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FBP1 is a nonenzymatic safety valve that prevents insulin hyperresponsiveness

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Insulin inhibits gluconeogenesis and stimulates glucose conversion to glycogen and lipids. How these activities are coordinated to prevent hypoglycemia and hepatosteatosis is unclear. Fructose-1,6 bisphosphatase (FBP1) is rate limiting for gluconeogenesis. Curiously, inborn human FBP1 deficiency does not cause hypoglycemia unless accompanied by fasting, which also triggers hepatomegaly, hepatosteatosis, and hyperlipidemia. Hepatocyte FBP1-ablated mice exhibit the same fasting-conditional pathologies along with hyperactivated AKT, whose inhibition reverses hepatomegaly, hepatosteatosis and hyperlipidemia but not hypoglycemia. We show that independently of gluconeogenesis, FBP1 prevents insulin hyperresponsiveness by forming an AKT inhibitory complex with Aldolase B and PP2A. Enhanced by fasting and weakened by insulin, complex formation, blocked by certain FBP1 deficiency mutations, prevents insulin-triggered liver pathologies, and maintains lipid and glucose homeostasis. Conversely, complex disruption reverses insulin resistance.