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Biochemistry 2018: Liver PPARÃŽÂ± is protective against NAFLD

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Abstract

The liver is a key organ of metabolic homeostasis with functions that oscillate in response to food intake. Under the control of PPARα in the mouse, the genes required for lipid catabolism are transcribed before birth so that the neonatal liver has a prompt capacity to extract energy from milk upon suckling. The mechanism involves a fetal glucocorticoid receptor (GR)PPARα axis in which GR directly regulates the transcriptional activation of PPARα by binding to its promoter. In adult mouse, PPARα deletion impairs fatty acid catabolism, resulting in hepatic lipid accumulation in preclinical models of steatosis. These findings underscore the relevance of hepatic PPARα as a drug target for NAFLD as they show that PPARα plays a central role in the clearance of free fatty acids released from adipocytes, the major source of lipid that accumulate in NAFLD. FGF21 is a hepatokine with beneficial metabolic effects, including control of sucrose preference. It is encoded in FGF21, a unique hepatic gene that the transcription factors PPARα and ChREBP both regulate to control sugar intake. In fact, ChREBP is required for the expression and secretion of hepatic FGF21 in response to carbohydrate intake. Interestingly, experiments using hepatocytespecific PPARα knockout mice reveal a physiological role for PPARα in the context of glucose challenge, as ChREBP is unable to induce FGF21 in the absence of hepatic PPARα. These observations suggest that FGF21's glucose-mediated response is dependent on both ChREBP and PPARα. Altogether, these findings underscore the relevance of hepatic PPARα as a drug target for NAFLDs as they show that PPARα plays a central role in the clearance of free fatty acids released from adipocytes, the major source of lipid that accumulate in NAFLD. Furthermore, they imply that drug targeting of PPARα may exert part of its beneficial effects on metabolic homeostasis by supporting the ChREBP-induced loop controlling sweet preference via FGF21.

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