Potential Mechanisms Influencing the Inverse Relationship Between Cannabis and Nonalcoholic Fatty Liver Disease: A Commentary

Nutrition and Metabolic Insights
Volume 12: 1–3
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1178638819847480
SAGE

Pratima Dibba[1], Andrew A Li[2], George Cholankeril[3], Muhammad Ali Khan[4], Donghee Kim[3] and Aijaz Ahmed[3]

[1]Division of Gastroenterology, Women & Infants Hospital/Warren Alpert School of Medicine, Brown University, Providence, RI, USA. [2]Department of Medicine, Stanford University School of Medicine, Palo Alto, CA, USA. [3]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, CA, USA. [4]Division of Gastroenterology and Hepatology, The University of Tennessee Health Science Center, Memphis, TN, USA.

ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) develops when the liver is unable to oxidize or export excess free fatty acids generated by adipose tissue lipolysis, de novo lipogenesis, or dietary intake. Although treatment has generally been centered on reversing metabolic risk factors that increase the likelihood of NAFLD by influencing lifestyle modifications, therapeutic modalities are being studied at the cellular and molecular level. The endocannabinoid system has been of recent focus. The agonism and antagonism of cannabinoid receptors play roles in biochemical mechanisms involved in the development or regression of NAFLD. Exocannabinoids and endocannabinoids, the ligands which bind cannabinoid receptors, have been studied in this regard. Exocannabinoids found in cannabis (marijuana) may have a therapeutic benefit. Our recent study demonstrated an inverse association between marijuana use and NAFLD among adults in the United States. This commentary combines knowledge on the role of the endocannabinoid system in the setting of NAFLD with the findings in our article to hypothesize different potential mechanisms that may influence the inverse relationship between cannabis and NAFLD.

KEYWORDS: nonalcoholic fatty liver disease, NAFLD, nonalcoholic steatohepatitis, NASH, cannabinoids, endocannabinoid system, endocannabinoid, exocannabinoid, cannabis, marijuana

RECEIVED: May 22, 2018. **ACCEPTED:** November 23, 2018.

TYPE: Commentary

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Aijaz Ahmed, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 750 Welch Road # 210, Palo Alto, CA 94304, USA. Email: aijazahmed@stanford.edu

COMMENT ON: Kim D, Kim W, Kwak MS, Chung GE3, Yim JY, Ahmed A. Inverse association of marijuana use with nonalcoholic fatty liver disease among adults in the United States. PLoS One. 2017 Oct 19;12(10):e0186702. DOI: 10.1371/journal.pone.0186702. PubMed PMID: 29049354. https://www.ncbi.nlm.nih.gov/pubmed/29049354.

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis in the absence of other known etiologies of hepatic injury such as significant alcohol consumption, viral hepatitis, metabolic/genetic disorders, and steatogenic medication use.[1] The histologic spectrum of NAFLD constitutes nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis.[1] The prevalence of NAFLD varies in the literature but has been estimated to be up to 30% of the world's population.[1] The clinical burden of NAFLD is projected to rise over the next decade and result in significant economic burden, largely attributed to the increasing prevalence of diabetes and obesity compounded by a lack of treatment.[2,3] Currently, there is no approved pharmacologic treatment for NAFLD. Patients are left with the challenge of "life style modifications," which are difficult to maintain in an effective and sustained fashion.[3] Therefore, there is an unmet need to find new treatment target(s) for NAFLD.[3,4] The endocannabinoid system may mechanistically provide a potential therapeutic target to treat patients with NAFLD. In fact, our population-based study using a national registry from the United States suggested an inverse association between marijuana use and NAFLD. A clear understanding of the pathophysiology of NAFLD plays an important role in the assessment of such therapeutic agents.

To briefly review, hepatic steatosis occurs when the liver is unable to oxidize or export free fatty acids resulting from adipose tissue lipolysis, de novo lipogenesis, or dietary intake.[5,6] Free fatty acids may overburden the liver from lipolyzed adipose triacylglycerol or dietary lipids, or there may be increased de novo lipogenesis in the setting of reduced hepatic fatty acid oxidation.[7] Insulin resistance is the central underlying mechanism that triggers the pathogenesis of NAFLD by increasing insulin levels and free fatty acid influx into the liver, promoting hepatic triglyceride synthesis, and stimulating secretion of very low-density lipoprotein (VLDL).[8,9] In addition, there may be a reduction in the ability of insulin to suppress peripheral lipolysis.[9] Visceral adipose tissue has also been implicated, which can expand and cause adipocyte hypertrophy associated with increased cytokines and adipokines, such as adiponectin, leptin, tumor necrosis factor-alpha (TNF-α), and interleukin-6.[5] Therefore, the role of insulin resistance in NAFLD may be the pathophysiologic mechanism in the association of marijuana use and NAFLD.[10]

