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Editorial

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The Influence of Diabetes and Metabolic Syndrome on Liver Fatty Acid Profile: What can we Learn from Animal Models

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Whole body fatty acids can originate from three different sources: food, de novo lipogenesis and bioconversion. Fatty acids generated de novo, as well as fatty acids derived from food can be bioconverted to longer-chain fatty acids with more carbon atoms and/or double bonds, by a series of steps of desaturation and elongation, or shortened by β-oxidation steps and recycled between peroxisomes and the endoplasmatic reticulum. Regulation of these steps involves desaturases (Δ9D, Δ6D, Δ5D) and elongases (Elovl2, Elovl5 and Elovl6), as well as different metabolites (glucose), hormones (insulin) and transcriptional factors (peroxisome proliferator-activated receptors α, PPARα; sterol response element-binding protein-1c, SREBP-1c; liver X receptor, LXR; carbohydrate-regulatory element binding protein, ChREBP; MAX-like factor X, MLX) and microRNA. Nutrition (substrate availability) and competition for rate-limiting enzymes for desaturation, as well as partitioning into oxidation could substantially contribute or even override other regulatory mechanisms.

Metabolic diseases, such as diabetes, obesity or metabolic syndrome (MS), are characterized by changes in lipogenesis in different tissues. The investigation of liver lipogenesis during metabolic disorders in animal models is challenging due to the highly complex regulation of liver lipogenesis, as well as the diversity of animal species and strains used. An additional challenge is the diversity of nutritional and pharmacological interventions used to induce diabetes type 1 or 2 or MS.

In the case of diabetes mellitus type 1 (DM1), the situation is relatively simple. Today, a large choice of rodent models is available for DM1, including those spontaneously developing the disease with and without autoimmunity (NOD and Ins2Akita, respectively), drug-induced (aloxan and streptozotocin), and genetically-modified animals [1]. The investigations of aloxan and streptozotocin induced DM1 discovered decreased expression of Δ desaturases. Consequently, the most consistent changes in the fatty acid composition of different tissues in DM1 experimental rats include a decrease in palmitic acid [2-4], and a decrease in monounsaturated fatty acids (MUFA) [3,5]. Other important changes are not consistent and include a decrease in arachidonic acid (ARA), an increase in its precursors (linoleic acid, LA and dihomo-gamma-linolenic acid, DGA), and an increase in docosahexaenoic acid (DHA) [6,7]. Additional variables, such as age [7] or dietary lipids [8], could further influence fatty acid profile in DM1.

In diabetes mellitus type 2 (DM2) or MS, the fatty acid profile of the organs is much more complex. Initial studies with glucose or fructose in the diet mostly showed the opposite influence on desaturases and consequently on the liver fatty acid composition, compared to DM1. The most consistent changes are an increase in desaturases and an increase in the content of oleic acid, and a decrease in the content of LA and DHA [3,5,6,9,10]. After introduction of high fat diets in experimental models, a difference was observed between high fat and high carbohydrate diets. In rodents fed high-fat diets the content of ARA increases, while LA and DHA decreases [11]. Comparison of high fat and high carbohydrate diets reveals that a high carbohydrate diet leads to a higher increase in SFA, PUFA and MUFA content and lipogenesis, while in high fat diets more PUFA are preserved [12]. Introduction of a high-fat low-streptozotocin model introduced additional variably into the investigation of liver lipogenesis. Using that model, Yao *et al.* (2015) found decreased desaturase expression along with increased liver DHA content, which resembles the results found in DM1 [13].

Today, different rodent models are available to scientists for the investigation of lipogenesis in DM1, DM2 and MS. These models give us an insight into the changes in liver fatty acid profile during the progression of these diseases. Considering the fact that the liver is the primary site of PUFA production for extrahepatic tissues, such as the brain, differences in the liver metabolism of important fatty acids (e.g. DHA) in DM1 and DM2 or MS could have significant nutritional and clinical implications. Further investigations should focus on these differences in order to assess in which diseases and stages of diseases particular fatty acids should be supplemented.

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