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METABOLISM

Leptin's role in starvation

The shift from glucose to fat oxidation is critical for survival during long-term starvation and is thought to be predominately orchestrated by insulin. A new study led by Gerald Shulman now identifies a novel role for leptin in mediating a glucose–fatty acid cycle that promotes this metabolic shift to maintain euglycaemia in rats during starvation.

A novel positional isotopomer NMR tracer analysis (PINTA) method was developed to measure in vivo rates of hepatic glycogenolysis, gluconeogenesis and mitochondrial oxidation, and was combined with liquid chromatography–tandem mass spectrometry (LC–MS/MS) analyses and stable isotope dilution methods to assess rates of whole-body glucose turnover, white adipose tissue (WAT) lipolysis, alanine turnover and lactate turnover. "This comprehensive metabolic approach allowed us to determine what key processes contribute to the maintenance of euglycaemia during the transition from the fed to the long-term fasted state," explains Shulman.

Short-term starvation in rats induced hepatic glycogen depletion and led to hypoleptinaemia, which, in the presence of hypo-insulinaemia, stimulated hypothalamic–pituitary–adrenal (HPA) axis activity. This led to enhanced WAT lipolysis and consequent increases in hepatic acetyl-CoA content, promoting a metabolic shift to fat oxidation and maintenance of hepatic gluco-neogenesis via acetyl-CoA-dependent allosteric activation of pyruvate carboxylase flux.

Another key finding was that rates of hepatic mitochondrial oxidation and gluconeogenesis were limited by substrate depletion owing to reduced muscle glucose–alanine cycling in the long-term fasted state.

Overall, these findings challenge the canonical view that insulin is the key orchestrator in glucose homeostasis in starvation. "The next step will be to understand whether these same mechanisms translate to humans during starvation using similar methodologies," concludes Shulman.

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ORIGINAL ARTICLE Perry, R. J. et al. Leptin mediates a glucose-fatty acid cycle to maintain glucose homeostasis in starvation. *Cell* https://doi.org/10.1016/j.cell.2017.12.001 (2018)
FURTHER READING Petersen, M. C., Vatner, D. F. & Shulman, G. I. Regulation of hepatic glucose metabolism in health and disease. *Nat. Rev. Endocrinol.* **13**, 572–587 (2017)

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