Biochimie xxx (2013) 1–9

Contents lists available at SciVerse ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Zonation of glucose and fatty acid metabolism in the liver: Mechanism and metabolic consequences

Brenda S. Hijmans [a,*], Aldo Grefhorst [b], Maaike H. Oosterveer [a], Albert K. Groen [a]

[a] Departments of Pediatrics and Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands
[b] Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 24 March 2013
Accepted 12 June 2013
Available online xxx

Keywords:
Metabolic zonation
Metabolic syndrome
Insulin signaling paradox
Non-alcoholic fatty liver disease

ABSTRACT

The liver is generally considered as a relatively homogeneous organ containing four different cell types. It is however well-known that the liver is not homogeneous and consists of clearly demarcated metabolic zones. Hepatocytes from different zones show phenotypical heterogeneity in metabolic features, leading to zonation of metabolic processes across the liver acinus. Zonation of processes involved in glucose and fatty acid metabolism is rather flexible and therefore prone to change under (patho)physiological conditions.

Hepatic zonation appears to play an important role in the segregation of the different metabolic pathways in the liver. As a consequence, perturbations in metabolic zonation may be a part of metabolic liver diseases. The metabolic syndrome is characterized by the inability of insulin to adequately suppress hepatic gluconeogenesis, leading to hyperglycemia, hyperinsulinemia and eventually to type II diabetes. As insulin promotes lipogenesis through the transcription factor sterol regulatory element binding protein (SREBP)-1c, one would expect that lipogenesis should also be impaired in insulin-resistant states. However, in the metabolic syndrome hepatic *de novo* lipogenesis is increased, leading to hyperlipidemia and hepatosteatosis, primarily in the pericentral zone. These observations suggest the co-existence of insulin resistant glucose metabolism and insulin sensitive lipid metabolism in the metabolic syndrome. Here we provide a theoretical framework to explain this so-called 'insulin signaling paradox' in the context of metabolic zonation of the liver.

1. Introduction

Due to its rather uniform histological appearance the liver is often unjustly regarded as a homogeneous organ. Already in 1856, when describing the anatomy of the liver in great detail, Lionel Beale noticed a heterogeneity of hepatocytes with regard to bile secretion and deposition of oil [1]. After this, it took more than a century until Jungermann and Sasse proposed a functional significance of heterogeneous enzyme distribution in the liver, thereby introducing the concept of metabolic zonation [2].

It was recognized that the liver may be divided into functional units which were designated acini. Inside the acinus blood flow is directional on basis of which the acinus may be subdivided into different zones [3,4]. The periportal zone receives nutrient rich blood from the portal vein and blood rich in oxygen from the hepatic artery. In the pericentral zone blood is drained from the liver by the central vein. Hepatocytes lining the sinusoids can be classified according to their location on the portocentral axis of the acinus (see Fig. 1). Three different zones are distinguished: 1 = periportal, 2 = intermediate, 3 = pericentral. The flow of blood through the liver generates gradients of oxygen tension, hormones and nutrients which cause hepatocytes to be exposed to different metabolic conditions depending on their location along the portocentral axis. Gradients in signals arise through interaction of blood borne components with hepatocytes, such that periportal hepatocytes are exposed to higher concentrations of blood borne components than pericentral hepatocytes [5].

Hepatocytes from different zones of the liver show phenotypical heterogeneity in metabolic features, leading to zonation of metabolic processes across the acinus [6]. Regarding glucose and fatty acid metabolism, periportal hepatocytes are more involved in gluconeogenesis and β-oxidation, while pericentral hepatocytes are more engaged in glycolysis and lipogenesis [7,8]. Other metabolic properties of the liver, such as ammonia metabolism, xenobiotic

* Corresponding author. Center for Liver, Digestive, and Metabolic Diseases, Laboratory of Pediatrics, Rm. Y2117, CMC IV, Univ. Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 503613156.
E-mail address: b.s.hijmans@umcg.nl (B.S. Hijmans).

0300-9084/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.biochi.2013.06.007

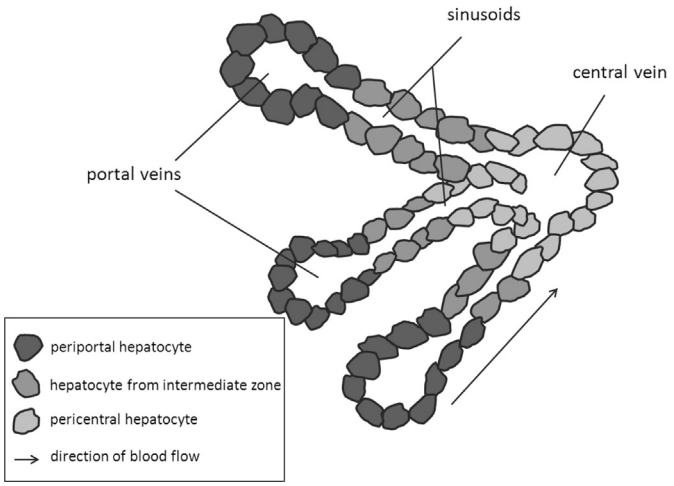

Fig. 1. Schematic depiction of the hepatic acinus.

reactions, cytoprotective functions and protein metabolism also show zonation along the portocentral axis [5].

