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Review

Zonation of hepatic fatty acid metabolism — The diversity of its regulation and the benefit of modeling

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ABSTRACT

A pronounced heterogeneity between hepatocytes in subcellular structure and enzyme activities was discovered more than 50 years ago and initiated the idea of metabolic zonation. In the last decades zonation patterns of liver metabolism were extensively investigated for carbohydrate, nitrogen and lipid metabolism. The present review focuses on zonation patterns of the latter. We review recent findings regarding the zonation of fatty acid uptake and oxidation, ketogenesis, triglyceride synthesis and secretion, *de novo* lipogenesis, as well as bile acid and cholesterol metabolism. In doing so, we expose knowledge gaps and discuss contradictory experimental results, for example on the zonation pattern of fatty acid oxidation and *de novo* lipogenesis. Thus, possible rewarding directions of further research are identified. Furthermore, recent findings about the regulation of metabolic zonation are summarized, especially regarding the role of hormones, nerve innervation, morphogens, gender differences and the influence of the circadian clock. In the last part of the review, a short collection of models considering hepatic lipid metabolism is provided. We conclude that modeling, despite its proven benefit for understanding of hepatic carbohydrate and ammonia metabolisms, has so far been largely disregarded in the study of lipid metabolism; therefore some possible fields of modeling interest are presented.

1. Introduction

The functions of human liver are rather diverse, including energy and metabolite storage in times of nutrient excess and release during starvation, with the goal to keep the body in homeostasis. Other important functions are the detoxification of ammonia, drugs, xenobiotica and alcohol, as well as the synthesis of essential compounds like bile, serum proteins and (membrane) lipids.

The proper functioning of the liver depends on its structure. The human liver has four main lobes each consisting of thousands of lobules, which are considered as the smallest functional liver units. Within a lobule, nutrient-rich blood from the portal vein and oxygen-rich blood from the hepatic artery flow through sinusoids (small blood vessels) to the central vein. Sinusoids (Fig. 1) are bordered by endothelial cells, and the space between the endothelial cells and the hepatocytes is called "Space of Disse".

Despite a homogeneous morphology of the individual hepatocytes [9], a pronounced heterogeneity in subcellular structure [10–12], mitochondrial physiology [10,11], and enzyme activities (e.g. [13,14]) was observed between hepatocytes along the sinusoid. This heterogeneity implies different metabolic capacities and a functional zonation of hepatic metabolism [2,8,15] (Fig. 1). Functional zonation means that different metabolic pathways are active in different zones along a sinusoid. The simplest, and most often used distinction is the one into a periportal (afferent; hepatocytes adjacent to the branches of the portal vein and the hepatic artery) and perivenous zone (efferent; hepatocytes surrounding the central vein). The perivenous zone is sometimes called pericentral, and in literature both terms are used synonymously. Occasionally a middle zone is distinguished, located between the periportal and perivenous zones. The definition of a zone, including the amount of hepatocytes assigned to a zone, is a semantic issue. It needs to be adapted to adequately describe the extent of the localization of the

Abbreviations: ACC, acetyl-CoA carboxylase; ACL, ATP-citrate lyase; AMPK, 5′-AMP-dependent protein kinase; *Apc*, adenomatous polyposis coli; BMAL1, brain and muscle Arnt-like 1; CCG, clock controlled genes; CLOCK, circadian locomotor output cycles kaput; CPT1/CPT2, carnitine palmitoyltransferase 1/2; DGAT1, diacylglycerol acyltransferase 1; DNL, *de novo* lipogenesis (fatty acid synthesis); ELOVL, elongation of very long chain fatty acids; FA, fatty acid; FAS, fatty acid synthase; FAT/CD36, fatty acid translocase/cluster of differentiation 36; FATP, fatty acid transport protein; FFA, free fatty acid; FoxO, forkhead transcription factors; HIF2, hypoxia-inducible factor 2; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; Hnf1α, hepatocyte nuclear factor 1α; L-FABP, liver-specific fatty acid binding proteins; NAD, nicotinamide adenine dinucleotide; NAFLD, non-alcoholic fatty liver diseases; NR, nuclear receptor; PPAR, peroxisome proliferator-activated receptor; REV-ERBα/β, reverse erythroblastoma virus; ROR, retinoic acid-receptor related orphan receptor; SCN, suprachiasmatic nuclei; SREBF1, sterol regulatory element-binding transcription factor 1; SCD1, stearoyl-CoA desaturase 1; TG, triglyceride; TCA cycle, tricarboxylic acid cycle/Krebs cycle; VLDL, very-low-density lipoproteins

