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Cannabinoid receptors as novel therapeutic targets for the management of non-alcoholic steatohepatitis

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Abstract

Prevalence of non-alcoholic steatohepatitis (NASH) rises steadily in Western countries with the obesity epidemic. NASH is associated with activation of liver fibrogenesis and predisposes to cirrhosis and associated morbi-mortality. The cannabinoid system is increasingly emerging as a crucial mediator of acute and chronic liver injury. Recent experimental and clinical data indicate that peripheral activation of cannabinoid CB1 receptors promotes insulin resistance and liver steatogenesis, two key steps in the pathogenesis of non-alcoholic fatty liver disease. Moreover, CB1 receptors enhance progression of liver fibrogenesis. These findings provide a strong rationale for the use of CB1 antagonists in the management of NASH.

Résumé

Les récepteurs des cannabinoïdes: de nouvelles cibles thérapeutiques dans la prise en charge de la stéatohépatite non alcoolique

La prévalence de la stéatohépatite non alcoolique est en progression dans les pays occidentaux, parallèlement à celle de l'obésité. La stéatohépatite non alcoolique est associée à une activation des mécanismes de fibrogenèse avec un risque d'évolution cirrhogène et de morbidité significative. Le système cannabinoïde est un médiateur important la physiopathologie des hépatopathies aiguës et chroniques. Des données expérimentales et cliniques récentes indiquent que l'activation des récepteurs CB1 des cannabinoïdes dans les tissus périphériques joue un rôle déterminant dans l'insulinorésistance et la stéatogenèse hépatique, deux étapes clés dans le développement de la stéatopathie métabolique. Les récepteurs CB1 sont également impliqués dans la progression de la fibrose associée aux hépatopathies chroniques. L'ensemble de ces données suggère que les antagonistes du récepteur CB1 des cannabinoïdes pourraient offrir une nouvelle approche thérapeutique au cours de la stéatohépatite non alcoolique.

Keywords: Fatty liver; Non-alcoholic steatohepatitis; Endocannabinoids; Cannabinoid receptors; Liver fibrosis; Review.

Mots clés : Stéatose ; Stéatohépatite non alcoolique ; Endocannabinoïdes ; Récepteurs des cannabinoïdes ; Fibrose hépatique ; Revue générale.

Preparations of the hemp plant *Cannabis sativa* have been used for medicinal purposes over centuries. THC was identified in 1964 as the predominant cannabinoid compound responsible for psychoactive effects of marijuana. Thereafter, cloning of cannabinoid receptors CB1 and CB2 in the early 1990s constituted a determinant milestone in the characterization of a novel biological system with a wide array of biological functions. Moreover, improvement in the understanding of the signaling mechanism responsible for cannabinoid actions has fostered research efforts in the development of therapeutic applications. Consequently, capsules of THC and its synthetic analog nabilone are approved in several countries for the management of chemotherapy-induced nausea and vomiting [1], and rimonabant, a selective CB1 receptor antagonist, has been available for 2 years in Europe as an adjunctive treatment of obesity or overweight with associated type 2 diabetes or dyslipidemia [2-4].

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In this context, accumulating experimental and clinical data have stressed the crucial role of the cannabinoid system in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). NAFLD is closely linked to the metabolic syndrome and the obesity epidemic [5], and is currently a rising cause of liver injury, with a 20-30% prevalence in Western countries. The spectrum of the disease ranges from simple steatosis, a condition generally associated with a benign liver outcome, to steatohepatitis, an entity that comprises steatosis, liver inflammation and hepatocellular injury. The latter stage is associated with activation of fibrogenic pathways and carries a 10-20% risk of cirrhosis after 10 or 20 years. As shown in several recent studies, non-alcoholic steatohepatitis (NASH) leads to increased liver-related mortality due to end-stage liver disease or development of hepatocellular carcinoma [6]. The present review summarizes evidence that cannabinoid receptor antagonism may offer novel therapeutic approaches for the management of NAFLD.

1. The endocannabinoid system

The endocannabinoid system comprises endogenous lipid ligands, specific G-protein-coupled receptors (CB1 and CB2), and proteins that are responsible for their biosynthesis, cellular uptake and degradation [7-9].

The CB1 receptor was originally cloned from a rat brain library due to its high level of expression in the central nervous system [10], and subsequent studies have shown its presence at lower levels in many peripheral tissues. Expression of CB2 receptors predominates in the immune system and, although more restricted, is increasingly demonstrated in several cells [8,11,12]. Recent reports also suggest the existence of additional cannabinoid receptors.

Endocannabinoids are hydrophobic fatty-acid-derived compounds with predominantly autocrine/paracrine effects, among which anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG) are the best known. Both compounds are synthesized on demand and are rapidly degraded by fatty-acid amide hydrolase (FAAH) or monoacylglycerol lipase, following ligand binding and cellular reuptake [8,9,11,12]. Anandamide shows a higher affinity for CB1 than CB2 receptors and is therefore considered a major endogenous CB1 ligand, whereas 2-arachidonoyl glycerol binds both receptors with similar affinity [13]. In addition, both compounds also induce CB1- and CB2-independent effects. Lipid mediators other than anandamide and 2-AG have been reported to bind CB receptors, but their biological significance remains undetermined.

2. Modulators of cannabinoid receptors as therapeutic agents

Rimonabant has been the first CB1 antagonist to reach the market in Europe [2-4]. The drug was initially developed for the treatment of obesity in light of the positive impact of phyto- and endocannabinoids on central appetite-regulating pathways. It soon became clear that CB1 antagonism produces metabolic effects beyond those expected from weight loss alone, including improvements in dyslipidemia, insulin resistance and diabetes [14]. In keeping with clinical data, experimental studies have established that multiple peripheral mechanisms contribute to the beneficial effects of CB1 antagonism by enhancing energy expenditure, peripheral lipolysis and insulin sensitivity, among others [15,16]. Accordingly, trials are underway to further define the impact of CB1 antagonism on dyslipidemia, type 2 diabetes and cardiovascular morbidity. Other therapeutic applications under evaluation also include management of alcohol- and nicotine-dependence or neurodegenerative disorders [9]. The safety of CB1 antagonists in obesity has been questioned, given the occurrence of modest rates of anxiety and depression in susceptible individuals [14]. As a result, the FDA denied approval of rimonabant pending additional data, whereas Merck recently suspended the development of taranabant for obesity due to safety concerns. In this context, the development of peripherally restricted CB1 antagonists could prove of interest by avoiding central adverse effects.

Although selective agonists and antagonists of CB2 receptors have not yet reached a clinical stage, preclinical studies nevertheless suggest meaningful therapeutic applications as anti-inflammatory, analgesic or anti-allergenic compounds [9,17]. Of particular interest, such compounds should be devoid of central adverse effects.

Identification of cannabinoid receptors as potential therapeutic targets for the management of liver diseases [7] has emerged recently with the demonstration that CB1 receptors contribute to the pathogenesis of cirrhotic portal hypertension [18,19]. Soon after, additional studies uncovered a key role of cannabinoids in metabolic and ethanol-induced fatty liver, ischemia reperfusion, and in the scarring process associated with chronic liver disease [20-25].

3. Pathogenesis of NAFLD

It is now admitted that metabolic steatosis and insulin resistance are in tight relationship [26]. Thus, rodent models have shown that resistance to insulin promotes lipolysis in adipose tissue, thereby increasing delivery of free fatty acids to the liver [26]. Moreover, in the liver, hyperinsulinemia triggers *de novo* fatty acid, and impairs β-oxidation and lipid dis-