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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Cannabinoid Receptor 1 Antagonism Demonstrates High Therapeutic Potential for the Treatment of Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a cholangiopathy that primarily targets cholangiocytes, leading to a ductular reaction, but can have effects on other hepatic cells promoting inflammation and fibrogenesis.[1] PSC, although rare, is accompanied by poor prognosis and curative therapeutics are still lacking, thus new treatment options are needed.[1]

The endocannabinoid system is facilitated by 2 cannabinoid receptors, CB1 and CB2, which have profound effects on hepatic inflammation, fibrosis, and metabolic function. CB1 expression is strongest in cholangiocytes, inflammatory cells, hepatic stellate cells, and portal fibroblasts.[2,3] In patients with chronic hepatitis C virus, daily cannabis intake is a risk factor for progressive fibrosis development.[4] Interestingly, agonism of CB2 is antifibrotic in hepatic stellate cells,[2] whereas antagonism of CB1 reduces liver inflammation and fibrosis in models of chronic liver damage.[3] Targeting CB1 and CB2 proves complicated considering their dynamic roles, and thus more work is needed to develop effective treatment approaches.

The manuscript by Helmrich et al,[5] published in the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, aimed to uncover the role of CB1 antagonism for the treatment of cholestasis using the multidrug resistance 2 knockout (*Mdr2*$^{-/-}$) mouse model of PSC. The authors provide interesting results that suggest the therapeutic potential for rimonabant (an CB1 antagonist) for the treatment of PSC, and provide evidence of novel pathophysiological roles for CB1 in the liver.

The authors used *Mdr2*$^{-/-}$ mice given rimonabant (CB1 antagonist) or arachidonyl-2-chloroethylamide (ACEA, CB1 agonist) ad libitum starting after weaning (3 weeks of age) until 16 weeks of age, and treated mice were compared with age- and sex-matched untreated wild-type and *Mdr2*$^{-/-}$ mice. First, periportal connective tissue remodeling was reduced and liver structure restored back to normal levels in *Mdr2*$^{-/-}$ plus rimonabant mice compared with *Mdr2*$^{-/-}$ mice. Surprisingly, these parameters were also reduced in *Mdr2*$^{-/-}$ plus ACEA mice, but to a lower extent. The ductular reaction associated with *Mdr2*$^{-/-}$ mice was reduced partially following ACEA treatment but was decreased to normal levels following rimonabant treatment. The most striking findings were in regard to immune cell infiltration and inflammation, where both parameters are sharply reduced with rimonabant treatment but were unchanged with ACEA administration in *Mdr2*$^{-/-}$ mice. Similarly, collagen deposition and liver fibrosis were significantly reduced in *Mdr2*$^{-/-}$ mice treated with rimonabant, but no change was found in *Mdr2*$^{-/-}$ mice given ACEA.

The authors also evaluated hepatic metabolism, which is understudied in PSC. They found that nuclear sterol regulatory element-binding protein-1 (SREBP1), a regulator of fatty acid synthesis, was induced in *Mdr2*$^{-/-}$ mice, but expression was unchanged following ACEA or rimonabant administration. SREPB1 is downstream of CB1,[6] thus its upregulation would suggest enhanced CB1 activity in *Mdr2*$^{-/-}$ mice; however, the lack of decreased nuclear SREBP1 expression may indicate that CB1 mediates metabolism independent of SREBP1 activity. The authors further investigated hepatic metabolism and found a disturbance of hepatocyte zonal expression of phosphoenolpyruvate carboxykinase (PCK1, rate-determining step of gluconeogenesis) in *Mdr2*$^{-/-}$ mice, but zonal pattern was restored to normal with both rimonabant and ACEA treatment. Other parameters of hepatic metabolism were measured with similar profiles, showing efficacy with both rimonabant and ACEA administration. A previous study noted changes in expression of glucose metabolism genes in both periportal and perivenous hepatocytes in a model of liver fibrosis.[7] During cholestasis, CB1 antagonization may normalize metabolic processes and zonation.

Bile acid levels were used to evaluate cholestasis, and it was found that serum bile acid levels were significantly reduced with rimonabant and ACEA treatment in *Mdr2*$^{-/-}$ mice, but no significant alterations in hepatic bile acid content and FXR expression were found in all groups of mice. Therefore, CB1 activity does not seem to reduce hepatic damage via altering bile acid synthesis or signaling. Lastly, the authors examined factors associated with liver carcinogenesis and noted that c-JUN activity and associated cell proliferation were enhanced in *Mdr2*$^{-/-}$ mice compared with normal. Both markers were reduced in *Mdr2*$^{-/-}$ mice treated with rimonabant but unchanged in *Mdr2*$^{-/-}$ mice given ACEA compared with untreated. Therefore, CB1 may impact liver cancer development, which is key considering that PSC is a risk factor for cholangiocarcinoma development.[1] This interesting signaling mechanism should be further evaluated to understand cholangiocarcinoma development to help understand PSC to cholangiocarcinoma transition.

Although strong effects for CB1 antagonism were shown, the CB1 agonist, ACEA, unexpectedly showed beneficial effects in some parameters. This discrepancy could be caused by ACEA ability to agonize the transient receptor potential vanilloid 1.[8] However, being unable to delineate outcomes

mediated by CB1 complicates the understanding of the function of this receptor during PSC.

Overall, this study offers strong evidence for CB1 antagonism (ie, rimonabant) for the treatment of PSC. The reduction of ductular reaction, inflammation, and fibrogenesis to normal levels is striking and lends support for the therapeutic potential of CB1 antagonism in cholestasis. However, rimonabant treatment began at 3 weeks of age and was performed until sacrifice at 16 weeks of age, and this treatment regimen does not allow for the damage to fully set in before therapeutic intervention. Therefore, rescue studies using rimonabant after damage has set in are necessary because they better reflect when treatment would begin for human patients. Future work into the endocannabinoid system and its effect on cholestasis and PSC are clearly worthwhile.

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Conflicts of interest
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