

# AMP-regulated and AMPK-related enzymes as drug target in the liver?

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会場

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Maintaining energy balance is central in managing body weight and blood glucose levels within a narrow range. AMP-activated protein kinase (AMPK) is a key energy-sensing enzyme that coordinates metabolic pathways in order to balance nutrient supply with energy demand. AMPK is considered an attractive drug target for metabolic disorders, as its activation elicits metabolic responses expected to counteract the metabolic abnormalities associated with obesity, insulin resistance, and type 2 diabetes. More than a decade ago, AMPK drew major attention when it was suggested as a key molecular target mediating the favorable metabolic effects of exercise and the anti-diabetic drug, metformin. Similar to the effect of exercise/contractions on myocytes, metformin mildly causes hepatocellular energy deficit (characterized by an increased AMP/ATP ratio) via inhibition of mitochondrial energy (ATP) production, which leads to enhanced fat oxidation to restore the cellular energy balance. Recent preclinical/genetic studies have confirmed that AMPK indeed plays a key role in metformin-induced improvements in insulin action by maintaining hepatic lipid homeostasis. In contrast, several lines of evidence suggest that the blood glucose-lowering effect of metformin, mediated through inhibition of hepatic glucose production (HGP), is AMPK independent. Interestingly, a well-known pharmacological AMPK activator called 5-aminoimidazole-4-carboxamide-1- $\beta$ -D-ribofuranoside (AICAR), an AMP mimetic, profoundly suppressed glucose output in hepatocytes genetically lacking AMPK, indicating AMP per se but not AMPK plays a vital role in suppressing HGP. Similarly, a close correlation between the magnitude of increase in AMP and inhibition of glucose output in hepatocytes was reported. Given that the anabolic process of gluconeogenesis is energetically costly, hepatocytes must balance this energy demand with production thereby maintaining energy homeostasis. We have recently generated a unique genetic preclinical model and tested the hypothesis that an AMP-dependent but AMPK-independent pathway plays an important role in controlling hepatic glucose production and hence blood glucose homeostasis. We also report the effects of small allosteric/direct activators of AMPK, that bind to recently identified ADaM (allosteric drug and metabolism) site, on hepatic lipid metabolism employing an AMPK mutant mouse model.

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