In our data using a nationally representative sample from the United States, we demonstrated that cannabis use was inversely associated with the prevalence of NAFLD in models that were adjusted for age, gender, and ethnicity.[10] Data were also adjusted for body mass index, diabetes, and hypertension

(known risk factors for NAFLD). Furthermore, variables such as education level, economic status, smoking status, alcohol consumption, and current use of cocaine, heroin, and/or amphetamine were also assessed.[10] We demonstrated that current or past marijuana use was associated with a lower risk of NAFLD.[10] These findings may coincide with some current literature that proposes that the endocannabinoid system plays a role in NAFLD. Within the endocannabinoid system, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) are receptors bound by lipophilic ligands called endocannabinoids and exogenous ligands called exocannabinoids.[6] Cannabinoid receptor 1 is primarily found in the brain but has been found in endothelial cells and hepatocytes.[6] Cannabinoid receptor 2 is found in the peripheral tissue and has been detected in Kupffer cells.[6] Agonism of CB1 is associated with increased de novo lipogenesis, decreased fatty acid oxidation, increased lipogenic gene expression, activation of lipoprotein lipase, and decreased secretion of VLDL.[11,12] Antagonism of CB1 has demonstrated an overall improvement in metabolic syndrome by reducing caloric intake and increasing energy expenditure in animal models.[13] In animal models, CB1 antagonism also inhibited de novo lipogenesis.[14] The CB1 antagonist, rimonabant, demonstrated reduced hepatomegaly and hepatic steatosis, improved markers of liver damage, and reduced hepatic TNF-α.[15] The literature regarding CB2 agonism and antagonism is conflicting.[13,16,17]

Endocannabinoids are endogenous ligands and include anandamide (arachidonoyl ethanolamide [AEA]) and 2-arachidonoyl glycerol (2-AG).[6] Exocannabinoids, however, are components of cannabis and include tetrahydrocannabinol (THC), tetrahydrocannabivarin (THCV), and cannabidiol (CBD).[18,19] These exocannabinoids vary in amounts per strain of cannabis.[20] Endocannabinoids function by activating CB1 and CB2.[6] Exocannabinoids vary in terms of function. THC acts on CB1 and CB2[18] and may increase AEA and 2-AG.[21] Cannabidiol functions as an antagonist of CB1 and CB2.[22] However, the function of THCV, which is an analog of THC, is dose-dependent; in high doses, it is a neutral antagonist of CB1 and CB2, and in low doses, it is an agonist of CB1 and a partial agonist of CB2.[22] Endocannabinoids are increased by steatogenic agents and potentiate CB1, which suggests that they may promote the pathogenesis of NAFLD.[12] Exocannabinoids, however, yield unclear results. Exocannabinoids in cannabis have anti-inflammatory effects by inhibiting cytokines, which may be protective against NAFLD.[23,24] The partial antagonist action of the nonpsychotropic exocannabinoid, CBD, on CB1 receptor may improve insulin sensitivity, which may offer a prudent approach in the development of drugs for the management of NAFLD. On the contrary, by activating CB1, THC should theoretically induce or worsen NAFLD. However, our data suggested that cannabis, composed of THC among other exocannabinoids, was independently associated with a lower risk of NAFLD.[10] Therefore, tolerance of CB1 from repetitive THC use may be the mechanism behind the inverse relationship that was noted in our study population. Repeated use of THC may result in decreased CB1 density, which may account for the dose-dependent relationship between marijuana and NAFLD exhibited in our study.[22,25] Cannabidiol and THCV can act as CB1 antagonists and may hypothetically reduce hepatic steatosis, hepatomegaly, markers of liver damage, and cytokines, while improving metabolic syndrome.[22]

The ambiguity and conflicting hypotheses as to pathogenetic mechanisms in the relationship between marijuana and NAFLD warrant further research and investigation. Perhaps the exact amount of cannabis used and the strain of cannabis used as related to its chemical content may clarify which exocannabinoids are responsible for the beneficial and/or harmful effects related to the pathogenesis of NAFLD. With this knowledge, further investigation can be done to delineate whether agonism and/or antagonism of either of the cannabinoid receptors predominate. It is important to consider that the inverse relationship between cannabis and NAFLD may be secondary to known anti-inflammatory properties of cannabis alone or in conjunction with modulation of the receptors. Nonetheless, the endocannabinoid system can be promising therapeutic target to treat NAFLD at the cellular and molecular level.

