Zonation of hepatic fat accumulation: insights from mathematical modelling of nutrient gradients and fatty acid uptake.

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Abstract

Intrinsic of non-alcoholic fatty liver diseases is an aberrant accumulation of triglycerides (steatosis), which occurs inhomogeneously within lobules. To improve our understanding of the mechanisms involved in this zonation patterning, we developed a mathematical multicompartment model of hepatic fatty acid metabolism accompanied by blood flow simulations. A model analysis determines the influence of the uptake process of fatty acids, the porto-central gradient of plasma fatty acid concentration, and the oxygen supply via blood on the zonation of triglyceride accumulation. From this theoretical perspective, the plasma oxygen gradient, but not the fatty acid gradient, leads the way to a zonated triglyceride accumulation by its decisive role in oxidative processes. In addition, the uptake mechanism of fatty acids seems to be fundamental for a pericentral dominance of steatosis. However, the mechanism of cellular fatty acid uptake from the blood is still under debate. Our theoretical approach supports the transporter-mediated uptake mechanism and reveals that the maximal velocity of fatty acid uptake affects the switching

between a periportal and a pericentral triglyceride accumulation. Further research on hepatic fatty acid uptake is needed to push forward our understanding of aberrant triglyceride accumulation in diet-induced steatosis.

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