Integrated metabolic spatial-temporal model for prediction of ammonia detoxification during liver damage and regeneration

Schliess F, Hoehme S, Henkel S, Ghallab A, Driesch D, Böttger J, Guthke R, Pfaff M, Hengstler J, Gebhardt R, Häussinger D, Drasdo D, Zellmer S (2014) Integrated metabolic spatial-temporal model for prediction of ammonia detoxification during liver damage and regeneration *Hepatology* 60(6), 2040-2051.

Details

PubMed

PAPER

Abstract

The impairment of hepatic metabolism due to liver injury has high systemic relevance. However, it is difficult to calculate the impairment of metabolic capacity from a specific pattern of liver damage with conventional techniques. We established an integrated metabolic spatial-temporal model (IM) using hepatic ammonia detoxification as a paradigm. First, a metabolic model (MM) based on mass balancing and mouse liver perfusion data was established to describe ammonia detoxification and its zonation. Next, the MM was combined with a spatial-temporal model simulating liver tissue damage and regeneration after CCl_4 intoxication. The resulting IM simulated and visualized whether, where, and to what extent liver damage compromised ammonia detoxification. It allowed us to enter the extent and spatial patterns of liver damage and then

calculate the outflow concentrations of ammonia, glutamine, and urea in the hepatic vein. The model was validated through comparisons with (1) published data for isolated, perfused livers with and without CCl_4 intoxication and (2) a set of in vivo experiments. Using the experimentally determined portal concentrations of ammonia, the model adequately predicted metabolite concentrations over time in the hepatic vein during toxin-induced liver damage and regeneration in rodents. Further simulations, especially in combination with a simplified model of blood circulation with three ammonia-detoxifying compartments, indicated a yet unidentified process of ammonia consumption during liver regeneration and revealed unexpected concomitant changes in amino acid metabolism in the liver and at extrahepatic sites. Conclusion: The IM of hepatic ammonia detoxification considerably improves our understanding of the metabolic impact of liver disease and highlights the importance of integrated modeling approaches on the way toward virtual organisms.

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Identifier

doi: 10.1002/hep.27136

PMID: 24677161