Author Contributions

PD – Manuscript concept and design; analysis and interpretation of data; drafting and critical revision of the manuscript. AAL, CG, MAK, DK – analysis and interpretation of data, drafting; and critical revision of the manuscript. AA – Manuscript concept and design; analysis and interpretation of data; drafting and critical revision of the manuscript; and study supervision.

REFERENCES

1. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55:2005–2023.
2. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology*. 2016;64:1577–1586.
3. Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: current knowledge and implications for management. *World J Hepatol*. 2017;9:533–543, http://doi.org/10.4254/wjh.v9.i11.533.
4. Mallat A, Lotersztajn S. Endocannabinoids and liver disease. I. Endocannabinoids and their receptors in the liver. *Am J Physiol Gastrointest Liver Physiol*. 2008;294:G9–G12.
5. Cimini FA, Barchetta I, Carotti S, et al. Relationship between adipose tissue dysfunction, vitamin D deficiency and the pathogenesis of non-alcoholic fatty liver disease. *World J Gastroenterol*. 2017;23:3407–3417, http://doi.org/10.3748/wjg.v23.i19.3407.
6. Mallat A, Teixeira-Clerc F, Deveaux V, Manin S, Lotersztajn S. The endocannabinoid system as a key mediator during liver diseases: new insights and therapeutic openings. *Br J Pharmacol*. 2011;163:1432–1440.
7. Matsuzaka T, Shimano H. Molecular mechanisms involved in hepatic steatosis and insulin resistance. *J Diabetes Investig*. 2011;2:170–175.
8. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology*. 2003;37:1202–1219.
9. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients*. 2013;5:1544–1560.

10. Kim D, Kim W, Kwak MS, Chung GE, Yim JY, Ahmed A. Inverse association of marijuana use with nonalcoholic fatty liver disease among adults in the United States. *PLoS ONE*. 2017;12:e0186702.
11. Tam J, Liu J, Mukhopadhyay B, Cinar R, Godlewski G, Kunos G. Endocannabinoids in liver disease. *Hepatology*. 2011;53:346–355.
12. Purohit V, Rapaka R, Shurtleff D. Role of cannabinoids in the development of fatty liver (steatosis). *AAPS J*. 2010;12:233–237.
13. Mallat A, Teixeira-Clerc F, Lotersztajn S. Cannabinoid signaling and liver therapeutics. *J Hepatol*. 2013;59:891–896.
14. Osei-Hyiaman D, DePetrillo M, Pacher P, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest*. 2005;115:1298–1305.
15. Gary-Bobo M, Elachouri G, Gallas JF, et al. Rimonabant reduces obesity-associated hepatic steatosis and features of metabolic syndrome in obese Zucker fa/fa rats. *Hepatology*. 2007;46:122–129.
16. De Gottardi A, Spahr L, Ravier-Dall'Antonia F, Hadengue A. Cannabinoid receptor 1 and 2 agonists increase lipid accumulation in hepatocytes. *Liver Int*. 2010;30:1482–1489.
17. Agudo J, Martin M, Roca C, et al. Deficiency of CB2 cannabinoid receptor in mice improves insulin sensitivity but increases food intake and obesity with age. *Diabetologia*. 2010;53:2629–2640.
18. Patsenker E, Stickel F. Cannabinoids in liver diseases. *Clin Liver Dis*. 2016;7:21–25.
19. Silvestri C, Paris D, Martella A, et al. Two non-psychoactive cannabinoids reduce intracellular lipid levels and inhibit hepatosteatosis. *J Hepatol*. 2015;62:1382–1390.
20. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. *Ther Adv Psychopharmacol*. 2012;2:241–254, http://doi.org/10.1177/2045125312457586.
21. McIntosh AL, Martin GG, Huang H, Landrock D, Kier AB, Schroeder F. Δ9-Tetrahydrocannabinol induces endocannabinoid accumulation in mouse hepatocytes: antagonism by Fabp1 gene ablation. *J Lipid Res*. 2018;59:646–657.
22. Pertwee RG. The diverse CB_1 and CB_2 receptor pharmacology of three plant cannabinoids: Δ^9-tetrahydrocannabinol, cannabidiol and Δ^9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153:199–215.
23. Ribeiro A, Ferraz-de-Paula V, Pinheiro ML, et al. Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. Eur J Pharmacol. 2012;678:78–85.
24. Braunersreuther V, Viviani GL, Mach F, Montecucco F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. *World J Gastroenterol*. 2012;18:727–735.
25. Hirvonen J, Goodwin RS, Li C-T, et al. Reversible and regionally selective downregulation of brain cannabinoid CB_1 receptors in chronic daily cannabis smokers. *Mol Psychiatry*. 2012;17:642–649.