Protection from liver fibrosis by a peroxisome proliferator-activated receptor δ agonist

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AUTHOR SUMMARY

Liver fibrosis is a common consequence of chronic liver injury and can progress to cirrhosis and hepatocellular carcinoma. Cirrhosis is a major health burden worldwide and is currently the 12th leading cause of death in the United States. The underlying causative agent (e.g., alcohol consumption, hepatitis B and C viral infections, biliary obstruction) is treated successfully only in subsets of patients, and there are no specific treatments for liver fibrosis. An ideal antifibrotic therapy would be liver specific, well tolerated when administered for prolonged periods, and effective in attenuating excessive collagen deposition (1). Peroxisome proliferator-activated receptor delta (PPARδ), a member of the nuclear receptor protein family, is emerging as a key metabolic regulator with pleiotropic actions on various tissues, including fat, skeletal muscle, and liver. The goal of our study was to determine whether PPARδ agonists ameliorate experimental liver fibrosis. For this purpose, we treated mice orally with either a PPARδ agonist, KD3010, or the well-characterized PPARδ agonist GW501516. Unexpectedly, KD3010, but not GW501516, showed dramatic hepatoprotective and antifibrotic effects in experimental and preclinical models of liver fibrosis. Our findings hold promise for evaluating this drug for treating patients with chronic liver disease.

We first showed that KD3010, but not GW501516, dramatically ameliorated liver injury induced by carbon tetrachloride (CCL\textsubscript{4}) injections. Deposition of extracellular matrix proteins was lower in the KD3010–treated group than in the vehicle- or GW501516-treated groups. The hepatoprotective and antifibrotic effects of KD3010 were confirmed in a model of cholestatic liver injury and fibrosis induced by bile duct ligation. Primary hepatocytes treated with KD3010, but not GW501516, were protected from starvation or CCL\textsubscript{4}-induced cell death, in part because of reduced production of reactive oxygen species. This reduction occurred in hepatocytes in a PPARδ-dependent fashion. The mechanism likely involves expression of cytochrome P450 isoforms, which are stimulated by KD3010 and result in oxidation and detoxification of organic substances, whereas GW501516 did not alter expression of cytochrome P450 isoforms. We were surprised to find significant differences in gene-expression profiles induced in cultured hepatocytes treated with either compound. Further, we found that profibrogenic connective tissue growth factor (CTGF) was induced by GW501516 but not by KD3010. The combination of cytoprotection and the absence of a profibrogenic cytokine confers protection from fibrosis and explains differences observed in our study between KD3010 and GW501516 (Fig. P1). Our study identifies hepatocytes as the main target cell population in the liver that mediates the beneficial effect of KD3010 in a PPARδ-dependent fashion.

We show here that two structurally distinct compounds classified as PPARδ agonists differ significantly in their hepatoprotective and antifibrotic effects in mouse models of liver disease. Although the reasons for the differing pharmacological effects of the two PPARδ agonists are yet to be elucidated fully, there are several possible explanations for their differential impact on hepatic gene expression. These explanations include differences in the specificities of these compounds for other members of the PPAR family, in their potencies, and in the in vivo pharmacological properties of the compounds, including differential tissue distribution, degradation, and clearance (2).

Chronic liver disease results in hepatic fibrosis. The only current treatments for patients with hepatic fibrosis target the underlying liver disease. Otherwise, there are no effective antifibrotic treatments for patients with chronic liver disease. Insights into the mechanisms of the development of hepatic fibrosis provide an opportunity to develop therapeutic interventions for human clinical use. Our present study suggests that a PPARδ agonist may serve as a treatment option.


The authors declare no conflict of interest.

This is a Contributed submission.

Data deposition: The microarray data reported in this paper have been deposited in the Gene Expression Omnibus (GEO) database (accession code GSE32121).

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