Zonation of glucose [8] and fatty acid metabolism [9] shows flexibility in different conditions in such a manner that dynamic adaptation of gene and protein expression can be observed in different nutritional states [10]. Interestingly, metabolic pathways performing opposing functions seem to follow inverse gradients and are distributed in a complementary manner. Interdependent metabolic pathways (e.g. lipogenesis and glycolysis) are co-localized to allow for synergistic action, whereas opposing pathways are segregated in different zones, likely to avoid interference and thereby waste of energy. Altogether, the heterogeneity of the liver enables the simultaneous performance of different and even opposing metabolic pathways while allowing for flexible adaptation to differing circumstances [5].

This paper will first briefly discuss the concept and mechanisms of hepatic metabolic zonation, with a special focus on zonation of glucose and fatty acid metabolism. Second, the physiological consequences of segregation of metabolic pathways in the liver will be discussed via examples of disturbed zonation in metabolic diseases of the liver. Finally we will provide a theoretical framework that may explain the relevance of hepatic zonation to aberrant metabolic states, such as insulin resistance and non-alcoholic fatty liver disease (NAFLD).

2. Metabolic zonation

2.1. Signals underlying hepatic metabolic zonation

Many different signals are involved in the establishment of zonal heterogenic properties of hepatocytes. First of all, liver innervation seems to play a substantial role (e.g. Ref. [11]). Sympathetic and parasympathetic nerve fibers enter the liver near the hepatic artery and the portal vein. The extent of further innervation of the acinus differs between species. In rats and mice innervation is limited to the periportal zone, while in humans also areas surrounding the central vein are innervated [10]. Furthermore, the directional blood flow inside the acini establishes oxygen, nutrient, nutrient intermediate and hormonal gradients along the portocentral axis [5,10]. In the periportal zone oxygen tension and concentrations of hormones and nutrients are higher. Hepatocytes in the pericentral zone are exposed to blood enriched in CO_2 and other products of metabolism.

While as of now it is not entirely clear how gradients of enzymes along the portocentral axis arise, blood borne humoral factors (e.g. oxygen and hormones) are thought to be mainly involved in the dynamic adaptation of their heterogeneous expression [12] as will be discussed below. This dynamic adaptation is mostly seen in enzymes that show a gradient-like distribution, such as those involved in glucose [8] and fatty acid [9] metabolism. Other enzymes, such as carbamoyl phosphate synthetase I (CPS I) [13] and glutamine synthetase (GS) [14], the key enzymes in ammonia metabolism, show a more compartmentalized distribution.

Recent studies have implicated different signaling pathways and molecules in the establishment of hepatic zonation. The following sections will provide a brief description of several of these pathways.

2.1.1. Wnt/β-catenin signaling

The involvement of β-catenin was suggested by the finding that liver tumors that contain mutations in activation of β-catenin express a pericentral-like transcription pattern [15,16]. Immunohistochemical studies in mice have shown that adenomatous polyposis coli (APC), which is part of the β-catenin degradation complex, shows a heterogeneous distribution along the portocentral axis, with a higher expression in periportal hepatocytes. The active unphosphorylated form of β-catenin was increased in hepatocytes surrounding the central vein [17,18]. Thus, there seems to be a mutually exclusive localization of active β-catenin and one of its negative regulators across the acinus.

By modulating the Wnt signaling pathway it was shown that Wnt/β-catenin promotes the expression of pericentral genes while downregulating periportal gene expression. When *Apc* expression is downregulated, β-catenin is activated and an induction of normally exclusive pericentral localized genes can be observed in periportal hepatocytes. On the other hand, specific blockade of Wnt signaling induces periportal gene expression in pericentral hepatocytes [17]. Finally, pharmacological inhibition of glycogen synthase kinase 3β, a component of the β-catenin degradation complex, leads to suppression of periportal gene expression and activation of pericentral gene expression in a resident liver stem cell line [19].

2.1.2. Ha-RAS/MAPK signaling

While β-catenin signaling imposes a pericentral pattern of gene expression, the periportal pattern is likely regulated by the Ha-RAS pathway. The first implications for involvement of Ha-RAS signaling in metabolic zonation were derived from the observation that mutated Ha-RAS liver tumors display a periportal pattern of gene expression [20]. Also, a portal to central gradient was found for the phosphorylated form of extracellular signal-regulated kinase (ERK), a downstream target of RAS. A discrepancy in this finding is however described: in female rats phosphorylated ERK (p-ERK) levels are higher in pericentral areas, especially during the pro-oestrous phase [21]. It may therefore be possible that the difference in zonation of p-ERK between females and males is dependent on female sex-hormone levels.

Activation of the RAS/MAPK pathway induces ERK expression in cells that do not express GS or other pericentral genes [16,20]. Furthermore, induction of the RAS/MAPK pathway by serum components also suppressed GS expression [22]. Combined, these studies indicate that Ha-RAS favors a periportal pattern of gene expression, while it abolishes a pericentral pattern.

2.1.3. HNF4α

Hepatic nuclear factor 4α (HNF4α) is a transcription factor that is highly expressed in liver, kidney, intestine and pancreas. HNF4α can bind to the promoter region of 12% of the genes expressed in the

Please cite this article in press as: B.S. Hijmans, et al., Zonation of glucose and fatty acid metabolism in the liver: Mechanism and metabolic consequences, Biochimie (2013), http://dx.doi.org/10.1016/j.biochi.2013.06.007