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Aberrant activation of aldose reductase promotes insulin insensitivity, hepatosteatosis and obesity in mice in part through modulating hepatic PPARα, LKB1/AMPKα and IRS-1

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It is well established that aldose reductase (AR) is a critical mediator for a variety of diabetic complications. Recent studies, however, indicate that aberrant activation of AR or overproduction of the polyol pathway-derived endogenous hepatic fructose might contribute to the development of fatty liver diseases as well as the metabolic syndrome. However, the mechanisms underlying AR/the polyol pathway-induced pathogenesis of related metabolic disorders were not clear. In this investigation, we aimed to investigate how the activity change of AR might affect insulin signaling, hepatosteatosis and obesity. We found that in mouse AML12 hepatocytes, overexpression of AR significantly reduced the abundance of phosphorylated LKB1, AMPKα and ACC. Conversely, lentivirus-mediated AR knockdown greatly elevated the levels of phosphorylated LKB1, AMPKα and ACC. Additionally, overexpression of AR reduced the mRNA and protein expression of *IRS-1*, whereas knockdown of AR greatly elevated *IRS-1* mRNA and protein expression. In the Agouti yellow obese mice, loss of AR (A^y/a::$AR^{-/-}$) significantly ameliorated the Agouti signaling peptide-induced insulin insensitivity, hepatosteatosis and obesity, as compared with that of the A^y/a::$AR^{+/+}$ control mice. In contrast, liver-specific transgenic overexpression of AR appeared to promote the development of glucose-induced hepatosteatosis and obesity. Together with our previous demonstrations that AR is capable of regulating the activity of PPARα to impact lipid homeostasis, our findings suggest that aberrant activation of AR might promote metabolic remodeling, insulin resistance, hepatosteatosis and obesity in part through modulating the expression or the activity of hepatic PPARα, IRS-1 and LKB1/AMPKα.

Biography

James Y Yang earned his PhD from the University of Houston, Houston, Texas, USA. He pursued his Postdoctoral studies at the Columbia University under the guidance of Dr. Abraham Spector. He worked as a Research Assistant Professor/Research Officer at the University of Hong Kong for 7 years. He is currently a Professor in the State Key Laboratory of Cellular Stress Biology and the School of Life Sciences, Xiamen University, Xiamen, China. He has published more than 30 papers in reputed journals including Hepatology, Gut, FRBM, JBC and Diabetologia.

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