Fenofibrate induced-hepatomegaly and liver regeneration is PPARα-dependent and partially related to the activation of YAP pathway

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Abstract

Fenofibrate, a peroxisome proliferator-activated receptor α (PPARα) agonist, has been widely used as a lipid-regulating agent in clinical practice. Recent studies found that fenofibrate treatment induced hepatomegaly in mice, but the underlying mechanisms remained unclear. Liver regeneration post-partial hepatectomy (PHx) is associated with hepatomegaly, and the effects of fenofibrate on liver regeneration remain unclarified. Yes-associated protein (YAP), the critical effector of Hippo signaling pathway, has a pivotal role in regulating the liver size and regeneration. This study aimed to identify the role of YAP and PPARα in fenofibrate-induced hepatomegaly and liver regeneration. Several strains of mouse models including wild-type, *Ppara*$^{fl/fl}$, and hepatocyte-specific *Ppara*-deficient (*Ppara*$^{\Delta Hep}$) mice were employed to investigate the effects of fenofibrate on liver size and liver regeneration. The results showed that fenofibrate dosing significantly induced liver enlargement and promoted liver regeneration after 70% PHx in mice, accompanied by increased hepatocyte size around the central vein area and enhanced hepatocyte proliferation around the portal vein area, which is PPARα-dependent and PPARα expressed in hepatocytes plays the dominant role in fenofibrate-induced liver enlargement and regeneration. Mechanistically, fenofibrate upregulated the expressions of YAP as well as its downstream proteins. Furthermore, fenofibrate activated YAP signaling via suppressing K48-linked ubiquitination and promoting K63-linked ubiquitination, and enhancing interaction and transcriptional activity of YAP-TEAD complex. Pharmacological inhibition of YAP-TEAD interaction or suppression of YAP using AAV *Yap* shRNA in mice significantly attenuated fenofibrate-induced hepatomegaly, as well as hepatocyte hypertrophy and proliferation. Other factors such as MYC, KRT23, RAS, and RHOA might also participate in fenofibrate-induced hepatomegaly and liver regeneration. These studies uncover a novel role for fenofibrate in promoting liver enlargement and regeneration is PPARα-dependent and partially through activating the YAP signaling pathway, which provided clinical implications of fenofibrate as a potential medication for promoting liver regeneration following PHx.

Key Words

fenofibrate; peroxisome proliferator-activated receptor α; hepatomegaly; liver regeneration; yes-associated protein