LIVER DISEASE

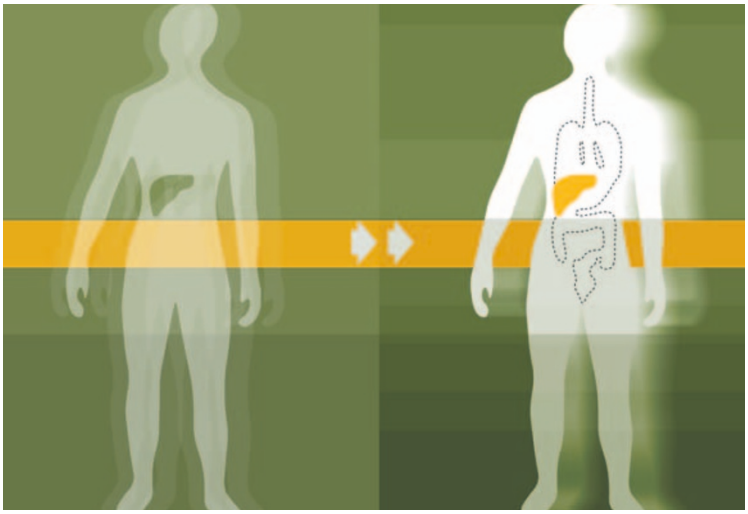
A new treatment for liver fibrosis?

Chronic liver injury in response to alcohol or hepatitis virus B or C is associated with liver fibrosis, and its endstage, cirrhosis, is a major public health problem. However, at present, there are no effective antifibrotic drugs approved for human use. In a recent paper in *Nature Medicine*, Teixeira-Clerc and colleagues now show that use of the cannabinoid CB1 receptor antagonist rimonabant could be a new therapeutic strategy for this condition.

The authors recently found that during the course of chronic hepatitis C, daily cannabis use is an independent predictor of fibrosis progression. They therefore sought to determine if CB1 receptors might be involved in liver fibrosis.

Firstly, using immuno-blotting and immunohistocytochemistry, Teixeira-Clerc *et al.* showed that CB1 receptor expression was upregulated in human cirrhotic liver samples, predominantly in hepatic myofibroblasts, the fibrogenic cells of the liver. They then used a murine model of acute liver injury to demonstrate that CB1 receptors are involved in the induction of two fibrogenic markers: the profibrogenic cytokine transforming growth factor (TGF)-β1 and smooth muscle α-actin. Administration of rimonabant reduced expression of both markers, and there was a similar reduction in fibrogenic marker expression in CB1 knockout mice, with or without rimonabant treatment.

To further assess the role of CB1 receptors in chronic liver injury, three mouse models were used: chronic CCl_4 intoxication, chronic thioacetamide intoxication and bile duct ligation. Rimonabant lowered the fibrogenic response, independently of the agent used to induce liver injury, as shown by a decrease in fibrosis area, reduced hepatic expression of TGF-β1, and decreased number of liver fibrogenic cells. Similar reduction of fibrogenesis was observed in CB1 knock-out mice.



The authors then focused on how antagonism of CB1 receptors might reduce the accumulation of hepatic myofibroblasts. Hepatic myofibroblasts from CB1 receptor knockout mice displayed increased apoptosis, whilst rimonabant was able to inhibit their proliferation. They also investigated the phosphatidylinositol 3-kinase-Akt and extracellular-regulated kinase (ERK) pathways, which are necessary for the growth and survival of hepatic myofibroblasts. Cells isolated from CB1 knockout mice showed decreased phosphorylation of ERK and Akt, as did rimonabant-treated wild-type hepatic myofibroblasts, suggesting that CB1 receptors on hepatic myofibroblasts may either be activated by an endogenous ligand or be constitutively active.

Overall, these results clarify the profibrogenic role of the CB1 receptor. And although yet to be tested for liver fibrosis in clinical trials, this study opens the possibility that rimonabant, which has been recommended to receive marketing authorization for the treatment of obesity by the European Medicines Agency, might also have potential in the treatment of liver fibrosis.

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ORIGINAL RESEARCH PAPER Teixeira-Clerc, T. *et al.* CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. *Nature Med.* **12**, 671–676 (2006)
FURTHER READING Lotersztajn, S. *et al.* Hepatic fibrosis: molecular mechanisms and drug targets. *Annu. Rev. Pharmacol. Toxicol* **45**, 605–628 (2005) | Kunos, G. *et al.* Cannabinoids hurt, heal in cirrhosis. *Nature Med.* **12**, 608–609 (2006)