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Endocannabinoids in Liver Disease

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Abstract

Endocannabinoids are lipid mediators of the same cannabinoid (CB) receptors that mediate the effects of marijuana. The endocannabinoid system (ECS) consists of CB receptors, endocannabinoids, and the enzymes involved in their biosynthesis and degradation, and is present both in brain and peripheral tissues, including the liver. The hepatic ECS is activated in various liver diseases, which contributes to the underlying pathologies. In cirrhosis of various etiologies, activation of vascular and cardiac CB₁ receptors by macrophage- and platelet-derived endocannabinoids contribute to the vasodilated state and cardiomyopathy, which can be reversed by CB₁ blockade. In mouse models of liver fibrosis, activation of CB₁ receptors on hepatic stellate cells is fibrogenic, and CB₁ blockade slows the progression of fibrosis. Fatty liver induced by high-fat diets or chronic alcohol feeding depend on activation of peripheral, including hepatic CB₁ receptors, which also contribute to insulin resistance and dyslipidemias. Although the documented therapeutic potential of CB₁ blockade is limited by neuropsychiatric side effects, these may be mitigated by using novel, peripherally restricted CB₁ antagonists.

The Endocannabinoid System

Marijuana has been used for its psychoactive and medicinal properties for millennia. As other plant-derived substances, marijuana has been slow to yield its secrets, with insights into its mechanism of action beginning to emerge only during the last decades. The existence of specific CB receptors in mammalian tissues was first revealed by radioligand binding, followed by the molecular cloning of two G protein-coupled cannabinoid receptors (1). CB₁ receptors are the most abundant receptors in the mammalian brain, but are also expressed in peripheral tissues, including various cell types of the liver, at much lower yet functionally relevant concentrations (2–8). CB₂ receptors are expressed primarily in immune and hematopoietic cells, and have also been detected in the liver in certain pathological states (9,10). Additional CB receptors may exist (11), but their potential role in liver biology is unknown.

The discovery of CB receptors triggered a search for endogenous ligands. Arachidonoyl ethanolamide (AEA, anandamide) was the first such ligand discovered (12), with 2-arachidonoyl glycerol (2-AG) identified 3 years later (13,14). Additional endogenous ligands have since been identified (1) but have received less attention. AEA and 2-AG are generated on demand in response to a rise in intracellular calcium or metabotropic receptor activation (1). Their biosynthesis from membrane phospholipid precursors may proceed along multiple, parallel pathways (15,16). Once released, they remain largely membrane associated due to their hydrophobic nature, and can be taken up by cells via a high affinity uptake mechanism (17), which is followed by their enzymatic degradation. AEA is

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metabolized primarily by the membrane associated fatty-acid amide hydrolase (FAAH)(18), whereas 2-AG is preferentially degraded by monoglyceride lipase (MAGL)(19).

The psychoactive properties of cannabinoids and the abundance of CB₁ receptors in the brain have suggested that the ECS is primarily a neuronal signaling system, therefore evidence for the presence and functional importance of the ECS in the liver (2) was unexpected. Indeed, early studies of brain CB₁ receptors have used the liver as negative control (20). However, recent reports have documented low level CB₁ expression in whole liver (2–4,21–23), hepatocytes (6,23–25), stellate cells (5,26), and hepatic vascular endothelial cells (27–30)(see Fig. 1). CB₁ receptors are present in human hepatocytes (25) and in whole human liver, with increased expression noted in hepatocellular carcinoma (7) and primary biliary cirrhosis (8). CB₂ receptors are undetectable in normal liver, but are induced in pathological conditions such as NAFLD (31), embryonic state (32), liver fibrosis (9), regenerating liver (33), and in hepatocellular carcinoma (7). Hepatic endocannabinoids levels are similar to those in brain (2,26), whereas FAAH expression is higher in liver than in brain. Evidence implicating the ECS in the regulation of hepatic hemodynamics, fibrogenesis as well as lipid metabolism, and in the dysregulation of these functions in pathological states such as cirrhosis, NAFLD, alcoholic fatty liver and ischemia-reperfusion injury is discussed below.

