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, autoimmunity 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.
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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. ENDOCANNABINOID 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)” cannabionoid 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 stimulilike 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 mammals. 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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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).

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 diet also 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 possibly be 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 autoimmune 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 therapeutical 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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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
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
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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