A theoretical study of lipid accumulation in the liver-implications for nonalcoholic fatty liver disease.

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Abstract

A hallmark of the nonalcoholic fatty liver disease is the accumulation of lipids. We developed a mathematical model of the hepatic lipid dynamics to simulate the fate of fatty acids in hepatocytes. Our model involves fatty acid uptake, lipid oxidation, and lipid export. It takes into account that storage of triacylglycerol within hepatocytes leads to cell enlargement reducing the sinusoids radius and impairing hepatic microcirculation. Thus oxygen supply is reduced, which impairs lipid oxidation. The analysis of our model revealed a bistable behavior (two stable steady states) of the system, in agreement with histological observations showing distinct areas of lipid accumulation in lobules. The first (healthy) state is characterized by intact lipid oxidation and a low amount of stored lipids. The second state in our model may correspond to the steatotic cell; it is marked by a high amount of stored lipids and a reduced lipid oxidation caused by impaired oxygen supply. Our model stresses the role of insufficient oxygen supply for the development of steatosis. We discuss implications of our results in regard to the experimental design aimed at exploring lipid metabolism reactions under steatotic conditions. Moreover, the model helps to understand the reversibility of

lipid accumulation and predicts the reversible switch to show hysteresis. The system can switch from the steatotic state back to the healthy state by reduction of fatty acid uptake below the threshold at which steatosis started. The reversibility corresponds to the observation that caloric restriction can reduce the lipid content in the liver.

Beteiligte Forschungseinheiten

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