Endocannabinoids and Altered Hemodynamics in Cirrhosis

The potent hypotensive action of THC has long been recognized and it even prompted attempts to exploit it for the treatment of hypertension (34). This and the similar effect of synthetic cannabinoid analogs and endocannabinoids are mediated by CB₁ receptors located, in part, in the peripheral cardiovascular system (35), and play a pathogenic role in various forms of shock (36,37), including endotoxic shock (38–40).

Advanced liver cirrhosis is associated with endotoxemia and hypotension, suggesting endocannabinoid involvement. Indeed, cirrhosis in rats is accompanied by progressive hypotension reversible by CB₁ blockade (27), which also reduces the elevated portal venous pressure and mesenteric blood flow. The likely source of endocannabinoids is activated macrophages, in which LPS induces CD14-dependent synthesis of anandamide (38,41). AEA levels are elevated in circulating macrophages of cirrhotic rats or patients, and such macrophages injected into normal rats elicit CB₁-mediated hypotension (27,42). Cirrhosis increases CB₁ expression in vascular endothelial cells (27), or in mesenteric arteries (29,43), and increases the vasodilator potency of AEA (29,43,44). In cirrhotic patients, circulating AEA, but not 2-AG, levels are increased in peripheral blood but not in hepatic veins or liver tissue, suggesting that the liver is not its source (45).

These findings implicate AEA as mediator of the vasodilated state in cirrhosis. Although in one study of cirrhotic patients, the increase in circulating AEA did not correlate with the degree of hepatic and renal dysfunction (46), in another study of patients with primary biliary cirrhosis, the CB₁ expression in hepatocytes and biliary epithelial cells and CB₂ expression in hepatocytes and cholangiocytes were positively correlated with the severity of the histological stage (8). Cirrhosis is associated with renal sodium retention, which has been attributed, in part, to portal hypertension secondary to liver parenchymal damage and fibrosis (47). In cirrhotic rats,rimonabant dose-dependently reduced ascites by ensuring a less positive sodium balance (48).

AEA induces CB₁-mediated mesenteric vasodilation independent of NO (49). However, the effect of higher doses of AEA is resistant to CB₁ blockade (49), and may be mediated via putative 'AEA receptors', implicated in the mesenteric vasorelaxant effect of AEA observed

in CB₁/CB₂ double knockout mice(11,50), which may also contribute to mesenteric vasodilation in cirrhosis.

The hyperdynamic circulation of advanced cirrhosis is associated with increased cardiac output and tachycardia. However, the cirrhotic heart has an underlying decrease in contractility and β -adrenergic hyposensitivity referred to as 'cirrhotic cardiomyopathy' (51), which has been attributed to endocannabinoid activation of cardiac CB₁ receptors, based on pharmacological studies using isolated myocardial preparations from bile duct-ligated rats (52). *In vivo* studies, using an intraventricular pressure-volume microcatheter system, revealed a profound decrease in baseline cardiac contractility, which was acutely normalized by CB₁ blockade (53). The suppression of cardiac contractility by CB₁ receptor activation may involve inhibition of L-type calcium channels (54) and/or reductions in myocardial cAMP content (55). Of the 2 major endocannabinoids, AEA is more likely to be involved, as suggested by a cirrhosis-related increase in myocardial AEA, but not 2-AG, levels (53).

These findings raise the therapeutic potential of CB₁ blockade in treating the hemodynamic abnormalities in advanced liver cirrhosis. Because the increase in mesenteric blood flow may precipitate the rupture of varicosities and also contributes to ascites formation, CB₁ blockade may avert these potentially fatal complications, thus keeping patients alive until a liver transplant becomes available.

