Current Research in Diabetes & Obesity Journal
ISSN: 2476-1435

Juniper Publishers
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Mini Review
Volume 4 Issue 1 – September 2017
DOI: 10.19080/CRDOJ.2017.4.555628

Curre Res Diabetes & Obes J

Cannabinoids Receptors in Liver: Diet and Physiopathology

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Submission: March 9, 2017; **Published:** September 14, 2017

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Abstract

The Endocannabinoid system (SEC), located in the central nervous system and several peripheral tissues, is an important modulator of many metabolic functions. This system, is composed by cannabinoid receptors type 1 and 2 (CB1R; CB2R), their endogenous ligands, known as Endocannabinoids, and the enzymes involved in their synthesis and degradation. It has been suggested that a hyperactivated SEC originates metabolic disruptions in several tissues, resulting in typical manifestations of the metabolic syndrome. Liver steatosis due to consumption of a high fat diet is a pathophysiological condition associated to a perturbed SEC. In this condition, it has been shown an increased expression of CB1R and/or higher endocannabinoid levels in hepatic cells, which may exert an autocrine/paracrine stimulation of CB1R and CB2R. Activation of CB1R stimulate the expression of several hepatocyte lipogenic factors, leading to increased *de novo* fatty acids synthesis and as a consequence, abnormal accumulation of triglycerides. In addition, CB1R activity is necessary for development of insulin and leptin resistance. A role for CB2R in hepatic function is still controversial, because on one side, its stimulation has an interesting protective effect on liver injury, while on the other, may worsen the development of hepatic steatosis and insulin resistance in experimental models of diet-induced obesity. In this minireview, we discuss a suggested sequential interaction of CB1R and CB2R, linking development of steatosis and insulin resistance, associated to a mechanism resulting in a deteriorated function of phosphorylated proteins involved in insulin signaling, due to tyrosine nitration of those proteins.

Keywords: Endocannabinoids; Cannabinoids receptors; Insulin resistance; Steatosis; Hepatic lipogenesis; Protein nitration

Introduction

The endocannabinoid system: general and historical features

Cannabis Sativa has been used for its psychoactive and medicinal properties for millennia. However, knowledge into its mechanism of action has only emerged the last decades. It was first demonstrated that brain had specific binding sites for Δ^9-tetrahidrocannabinol (Δ^9-THC; the psychoactive compound of cannabis) named type 1-cannabinoid receptors (CB1R) and then cloned [1,2]. Discovery of CB1R, stimulated research to find its endogenous ligand (s). Arachidonoylethanolamide (Anandamide, AEA) a compound discovered and isolated from porcine brain was able to specifically bind CB1R and had a Δ^9-THC-like behavior in selected bioassays [3]. This important finding led to the endocannabinoids (ECs) research era, with extensive research activity during the last 25 years. Subsequently, type 2 cannabinoid receptors (CB2R) were then cloned [4,5], and other lipid molecule, 2-arachidonoylglycerol (2-AG), was proposed to be its physiological agonist [6]. At present, some others molecules are considered ECs such as Homo-γ-linoleylethanolamide and docosatetraenoylethanolamide, but most of research in this area has been carried out with AEA or its synthetic agonists, and 2-AG. At present, AEA is considered the ligand for CB1R and less selective for CB2R, while 2-AG binds with almost same affinity to CB1R and CB2R [7]. Anandamide and 2-AG derive from membrane phospholipids and are biosynthesized through different pathways [8,9]. Enzymes able to hydrolyze AEA (fatty acid amido hydrolase, FAAH) and 2-AG (monoacylglicerol lipase, MAGL) are becoming very important by their ability to modulate availability of endocannabinoids to exert their endocrine/paracrine actions [10]. Type 1 and 2 cannabinoid/endocannabinoid receptors are G-protein coupled receptors sensitive to pertussis toxin (Gi/o). Classical signaling mechanisms involve modulation of cAMP levels, intracellular free calcium concentration by internal ion

mobilization or calcium channels gating regulation, and nitric oxide production [11-15]. Type 1 CBR were first described in brain; subsequently, they have been reported to be present in several peripheral tissues such as pancreas, adipose tissue, gastro-intestinal tract, muscle, heart, thyroid, liver etc., where they are involved in several metabolic actions [16]. The type 2 CBR mainly present in immune and hematopoietic cells have been described more recently in brain (as heteromers together with CB1R), pancreas and liver [14,17-19]. All the molecules previously described constitute the Endocannabinoid System (ECS).

