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Is There A Role of Vitamin A in Hepatic Glucose and Fatty Acid Metabolism?

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General Overview of VA and its Metabolism in the Liver

Vitamin A (VA, retinol) is an indispensible, lipid-derived micronutrient contributing to the general health of an individual. Retinoids are VA and its derived metabolites that have profound effects on a variety of physiological processes, such as embryogenesis and cellular differentiation [1]. More recently, retinoids have been proposed to play roles in energy homeostasis such as adaptive thermogenesis and adipogenesis [2]. The roles of retinoids in lipid and glucose metabolism have been indicated and potentially linked to the development of chronic metabolic diseases such as obesity and diabetes [3-7]. Obesity and comorbidities are the physiological consequences of a disruption in the regulation of body energy storage, which is associated with profound changes in hepatic glucose and lipid metabolism. These changes are often attributed to the expression levels of hepatic genes involved in glucose and lipid metabolism. The active metabolite of VA responsible for the regulation of gene expression is retinoic acid (RA), which exists in multiple isomeric forms. They activate two families of nuclear receptors: retinoic acid receptors (RARα, β, and γ; activated by all-trans and 9-cis RA) and retinoid X receptors (RXRα, β, and γ; activated by 9-cis RA). RAR/RXR hetero- and RXR/RXR homo-dimer bind to RA-responsive elements (RAREs) in the promoters of the RA responsive genes, and regulate their expression upon activation [1].

The liver plays an essential role in the regulation of energy homeostasis. It also serves as the principle site of postprandial uptake and storage of VA. The retinol available in hepatic tissues can be oxidized to retinal, which is further oxidized into RA [8]. Those enzymes facilitating the reversible oxidation/reduction reaction of retinol to retinal are termed dehydrogenases and exhibit properties as an alcohol dehydrogenase \ or a short-chain dehydrogenase reductase [9]. For the irreversible oxidation of retinal to RA, these enzymes are classified in the aldehyde dehydrogenase family. This complex network of enzymes consists of 17 different isoforms, all proposed to exhibit essential properties to retinoid homeostasis which are indicated through knock-out and transgenic rodent models [9]. Recently, it has been shown that retinoids regulate the expression of genes involved in glucose and lipid metabolism, which proposes a link between micronutrient actions and the development of metabolic diseases [3].

Roles of VA in the Hepatic Glucose Metabolism

For glucose utilization in hepatocytes, it is first phosphorylated into glucose 6-phosphate by hexokinase D, also known as glucokinase (GK). Insulin induces the expression levels of GK gene (Gck) in the liver. It has been shown that all-trans retinol, retinal, and RA are able to synergize with insulin to induce Gck expression via the activation of RAR/RXR in primary rat hepatocytes [10]. Furthermore, the Gck expression level is reduced in the VA deficient (VAD) rats in comparison to the VA sufficient (VAS) controls. RA treatment rapidly recovered this reduction [10].

The liver generates glucose via gluconeogenesis in response to nutrient and hormonal status. The first rate limiting enzyme for hepatic gluconeogenesis is the cytosolic form of phosphoenolpyruvate carboxykinase, whose activity is controlled by the expression of its gene (Pck1) [11]. Insulin suppresses the hepatic expression of Pck1 [12] . It has been shown that RA stimulates the Pck1 expression in hepatoma cells via two RAREs in its promoter [13]. To understand the effects of the endogenous lipophilic molecules on the expression of insulin-regulated hepatic genes, the lipophilic extracts were prepared from rats. The lipophilic extracts induced the Pck1 expression levels and attenuated insulin-mediated reduction of its expression in primary rat hepatocytes [14]. Subsequently, the active molecules in the extract were identified as retinol and retinal, and the proximal RARE in the *Pck1* promoter was found to be responsible for arbitrating retinoids effects in primary rat hepatocytes [10,15] . An increase in the hepatic VA content has been observed in diabetic patients [16] as well as streptozotocin-induced diabetic rats [7] which may contribute to the alterations in insulin-regulated gene expression. The retinoids effects on the hepatic expression of Pck1 [15] and Gck [10] demonstrate the interaction between the insulin and retinoid signaling pathways, which deserves further investigation.