Endocannabinoids and Liver Fibrosis

CB₂ receptors, which are normally undetectable in the liver, are prominently expressed in the cirrhotic human liver, and are also detectable in non-parenchymal liver cells in fibrotic mouse liver (9). THC suppresses the proliferation and induces apoptosis of human hepatic myofibroblasts and stellate cells via CB₂ receptors (9), and thus may be antifibrotic and hepatoprotective (56). Accordingly, CB₂^{-/-} mice had an enhanced response to fibrogenic stimuli (9). CB₂ receptor activation by AEA also inhibits the hyperplastic proliferation of cholangiocytes, a frequent consequence of extrahepatic biliary obstruction, cholestasis and toxic liver injury. This was associated with increased production of reactive oxygen species and cell death, via the induction of the AP-1 complex and thioredoxin-1 (3). In cirrhotic rats, chronic treatment with the CB₂-selective agonist JWH-133 attenuated cellular markers of fibrosis (57), and enhanced the regenerative response to acute liver injury. Accordingly, CB₂^{-/-} mice had delayed liver regeneration in response to CCl₄-induced injury, whereas JWH-133 treatment reduced the injury and accelerated liver regeneration (33). These findings signal the therapeutic potential of non-psychoactive CB₂ agonists in the treatment of liver fibrosis.

Paradoxically, in patients with hepatitis C virus infection, daily cannabis use increased rather than protected from fibrosis progression (58). Thus, endocannabinoids also exert a profibrotic effect, possibly mediated by CB₁ receptors. This is compatible with the finding of increased CB₁ expression in stellate cells and hepatic myofibroblasts in cirrhotic human liver, and in the livers of mice with three different models of fibrosis (5). Genetic or pharmacological ablation of CB₁ receptors protected mice against liver injury, as reflected in the reduced expression of smooth muscle α -actin and transforming growth factor- β (5). 2-AG is the likely fibrogenic mediator, as its hepatic level is preferentially increased by CCl₄-treatment of mice (26) and rats (53). Higher doses of 2-AG induce apoptosis in activated HSC *in vitro* through a receptor-independent, membrane cholesterol-dependent mechanism, which means that 2-AG also has antifibrotic activity (26). AEA had a similar effect, although the eventual cell death was by necrosis rather than apoptosis (59). For both endocannabinoids, these effects occur at the 2-50 μ M range. The hepatic concentration of AEA is orders of magnitude below such levels, whereas 2-AG may reach low micromolar

concentrations (26). As the pro-apoptotic effect of 2-AG is independent of cannabinoid receptors, it could contribute to the reduction in fibrotic activity observed following CB₁ blockade (48). The profibrotic and adverse hemodynamic effects of CB₁ activation could provide a rationale for the use of CB₁ antagonists in the medical management of advanced liver cirrhosis.

Endocannabinoids and the Metabolic Syndrome

The CB₁-mediated appetite promoting effect of endocannabinoids (60) was the primary impetus for the development of brain-penetrant CB₁ receptor antagonists for the treatment of obesity. The first-in-class compound, rimonabant, caused weight reduction and improved the associated cardiometabolic risk factors, but neuropsychiatric side effects, including depression and anxiety, have prevented its approval in the United States and led to its withdrawal from the market in other countries (reviewed in(61)). Accumulating evidence indicates, however, that the metabolic effects of endocannabinoids are mediated, at least in part, by peripheral CB₁ receptors, as discussed in some detail below. Indeed, a non brain-penetrant CB₁ antagonist was recently reported to retain the beneficial metabolic effects of rimonabant without producing the behavioral effects that predict neuro-psychiatric side effects in humans, which may revive interest in the therapeutic potential of CB₁ antagonism (62).