Our review will be focused now in the liver ECS, which has been recently recognized to have pleiotropic functions under physiological and pathological conditions [20,21]. It is well documented now that up regulation of CB1R and elevated AEA levels in liver play an important role in the development of fatty liver associated with ethanol intake, high-fat diet, and obesity [22,23]. Although CB2R up regulation also appears to contribute to fatty liver [24], this finding needs more research to clarify whether CB2R up regulation is a cause or consequence of hepatic steatosis. In our opinion CB2R up regulation is a consequence of a primary CB1R overactivity leading to steatosis as a first signal of liver dysfunction. Thus, exacerbated steatosis should be the alarm signal to up-regulate CB2R, a fact that may be important for hepatoprotection, as previously suggested by Lotersztajn et al. [20]. However, consequences derived from long lasting CB2R over expression and activity deserve further research to have a clear picture of its effects on liver physiology and pathophysiology.

Discussion

CB1R and CB2R in liver, from steatosis to insulin resistance?

Last ten years, studies have been focused to examine the liver and its molecular machinery as a target for metabolic actions of the endocannabinoid system. Hepatocytes express CB1R; these activated receptors stimulate expression of the lipogenesis transcription factor named Steroid Regulatory Element Binding Protein 1c (SREBP-1c) and its targets enzymes Acetyl Coenzyme A carboxilase-1 (ACC1) and Fatty Acid Synthase (FAS) leading to *de novo* fatty acid synthesis [22]. There is no liver lipogenic response in CB1R-/- mice and SR141716A-treated (antagonist/inverse agonist of CB1R) native mice show decreased hepatic *de novo* fatty acids synthesis [22]. In addition, a high fat diet contribute to elevate hepatic AEA levels, increase CB1R expression, and as a result, a CB1R-mediated increase in *de novo* fatty acids synthesis and triglycerides accumulation in hepatocytes [22]. It is important to mention that elevated hepatic AEA levels and subsequent CB1R overactivation is also a consequence of depressed AEA degradation due to decreased FAAH activity and a sustained synthesis rate. Interestingly, we have demonstrated that nociceptive stress during lactation leads to a decreased protein amount and activity of FAAH in adult mice liver concomitant to accumulation of triglycerides [25,26]. Results reported in a liver-specific CB1R knockout mouse (LCB1R-/-), clearly demonstrated that hepatic CB1R are required for development of diet induced hepatic steatosis, dyslipidemia, and insulin and leptin resistance in mice [27]. Furthermore, high fat diet (HFD)-induced elevation of plasma insulin and leptin concentrations with simultaneous hyperglycemia found in native mice, were greatly attenuated in LCB1R-/- mice. More interestingly, deletion of hepatic CB1R led to dissociate obesity from insulin and leptin resistance due to a HFD [27]. The question how hepatic CB1R activation could help to develop a permissive effect in insulin resistance development?, has been an interesting issue to face with different scientific approaches. Previous reports have demonstrated that activation of hepatic CB1R suppresses insulin-induced phosphorylation of Akt-2, increased expression of serine/threonine phosphatases Phlpp1 [28] and specific ceramides species, which are involved in HFD-associated hepatic insulin resistance. More recently, the involvement of CB1R in insulin resistance has been associated to the increased activity of the forkhead box O1 (FoxO1) [29].

The other crucial endocannabinoid/cannabinoid receptor with important implications in liver physiology is the CB2R. It has been reported that CB2R, which are normally undetectable in the liver, are strongly induced by steatosis and non-alcoholic fatty liver disease [30]. In these conditions, they are mainly found in hepatocytes and cholangiocytes, while in cirrhosis they are found in hepatocytes, cholangiocytes, stellate cells and myofibroblasts. Type 2 CBR are also important in Kupffer cells during embryogenesis [23]. In cirrhotic rats, the CB2R agonist JWH-133 improves regenerative response to acute liver injury and decreases fibrosis [31]. Type 2 CBR activity may also have beneficial effects on liver injury due to CCl4-induced hepatitis promoting liver regeneration via a mechanism on hepatocytes originating from myofibroblasts [32,33]. All these antecedents indicate that activation of CB2R by its agonist(s) could play an important role in a paracrine mechanism leading to liver regeneration in cases of liver injury. In this sense, the finding that CB2R are induced by steatosis with a primary function to protect the liver is important but may have future physiological consequences for this tissue. Molecular mechanisms associated to CB2R-mediated liver physiology/pathophysiology may constitute an important issue to develop future research in this area.

