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Metabolic network analysis of perfused livers under fed and fasted states: incorporating thermodynamic and futile-cycle-associated regulatory constraints. (English) Zbl 1307.92086

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Summary: Isolated liver perfusion systems have been extensively used to characterize intrinsic metabolic changes in liver under various conditions, including systemic injury, hepatotoxin exposure, and warm ischemia. Most of these studies were performed utilizing fasted animals prior to perfusion so that a simplified metabolic network could be used in order to determine intracellular fluxes. However, fasting induced metabolic alterations might interfere with disease related changes. Therefore, there is a need to develop a "unified" metabolic flux analysis approach that could be similarly applied to both fed and fasted states. In this study we explored a methodology based on elementary mode analysis in order to determine intracellular fluxes and active pathways simultaneously. In order to decrease the solution space, thermodynamic constraints, and enzymatic regulatory properties for the formation of futile cycles were further considered in the model, resulting in a mixed integer quadratic programming problem. Given the published experimental observations describing the perfused livers under fed and fasted states, the proposed approach successfully determined that gluconeogenesis, glycogenolysis and fatty acid oxidation were active in both states. However, fasting increased the fluxes in gluconeogenic reactions whereas it decreased fluxes associated with glycogenolysis, TCA cycle, fatty acid oxidation and electron transport reactions. This analysis further identified that more pathways were found to be active in fed state while their weight values were relatively lower compared to fasted state. Glucose, lactate, glutamine, glutamate and ketone bodies were also found to be important external metabolites whose extracellular fluxes should be used in the hepatic metabolic network analysis. In conclusion, the mathematical formulation explored in this study is an attractive tool to analyze the metabolic network of perfused livers under various disease conditions. This approach could be simultaneously applied to both fasted and fed data sets.

MSC:

92C40 Biochemistry, molecular biology
92C45 Kinetics in biochemical problems (pharmacokinetics, enzyme kinetics, etc.)
92C42 Systems biology, networks

Keywords:

pathway analysis; thermodynamic constraints; futile cycles; liver metabolism; effect of fasting

Software:

YANA

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