Reduced food intake is not the primary mechanism of weight reduction by CB₁ blockade in obesity. In mice with diet-induced obesity (DIO), chronic rimonabant caused a transient reduction in food intake and sustained weight loss, indicating food intake-independent effects on energy balance (2,63). Increased *de novo* hepatic lipogenesis has been documented in DIO mice (2,64,65) as well as in people with NAFLD (66,67), and may be mediated by endocannabinoids. Indeed, lipogenic gene expression and the rate of *de novo* hepatic lipogenesis were increased by CB₁ agonists and decreased by CB₁ antagonists in rodents (2,25,68–70). High-fat diet increases hepatic CB₁ expression (2,21,25,69) and the hepatic levels of AEA (2). Thus, endogenous AEA acting via hepatic CB₁ receptors contributes to increased *de novo* lipogenesis in mouse models of obesity. CB₁-mediated lipogenesis may explain the finding that in patients with chronic hepatitis C infection, daily cannabis smoking was an independent risk factor for steatosis severity, but not for obesity (71).

Although lipogenesis via hepatic CB₁ receptors may contribute to lipid accumulation, extrahepatic CB₁ must play a major role, because liver-specific CB₁^{-/-} mice are only partially protected from steatosis (24), whereas CB₁^{-/-} mice with selective transgenic re-expression of CB₁ in hepatocytes remain largely resistant to the steatotic effect of high-fat diet, similar to their global CB₁ knockout littermates (62). The source of liver fat may be adipose tissue, as activation of CB₁ receptors in adipocytes promotes lipogenesis (72), and the released fatty acids may be taken up and converted to triglycerides by the liver (4). On the other hand, the rapid depletion of excess hepatic triglycerides following CB₁ blockade may involve hepatic CB₁ receptors, as indicated by the increased rate of secretion of triglyceride-rich VLDL from the liver of both DIO and *ob/ob* mice following treatment with a peripherally restricted CB₁ antagonist (62)(see Fig. 2).

Endocannabinoids are also involved in the diet-induced decrease in fatty-acid oxidation. The activity of hepatic carnitine palmitoyltransferase-1 (CPT-1), the rate limiting enzyme in mitochondrial fatty acid β-oxidation, is suppressed by either high-fat diet or treatment with a CB₁ agonist, and both effects are prevented by rimonabant (24). Conversely, hepatic CPT-1 activity is increased in CB₁^{-/-} mice (24), and in DIO mice following chronic CB₁ blockade (24,62,73). Adiponectin is a key stimulator of fatty acid β-oxidation, and CB₁ blockade

increases plasma adiponectin (74). The improved insulin sensitivity following CB₁ blockade was found to have both adiponectin-dependent (75,76) and adiponectin-independent components (76), although the role of adiponectin in the effects of CB₁ blockade on hepatic mitochondrial function and fatty acid oxidation has not been explored. Increased energy expenditure, due to increased fat oxidation, following CB₁ blockade has been documented using indirect calorimetry in rats (77–79) and mice (62). These effects likely contribute to the food-intake-independent sustained weight loss (62,80) as well as reversal of hepatic steatosis (62,81,82) following chronic CB₁ blockade.

The DIO-related hypertriglyceridemia was modestly attenuated, whereas the accompanying increase in plasma LDL cholesterol and decrease in HDL cholesterol were absent in both CB₁^{-/-} and LCB₁^{-/-} mice on the high-fat diet. This suggests that hepatic CB₁ mediate diet-induced changes in hepatic lipoprotein metabolism and/or secretion. In a recent study, treatment of mice with an inhibitor of monoglyceride lipase resulted in elevated hepatic levels of 2-AG, increased hepatic expression of SREBP1c and FAS, hypertriglyceridemia, and accumulation in plasma of apoE-depleted, triglyceride-rich apolipoproteins (68). These changes were absent in CB₁^{-/-} or ApoE^{-/-} mice and could be prevented by CB₁ blockade. Furthermore, despite the elevated hepatic lipogenic gene expression, triglyceride secretion rates were unchanged, but triglyceride clearance from plasma was inhibited (68). In contrast, in DIO mice with long-term upregulation of the ECS, peripheral CB₁ blockade does increase triglyceride secretion (62), as discussed above.

