that endocannabinoids might be involved in liver-related pathologies came from the pioneering studies by Kunos's group (1). They demonstrated that circulating macrophages and platelets from cirrhotic animals and patients had elevated levels of endocannabinoids and, when isolated and injected into normal rats, these cells elicited hypotension, which could be reversed by CB_1 antagonist rimonabant (SR141716) (1,25). It was hypothesized that bacterial endotoxin could be responsible for the increased endocannabinoid production of macrophages and platelets, since patients with cirrhosis often have endotoxemia which stimulates the synthesis of AEA in macrophages in vitro (reviewed in Ref. 19). More recently we have documented up to sixfold increases in endocannabinoid AEA and/or 2-AG levels in hearts and livers of cirrhotic rats and found that the contractile dysfunction associated with cirrhotic cardiomyopathy could significantly be attenuated by CB_1 receptor antagonists (2,17). Likewise, we observed increased myocardial AEA levels in an acute mouse heart failure model triggered by overwhelming oxidative-nitrosative stress, in which CB_1 antagonists also attenuated the contractile dysfunction, in addition to decreasing cell death (18). These studies are in agreement with previous reports on hemorrhagic and endotoxic shock suggesting that endocannabinoids and CB_1 receptors could play an important role in the cardiodepression and hypotension associated with various pathological conditions, including liver cirrhosis (reviewed in Ref. 19).

Increased endocannabinoid levels were also reported following cerebral and myocardial I/R; however, the triggers and sources of endocannabinoids in these models were not determined (reviewed in Ref. 21). Therefore, in our recent study we aimed to ascertain triggers and cellular sources of endocannabinoids during hepatic I/R in a mouse model (3). Interestingly, I/R, but not ischemia alone, triggered severalfold increases in the hepatic levels of AEA, 2-AG, and oleoylethanolamide (3). Detailed analysis of isolated cell fractions have demonstrated that virtually all cell types isolated from livers exposed to I/R contained severalfold elevated endocannabinoid levels (e.g., hepatocytes; Kupffer and endothelial cells). Since the increase in hepatic endocannabinoid levels occurred only during reperfusion, where the burst of superoxide, H_2O_2, and peroxynitrite generation happens, we hypothesized that these reactive oxidants coupled with acute inflammatory response cytokines (e.g., TNF-α) might trigger endocannabinoid production during reperfusion. Indeed, rapid exposure of isolated primary hepatocytes to various inflammatory stimuli (TNF-α, endotoxin) and oxidants (H_2O_2, peroxynitrite) triggered marked increases in cellular endocannabinoid levels (3), suggesting that not only inflammatory stimuli but also oxidativenitrosative stress can modulate

endocannabinoid production in hepatocytes, and most likely in other cell types too. This conclusion is also supported by recent observation that the commonly used chemotherapeutic agent doxorubicin, which is known to induce heart failure by generating overwhelming oxidative-nitrosative injury, increased endocannabinoid levels both in the myocardium in vivo and in cardiomyocytes in vitro (18). Thus, in addition to the previously reported activated macrophages, parenchymal cells may also serve as a very significant source of endocannabinoids in various disease states associated with increased inflammation and/or oxidative tissue injury (Fig. 1).

