# Modeling the dynamics of hepatic metabolism: the predominance of 12-hour rhythmicity in metabolic adaptation

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Autoren

Madlen Matz-Soja Christiane Körner Fritzi Ott Janett Fischer Eugenia Marbach-Breitrück Christian Bergmann Ute Hofmann Andrej Shevchenko Iwona Wallach Kathrin Textoris-Taube Michael Mülleder Rolf Gebhardt Thomas Berg Nikolaus Berndt

## Abstract

Background and objectives The liver continuously adjusts its metabolic activity to synchronize the nutrient supply with the body's demands. This synchronization involves the complex coordination of acute metabolic needs, nutrient availability, and activity levels, which is orchestrated according to cyclic internal rhythms governed by the circadian clock. This study aimed to decipher the role of circadian rhythms in liver metabolic functions, including mitochondrial activities that are critical for energy production and metabolic adaptation.

Methods We investigated rhythmic changes in liver metabolism via comprehensive multiomics and kinetic mathematical modeling. The liver proteome of male mice was analyzed and modeled, and complementary serum lipidomic and metabolomic analyses were performed. Mitochondrial proteins were examined to evaluate the role of mitochondria in the oscillating regulation of energy production.

Results Most metabolic functions, particularly those related to carbohydrate and fatty acid metabolism, exhibit rhythmic patterns on a 12-hour rather than a 24-hour cycle. The importance of this rhythmicity is function-dependent and can account for 25% to 50% of the overall variability. Mitochondrial activities also exhibit temporal fluctuations that are closely linked to nutrient availability. The strong correlation between metabolic functions and serum metabolites highlights the precise alignment between physiological demand and metabolic performance.

Conclusions Hepatic metabolic functions follow a 12-hour cycle rather than a 24-hour cycle, significantly contributing to the liver's ability to meet nutrient demands throughout the day. Mitochondrial dynamics, which are influenced by nutrient availability, play a central role in adapting energy production to the body's metabolic needs.