High fat diets also result in elevated plasma insulin and leptin levels accompanied by hyperglycemia, indicating insulin resistance (24,83), as well as leptin resistance (84,85). Interestingly, both CB₁^{-/-} and LCB₁^{-/-} mice remained glucose-tolerant and insulin sensitive and did not display the hyperleptinemia associated with high-fat diets (24). Moreover, the insulin and leptin resistance of DIO mice was normalized by the peripheral CB₁ antagonist, AM6545 (62). There is also evidence that THC induces glucose intolerance in humans (86) and rodents, via activation of CB₁ receptors (87). Thus, endocannabinoids and hepatic CB₁ play an important role in diet-induced insulin and leptin resistance.

Diet-induced insulin resistance involves adipose tissue, skeletal muscle and liver, and interactions among the three tissues through neurogenic (88) and/or humoral factors (89). In mice, high-fat diet induces CB₁ expression in skeletal muscle (90), and CB₁ blockade increases insulin-induced glucose uptake and phosphorylation in skeletal muscle of genetically obese mice (79). The possibility that activation of hepatic CB₁ may influence insulin sensitivity of extrahepatic tissues via the release of soluble mediators, remains to be explored.

CB₂ receptors may also be involved in diet-induced hormonal and metabolic changes. In rats, the selective CB₂ agonist JWH-133 improved glucose tolerance, whereas the CB₂-antagonist AM630 had the opposite effect and it also prevented the effect of JWH-133 (91). These are opposite to the glucose intolerance induced by CB₁ receptor activation (see above), and could minimize the effects of mixed CB₁/CB₂ agonists on glucose homeostasis. The well documented insulin sensitization by chronic CB₁ blockade (92,93) may be due to reversal of the action of AEA, which has low CB₂ efficacy (94). This is also consistent with findings that high-fat diet-induced glucose intolerance and insulin resistance are associated with increased hepatic AEA, but not 2-AG, levels (2).

In a recent study, CB₂ expression was strongly induced by both steatosis and non-alcoholic steatohepatitis (31), which suggests CB₂ involvement in hepatic fat metabolism. Indeed, a modest increase in CB₂ expression was reported in hepatocytes from both *ob/ob* and DIO mice. On the other hand, CB₂^{-/-} mice were resistant to diet-induced steatohepatitis, and

were less insulin resistant than wild-type littermates on the same diet. Furthermore, JWH-133 increased the hepatic accumulation of triglycerides in DIO mice (95). The CB₂-induced insulin resistance suggested by these findings in mice is opposite to the insulin sensitizing effect of CB₂ agonists in rats (91). Further studies are needed to resolve this discrepancy.

Alcoholic Fatty Liver

Chronic alcoholism may lead to steatosis that can further progress into steatohepatitis, liver cirrhosis and hepatocellular carcinoma. Ethanol enhances hepatic lipogenesis (96,97) and decreases fatty acid oxidation (98). The similar mechanisms of diet- and alcohol-induced steatosis, together with ethanol's ability to increase endocannabinoid levels, at least in brain (99), suggest ECS involvement in alcoholic fatty liver. Indeed, exposure of male mice to a low fat, liquid ethanol diet for 4 weeks increased hepatic CB₁ expression and 2-AG but not AEA levels. 2-AG was increased in HSC, but not in hepatocytes. The expression of diacylglycerol lipase- β (DAGL β) was also increased in HSC (23), suggesting increased biosynthesis of 2-AG. Rimonabant treatment attenuated the ethanol-induced steatosis without affecting alcohol intake and blood ethanol levels, suggesting CB₁ involvement. This was further supported by the resistance to ethanol-induced steatosis of both CB₁^{-/-} and LCB₁^{-/-} mice (23).

The hepatic nuclear expression of SREBP1c and its target FAS were increased, whereas CPT-1 expression and activity decreased in ethanol-fed mice, in agreement with earlier findings (97). In both CB₁^{-/-} and LCB₁^{-/-} mice, effects of ethanol on SREBP1c, FAS and CPT-1 were blunted or absent. Furthermore, CPT-1 activity was increased and resistant to suppression by ethanol in both CB₁ knockout strains (23). This supports the notion that in AFLD, hepatic lipogenesis is increased and fatty acid oxidation is decreased via CB₁ activation.