Interestingly, in our study the hepatic endocannabinoid levels during I/R positively correlated with the degree of tissue injury and serum inflammatory cytokine and chemokine levels (TNF-α, MIP-1α, and MIP-2 levels). With more severe injury and inflammation more endocannabinoids were produced in the liver. So, what is the role of endocannabinoids during liver I/R? Are endocannabinoids beneficial or detrimental in hepatic I/R? This is a difficult question to answer. On the one hand, one can envision that I/R-induces hepatic overproduction of endocannabinoids to limit hepatic injury by decreasing the inflammation-triggered increased expression of adhesion molecules in endothelial cells, and the infiltration and activation of inflammatory cells (both mononuclear and polymorphonuclear leukocytes express CB_2 receptors, and most likely Kupffer cells as well) via CB_2-dependent or -independent mechanisms (Fig. 1). Consistently with this protective role, AEA in vitro markedly decreased endothelial cell activation, adhesion of inflammatory cells to the activated endothelium and interrelated signaling (4). The beneficial effect of AEA is also supported by the anti-inflammatory phenotype of FAAH knockout mice, in which the AEA levels are elevated in most tissues, in various inflammation injury models (reviewed in Ref. 19), and in cardiovascular aging (4). On the other hand, endocannabinoid anandamide can promote stellate cell and hepatocyte apoptosis in vitro by a mechanism not related to CB receptors [possibly involving increased oxidative stress generation (15,26)], suggesting that it may facilitate the elimination of damaged cells in the liver (19), in addition to its CB_1 receptor-dependent cardiovascular depressive effects. It is also important to consider that AEA and 2-AG may have different, sometimes even opposing, role(s) in many inflammatory diseases (5).

Endocannabinoid System in Hepatitis, Liver Fibrosis, and Cirrhosis

To date only very limited and controversial information is available on the possible role of the endocannabinoid system in hepatitis. Chronic marijuana use has been linked with hepatotoxicity rather than hepatoprotection in humans. Likewise, a recent epidemiological study indicates that daily marijuana smoking is a risk factor for progression of liver fibrosis among people with chronic hepatitis C infection (8,15). Contrary to the plausible hepatotoxicity associated with chronic marijuana use in humans, a synthetic, nonpsychoactive cannabinoid derivative (PRS-211,092) was reported to attenuate concanavalin A-induced acute hepatitis (a well-established model for viral or autoimmune hepatitis in which the liver injury is predominantly T cell mediated) via negative cytokine regulation in mice (13). However, these effects were mediated most likely by cannabinoid receptor-independent mechanisms (13).

In preclinical models of liver fibrosis both CB_2 receptor agonists and CB_1 antagonists have been reported to exert various beneficial effects via different mechanisms, which may also involve, at least in part, modulation of secondary inflammatory response (15,26). A recent study has also suggested that the anti-inflammatory effects of CB_1 antagonist SR141716 may also contribute to the benefits observed in the treatment of obesity-associated hepatic steatosis and related features of metabolic syndrome (7), which is to be overviewed by Dr. Kunos in this Themes series.

Conclusions and Future Directions

Collectively, the studies discussed above emphasize the potential immunoregulatory role of the endocannabinoid system in a variety of inflammatory liver disorders, opening new avenues for their pharmacotherapy. There is considerable interest in the development of selective CB_2 receptor agonists, which are devoid of psychoactive properties of CB_1 agonists, for various inflammatory disorders. Selective CB_2 cannabinoid agonists may protect against hepatic inflammatory disorders by attenuating the endothelial cell activation/inflammatory response (e.g., the expression of adhesion molecules, release of chemotactic factors, inflammatory mediators, etc.) and by decreasing the migration and the adhesion of inflammatory cells to the endothelium, transendothelial migration, adhesion to parenchymal cells and activation, and interrelated oxidativenitrosative stress-inflammatory response (Fig. 1). It appears that CB_1 antagonists might be beneficial in slowing the progression of liver fibrosis and the neurological decline associated with hepatic encephalopathy, in addition to the attenuation of the adverse hemodynamic consequences of cirrhosis, thus extending life until a suitable liver becomes available for transplantation (overviewed in Ref. 26 and by Drs. Gaskari and Lee in this Themes series). CB_1 antagonists may also be useful in the treatment of obesity-associated liver diseases and related features of metabolic syndrome by improving dyslipidemia and attenuating systemic and liver inflammation (overviewed by Dr. Kunos in this Themes series).

Despite the clear evidence (reviewed above) indicating that the endocannabinoid system plays an important role in modulating inflammatory response in a variety of liver disorders, the exact mechanisms remain largely elusive. For example, liver contains a large number of immune cells representing the innate immune system (e.g., NK cells, NKT cells, γ/δ T cells, and Kupffer cells), which play a key role not only in the host defenses against invading microorganisms and tumor formation, but also in the pathogenesis of various inflammatory liver diseases (6). Further studies should determine how the endocannabinoid system interacts with these immune cells to design better therapeutic approaches for the treatment of inflammatory liver diseases based on CB_1/CB_2 agonists or antagonists or their combinations.