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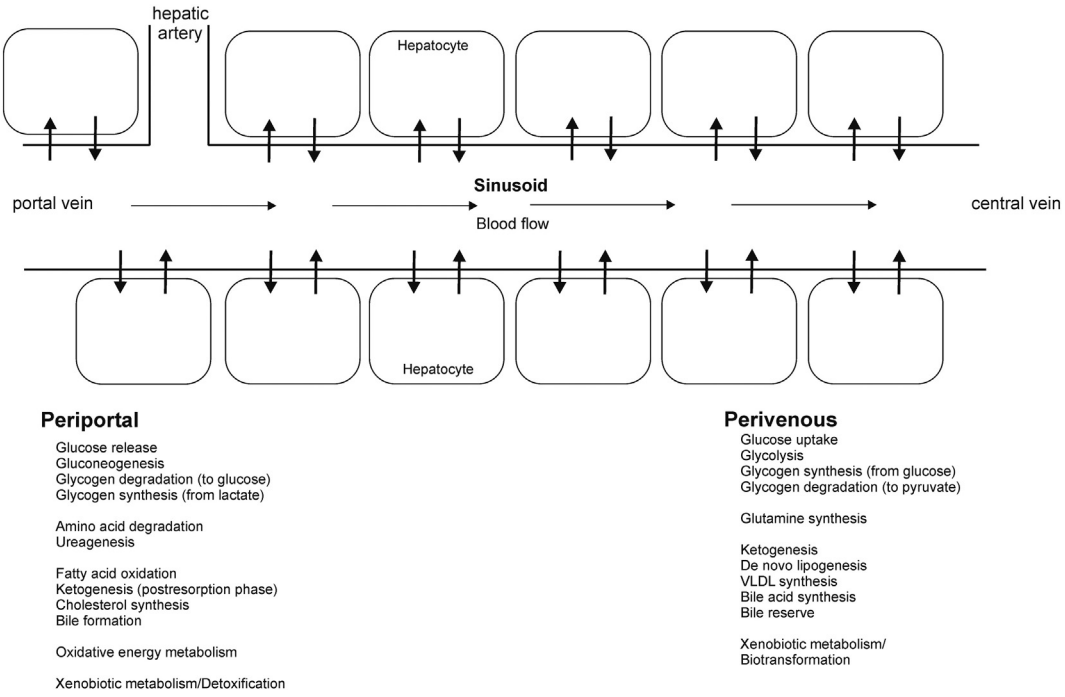

Fig. 1. Schematic structure of a sinusoidal segment and zonation of hepatic fatty acid metabolism along a sinusoid. Portal vein provides nutrient-rich but oxygen-poor blood, hepatic artery provides oxygen-rich blood [1]. Metabolic processes predominant in the periportal or perivenous zone are indicated following [2–8]. Currently, these zonation patterns are widely accepted in the scientific community; however, some experimental results cast doubt on the zonation patterns of fatty acid metabolism. These contradictory results are discussed in the text.

investigated enzymes and metabolic processes [16] and cannot be classified generally.

Zonation patterns can be "stable" or "dynamic" [8,17] and fall into categories of a "gradient" or a "compartment" type [7]. A zonation pattern that does not change under different nutritional and hormonal conditions is called stable. An example is the zonation pattern of the glutamine synthetase [7,18]. However, most enzymes show a dynamic zonation pattern, i.e. the zone of enzyme activity changes with nutritional and hormonal conditions. If an enzyme is present in each hepatocyte (but in different amounts or activities), it is assigned to the gradient type of zonation, whereas enzymes present only in one zone are assigned to the compartment type.

The zonation of hepatic metabolism is a prerequisite to keep the organism in homeostasis [4,7,19] by fulfilling certain important requirements [20]: (i) anabolic and catabolic opposing pathways (e.g. fatty acid oxidation and fatty acid synthesis) can be spatially separated to prevent futile cycling, (ii) competition for a common substrate between two pathways can be diminished, and (iii) pathways complementing one another (e.g. fatty acid synthesis and NADPH producing enzymes) can be spatially linked. Furthermore, (iv) spatial separation of pathways may lead to a more efficient detoxification (e.g. ammonia by ureogenesis and glutamine synthesis) and (v) clustering of oxygen-demanding metabolic pathways at the periportal zone ensures proper functioning due to high partial oxygen pressure.

In the last two decades, the question of (molecular) causes and mechanisms of zonation patterns arose (see Section "3. Regulation of zonation patterns"). Hitherto, investigation of the hepatic zonation has been focused mainly on carbohydrate, amino acid, ammonia, and xenobiotic metabolisms (reviewed in [2,4,7–9,17,21,22]). So far, hepatic fatty acid metabolism has been considered relatively superficially, notably in some studies focusing on carbohydrate metabolism. Due to the connection of glycolysis and *de novo* lipogenesis (DNL), some data are available about the zonation pattern of lipogenic enzymes (e.g. [13,14,16,23–27]) and NADPH-generating enzymes (e.g. [4,28,29], reviewed in [7]). Besides this connection, hepatic lipid metabolism fulfills independent and rather important functions for our body, e.g. regulating the plasma concentration of fatty acids (FAs), triglycerides (TGs), and ketone bodies. It plays a key role in body lipid accumulation (e.g. fat storage in adipose tissue), in energy delivery to the brain and kidney via ketone bodies during low glucose supply (e.g. during fasting periods), and in the removal of toxic FAs from the blood. In addition, hepatic lipid metabolism, its regulation and zonation are essential in the development of diseases like ketoacidosis [30], non-alcoholic fatty liver diseases (NAFLD, [31]), and cancer cachexia [32].

Except for a review by Hijmans et al. [33] focusing on zonation of steatosis and insulin signaling, the last reviews about zonation of FA metabolism date back more than a decade ago [2–5,7,8]. Since then, knowledge about molecular processes involved in hepatic FA metabolism and in the establishment of zonation patterns has emerged. We review in detail the zonation of hepatic lipid metabolism and theories about the regulation of this zonation. We pay special attention to the role of the circadian rhythm and also include a section on mathematical modeling. For a recent review on disturbed zonation patterns of glucose and fatty acid metabolism under metabolic disorders the reader is referred to Hijmans et al. [33].

2. Zonation of fatty acid metabolism

In Fig. 1 the established view is presented of how metabolism is zonated along the liver sinusoid. However, in the last two decades contradictory experimental findings cast doubt on some of the zonation patterns of FA metabolism. It seems that the zonation of lipid metabolism is less pronounced and more flexible than that of ammonia and xenobiotic metabolism. This section summarizes the literature about zonation patterns of the main FA metabolism processes, which are depicted in Fig. 2.

2.1. Uptake and cytosolic transport

Uptake of FAs from the blood is a complex process, in which different lipoproteins, albumin and several plasma membrane protein transporters are involved (e.g. fatty acid transport proteins FATP; fatty acid