CB₁^{-/-} hepatocytes are resistant to ethanol-induced steatosis, whereas the ethanol increases 2-AG exclusively in HSC. This suggests a paracrine mechanism whereby HSC-derived 2-AG activates CB₁ receptors on adjacent hepatocytes to stimulate lipogenesis and inhibit fatty acid oxidation in the latter. Indeed, co-culturing HSC from alcohol-fed mice with hepatocytes from control mice resulted in increased lipogenic gene expression in the latter. The paracrine effect of ethanol-primed HSC was blunted when the hepatocytes in the co-culture were from LCB₁^{-/-} mice, confirming the role of CB₁ receptors (23). This paracrine interaction, together with high levels of retinoic acid in HSC and its well known role in the control of gene expression, prompted a study of the possible role of retinoic acid and its receptors in regulating hepatic CB₁ expression. CB₁ expression in mouse or human isolated hepatocytes was upregulated by RAR γ or panRAR agonists, and the effect could be attenuated by siRNA knockdown of RAR γ , but not other RAR subtypes (25). Both CB₁ and RAR γ were upregulated in hepatocytes from mice fed either high-fat diet or liquid alcohol diet. Furthermore, 2-AG upregulated CB₁ in normal but not in retinaldehyde dehydrogenase-1^{-/-} hepatocytes, which are deficient in retinoic acid. Thus, CB₁ 'autoinduction' may also involve retinoic acid (25). Interestingly, autoinduction of hepatic CB₁ receptors is also suggested by the finding that chronic rimonabant treatment of DIO mice reversed the diet-induced upregulation of hepatic CB₁ (4). The findings reviewed above suggest that CB₁ antagonists could be effective in the treatment of both AFLD and NAFLD.

Endocannabinoids and Ischemia-Reperfusion Injury

Ischemia/reperfusion (I/R) injury may develop in conditions where blood and oxygen supply to a tissue is transiently disrupted and then restored. Hepatic I/R injury is a potentially fatal

complication of liver surgery, including liver transplantation. Substances that improve hypoxia tolerance may also protect against I/R injury. Cannabinoids induce hypomotility and hypothermia, both of which result in reduced oxygen demand. The metabolic effects of cannabinoids that promote energy storage and reduce energy expenditure (see above) may also reduce oxygen demand. There is evidence that endocannabinoids acting via CB₂ protect against hepatic I/R injury (100,101).

In mice, segmental ischemia followed by reperfusion (but not ischemia alone) markedly increased the hepatic levels of AEA and 2-AG, which correlated with the severity of tissue damage (100). I/R-induced tissue damage, including neutrophil infiltration and lipid peroxidation, was attenuated by pretreatment with JWH-133 in wild-type but not in CB₂^{-/-} mice, in which the damage was more severe than in wild-type littermates (100). Another potent and selective CB₂ agonist, HU-308, caused similar effects and also attenuated I/R-induced hepatocyte apoptosis and mitigated the TNF α -induced expression of the cell adhesion molecules ICAM-1 and VCAM-1 in hepatic sinusoidal endothelial cells (101). Thus, CB₂ agonists may afford protection at multiple levels against I/R injury, highlighting their therapeutic potential.

CB₁ receptor blockade also protects the liver from I/R injury and superimposed endotoxaemia (102). In this study, rats subjected to LPS plus I/R had an immediate increase in CB₁ expression in perisinusoidal hepatocytes. Rimonabant treatment reduced both tissue necrosis and serum ALT in the late phase of reperfusion, and attenuated the oxidative injury (102). Further studies with peripherally restricted CB₁ receptor antagonists could reinforce the therapeutic potential of this approach.