GRANTS

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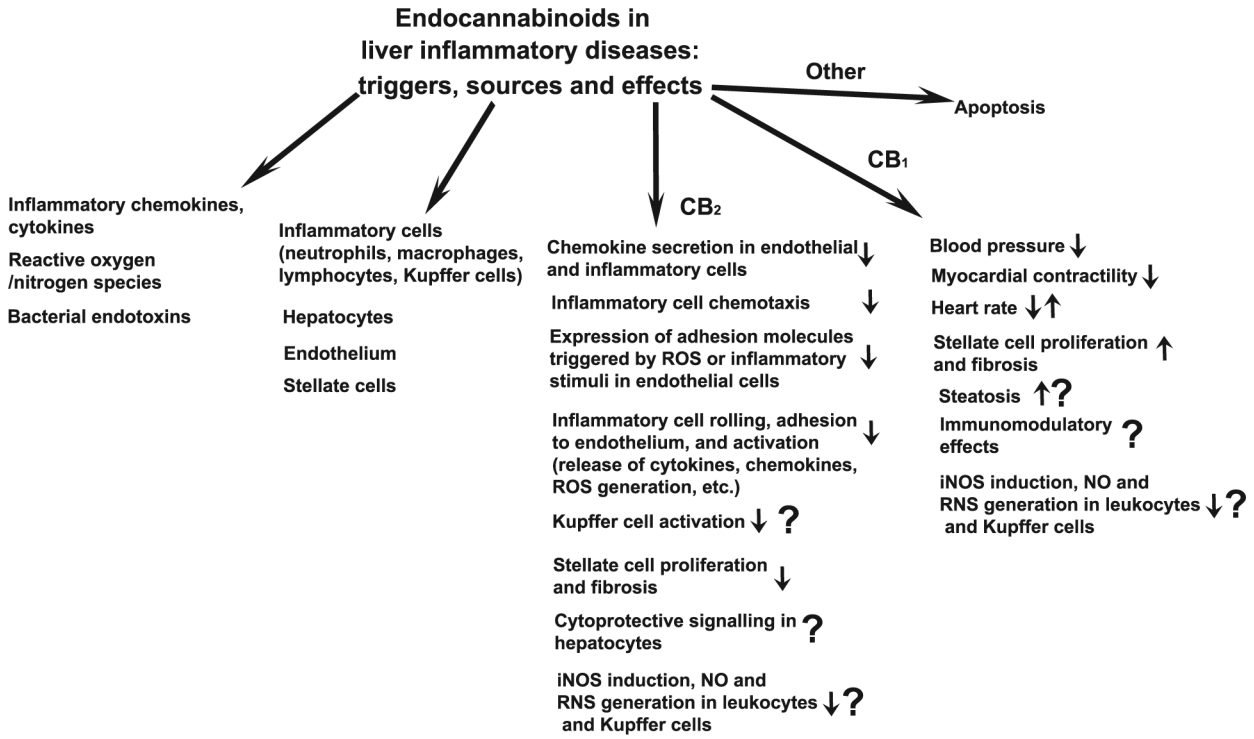

Fig. 1.

Sources, triggers, and targets of endocannabinoid production during liver inflammatory and other disorders. Bacterial endotoxins, inflammatory chemokines and cytokines, and reactive oxygen and nitrogen species (ROS and RNS) may trigger increased endocannabinoid production and release or decrease endocannabinoid inactivation in hepatocytes, endothelial, Kupffer, and stellate cells and in leukocytes infiltrating the liver during the course of hepatic inflammatory diseases. These endocannabinoids may mediate various cannabinoid CB_1 and CB_2 receptor-dependent and -independent protective or detrimental effects shown in the figure, thereby modulating the early development and progression of inflammatory and other liver diseases and the development of their complications. iNOS, inducible nitric oxide (NO) synthase.