Roles of VA Status and Retinoids in Hepatic FA Metabolism

The hepatic fatty acid (FA) biosynthesis is controlled by sterol regulatory element–binding protein 1c (SREBP-1c), a transcription factor that induces the expression of hepatic lipogenic genes [17] . The expression of its gene (Srebp-1c) is induced by insulin, or the activations of liver x receptor (LXR) and RXR [18]. The insulin-responsive elements in the Srebp-1c promoter have been identified as two LXR receptor elements (LXRE) and one sterol regulatory element (SRE) in its promoter [19]. Later, it was shown that RA was capable of inducing Srebp1-c in primary rat hepatocytes and the previously identified two LXREs are also RAREs [20].

A significant portion of patients with acne receiving isotretinoin (13-cis RA) treatment developed hypertriglyceridemia [21]. In addition, clinical studies have indicated that the excessive VA supplementation resulted in hepatic hypervitaminosis A, which exacerbated abnormal lipid storage in the liver [22]. Rats fed multiple

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isomeric forms of RA all displayed hypertriglyceridemia, consistent with human observations [23]. Rats on a VAD diet exhibited a lowered plasma lipid profile compared to VAS controls [24]. This may be caused by the dual existence of VA deficiency and hypoinsulinemia, which may cause the reduction of hepatic lipogenesis [25]. The activation of RXR by its specific agonist (LG100268) induced hepatic lipogenesis, which interestingly increased insulin sensitivity in obese and diabetic rats [26]. Since Srebp1-c is a critical transcription factor for lipid homeostasis [27] and RA has been shown to affect the insulin-mediated expression of Srebp-1-c [20], it is reasonable to conclude that VA status and retinoids play roles in hepatic FA homeostasis.

VA Status in Animals and Retinoids affect Insulin Secretion from Pancreatic B-Cells

Insulin controls hepatic glucose and fatty acid metabolism in response to macronutrients. Glucose metabolism causes the rise of ATP/ADP ratios and subsequently stimulates the release of insulin granules in pancreatic β-cells [28]. Glucose stimulated insulin secretion (GSIS) is impaired in VAD rats and is recovered by VA repletion [25]. Additionally, VAD rats had pancreatic β-cell dysfunction, which may be attributed to a reduction in fetal β-cell mass [29]. In isolated rat pancreatic islets, retinol either potentiated (0.1μmol/L) or inhibited (100 μmol/L) GSIS [30]. RA was capable of potentiating GSIS via induction of transglutaminase activity in INS-1 insulin secreting cells [31]. Recently, it has been shown that pancreatic β-cells produce 9-cis RA which level is elevated in islets of diet-induced obesity, ob/ob and db/db mice [32]. When mouse islets were treated with 9-cis RA, GSIS was reduced due to a reduction in GLUT2 and GK activities [32]. In addition, lipid depletion in pancreatic β-cells caused impairment of GSIS, which can be restored in the presence of FAs [33]. RA has been reported to induce Srebp-1c mRNA in INS-1 cells [20]. Taken together, VA status or retinoid levels can indirectly control hepatic glucose and FA metabolism through regulating the insulin secretion from pancreatic β-cells. If RA is produced in the islets, it becomes essential to learn the mechanism for the production of the various RA isoforms to fully understand the roles of the retinoids in pancreatic β-cell functions.

Summary and Future Perspectives

Micronutrients play essential roles in various physiological processes. Despite the obvious link between nutrition and metabolic diseases, the roles of individual micronutrients in their development have not yet been revealed. It is safe to say that VA status and retinoids affect the hepatic glucose and FA metabolism directly through the regulation of the expression of genes involved or indirectly via controlling insulin secretion. It is imperative to understand the molecular mechanisms that VA employs to regulate hepatic and glucose metabolism, the impact of VA status in the development of obesity and diabetes, as well as the physiological effects of retinoids on hormonal actions leading to metabolic diseases. This understanding may provide a novel therapeutic technique for controlling abnormal hepatic glucose and lipid metabolism, and thus improving diabetic and obese phenotypes.

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