Hepatic Encephalopathy, Autoimmune Hepatitis

Hepatic encephalopathy is a neuropsychiatric syndrome that may accompany acute liver failure. The underlying mechanisms are not completely understood, although there is evidence for the pathogenic role of ammonia, alterations in various central neurotransmitter systems as well as altered cerebrovascular function. Mice with thioacetamide-induced fulminant liver failure have elevated brain 2-AG content. Treatment of such mice with 2-AG or the CB₂ agonist HU-308 improved the neurological score and cognitive function, and these effects were blocked by a CB₂ antagonist. The beneficial effects of CB₂ agonists could be mimicked by treatment with the CB₁ antagonist rimonabant (103). In another study by the same group, thioacetamide treatment or BDL induced CB₂ expression in the brain, and also resulted in activation of AMP-activated protein kinase (AMPK). The absence of both effects in CB₂^{-/-} mice indicated the role of CB₂ receptors (104), although there is also evidence for the additional involvement of TRPV₁ receptors (105).

Cannabidiol (CBD) is a non-psychoactive constituent of marijuana with no significant CB₁ or CB₂ activity. CBD was found to improve cognitive and motor function as well as the neuroinflammation found in hepatic encephalopathy (106). The cerebral inflammatory response of mice to BDL was reduced by CBD treatment, and the effect was attributed to indirect activation of hippocampal A₂A adenosine receptors. It is possible that combined treatment with a CB₂ agonists and CBD offers additive therapeutic benefits in hepatic encephalopathy.

In a murine model of concanavalin A (ConA)-induced autoimmune hepatitis, THC attenuated the hepatitis, as judged by decreased plasma levels of liver enzymes and inflammatory cytokines and reduced tissue injury (107). Interestingly, FAAH^{-/-} mice responded with reduced hepatic damage to ConA treatment, suggesting hepatoprotection by endogenous AEA (107). In contrast, the results of another study suggest that hepatoprotection may be achieved by blocking CB₁ receptors (108).

Concluding Remarks

The ECS is present in the liver and is involved in the control of various hepatic functions with important therapeutic implications. Increased CB₁ activity contributes to the hemodynamic abnormalities and promotes fibrosis in liver cirrhosis, whereas CB₁ blockade attenuates and delays these changes. Endocannabinoids acting via hepatic CB₁ receptors have emerged as mediators of both diet-induced and alcoholic fatty liver which, together, account for the majority of cirrhosis in Western societies. Additionally, hepatic CB₁ activation contributes to obesity-related insulin- and leptin-resistance and dyslipidemias. This provides strong rationale for the therapeutic use of CB₁ antagonists in these conditions. Although neuropsychiatric side effects limit the therapeutic potential of brain-penetrant CB₁ antagonists, the recent emergence of second generation, peripherally-restricted CB₁ antagonists may mitigate this problem. Additionally, non-psychoactive CB₂ agonists may offer therapeutic benefit in attenuating liver injury and promoting tissue repair in the fibrotic liver.

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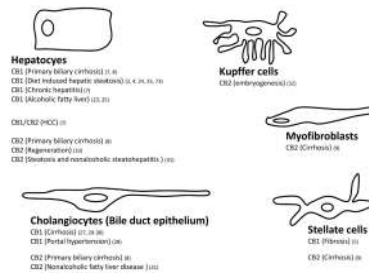


Figure 1. Cellular distribution of hepatic CB1 and CB2 receptors and their involvement in liver diseases

Numbers in parentheses refer to original reports as listed in References.

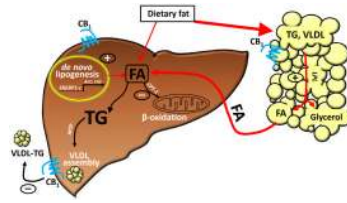


Figure 2. CB1 mechanisms involved in liver fat accumulation

The major pathway is CB1 activation of lipoprotein lipase (LPL) in adipose tissue, resulting in increased fatty-acid (FA) release and transfer to liver (72). Additional mechanisms mediated via hepatic CB1 receptors include increased *de novo* hepatic lipogenesis, decreased FA oxidation (2) and decreased secretion of TG-rich VLDL (62).