Conclusions and perspectives

Even if a slight level of hepatic steatosis becomes chronic, a chronic overactivity of CB2R may be displayed and together with protective effects, a late consequence on liver physiology may arise, such as a state of hepatic insulin resistance. In this regard, it has been reported that CB2R potentiates insulin resistance associated to obesity in a murine obesity model [24]. Thus, in addition to CB2R effects on fat inflammation, presence of CB2R in other insulin sensitive tissues such as skeletal muscle and liver, may also contribute to systemic insulin resistance. In this case, treatments with CB2R antagonists may become a therapeutic contribution to manage obesity and its long term associated metabolic perturbations. In rats, however, the selective

How to cite this article: Valeska C, Cynthia B, Rodrigo T, Ana María R, Miguel Llanos. Cannabinoids Receptors in Liver. Diet and Physiopathology. Curre Res Diabetes & Obes J. 2017; 4(1): 555628. DOI: 10.19080/CRDOJ.2017.4.555628.

CB2R agonist JWH-133 recuperate glucose tolerance, while the compound AM630, a CB2R-antagonist, had opposite effects [34]. Further studies in other animal models, are needed to solve this discrepancy.

Inducible nitric oxide synthase (iNOS) has been identified as the key molecule able to mediate beneficial effects of CB2R in liver [32]. Thus, CB2R knockout mice (CB2R-/-) show decreased induction of hepatic iNOS when challenged with CCl4, and iNOS-/- mice have increased hepatocyte apoptosis when exposed to CCl4 [35]. Interplay of CB2R and nitric oxides synthases has been also demonstrated in remote neurodegeneration due to oxidative and nitrative stress [36]. Although iNOS activity was shown to be beneficial to liver function, a previous report has demonstrated that liver insulin resistance is associated to an increased induction of the hepatic iNOS [37]. This effect was obtained after lipid infusion to wild type mice. Conversely, iNOS-/- mice were protected from hepatic and peripheral insulin resistance when challenged with the lipid infusion. Hepatic insulin resistance was due to tyrosine nitration of insulin signaling molecules instead of optimum extent of tyrosine phosphorylation. Thus, lipid infusion induced tyrosine nitration of insulin receptor β subunit (IRβ), insulin receptor substrate (IRS-1, IRS-2) and Akt in wild type mice but not in iNOS-/- mice. Tyrosine nitration of proteins is due to peroxynitrite (ONOO-) action, a compound formed by the quick reaction of nitric oxide (NO) with superoxide radicals (O_2-). Although the role of ONOO- in protein tyrosine nitration is still debated, is not less true that it is recognized as the most efficient mechanism for nitrating proteins under biological conditions [38]. It is important to remember that NO overproduction due to induction of iNOS occurring in one type of hepatic cell may exert paracrine actions in other type of hepatic cells, included hepatocytes, due to NO ability to diffuse throughout the whole tissue.

Being increased induction of hepatic iNOS a crucial player in hepatic insulin resistance, an elegant study of Shinozaki et al. [39] has generated a liver-specific iNOS transgenic mice (L-iNOS-Tg), showing that its increased expression is sufficient to cause hepatic insulin resistance. In this case, insulin-stimulated phosphorylation of signaling proteins such as IRS-1 and Akt was diminished in liver but not in skeletal muscle. In this way, it was demonstrated that selective expression of iNOS in liver plays a key role in inducing insulin resistance. Interestingly, L-iNOS-Tg mice also showed mild elevated levels of circulating glucose and insulin, together with peripheral insulin resistance. Under these circumstances, we propose a sequential link involving CB1R-mediated triglycerides accumulation, leading to over expression and activity of CB2R, then, a long lasting induction of iNOS expression and activity and as a result elevated levels of NO available to form ONOO-. Hepatic insulin resistance should be a consequence of abnormally levels of protein phosphorylation and function, through a mechanism involving tyrosine nitration of proteins involved in insulin signaling. This topic is matter of present investigation in our laboratory.

Acknowledgements

This work received financial support from Fondo Nacional de Ciencia y Tecnología de Chile (FONDECYT) Grant Nº 1130106 to MLl.

Conflict of Interest

The authors declare no conflicts of interests

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DOI: 10.19080/CRDOJ.2017.4.555628

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