Minireview

MOLECULAR METABOLISM

De novo lipogenesis in metabolic homeostasis: More friend than foe?

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ABSTRACT

Background: An acute surplus of carbohydrates, and other substrates, can be converted and safely stored as lipids in adipocytes via de novo lipogenesis (DNL). However, in obesity, a condition characterized by chronic positive energy balance, DNL in non-adipose tissues may lead to ectopic lipid accumulation leading to lipotoxicity and metabolic stress. Indeed, DNL is dynamically recruited in liver during the development of fatty liver disease, where DNL is an important source of lipids. Nonetheless, a number of evidences indicates that DNL is an inefficient road for calorie to lipid conversion and that DNL may play an important role in sustaining metabolic homeostasis.

Scope of review: In this manuscript, we discuss the role of DNL as source of lipids during obesity, the energetic efficiency of this pathway in converting extra calories to lipids, and the function of DNL as a pathway supporting metabolic homeostasis.

Major conclusion: We conclude that inhibition of DNL in obese subjects, unless coupled with a correction of the chronic positive energy balance, may further promote lipotoxicity and metabolic stress. On the contrary, strategies aimed at specifically activating DNL in adipose tissue could support metabolic homeostasis in obese subjects by a number of mechanisms, which are discussed in this manuscript.

Keywords Ectopic lipids; Glucose disposal; Thermogenesis; Lipokines; Obesity; Metabolic flexibility

1. INTRODUCTION

Metabolic homeostasis is an essential condition to sustain life, and metabolic derangements are at the origin of several debilitating diseases. Obesity, a pathological condition characterized by excessive accumulation of body lipids, is by far the most prevalent metabolic disease affecting hundreds of millions of people worldwide. The leading cause of this excessive lipid accumulation is a chronic positive energy balance combined with energy partitioning toward lipids. Lifestyle interventions are in principle ideal solutions to fight the obesity pandemics, although in practice the implementation of such measures has largely failed so far [1]. Hence, it is important to better understand the mechanisms driving excessive lipid deposition and the role of such mechanisms in impaired metabolic homeostasis. In this context, it has been proposed that lipids stored in non-adipose tissues (i.e., ectopic lipid accumulation) play a major role in the pathogenesis of obesity-related diseases [2,3]. It is also established that de-novo lipogenesis (DNL) in humans can be, under specific conditions, an important source of adipose tissue lipids and ectopically stored lipids. Indeed, DNL was shown to be an important source of intrahepatocellular lipids in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Here we review the current literature on the role of DNL in metabolic homeostasis. We conclude that although DNL significantly contributes to ectopic lipid accumulation, the specific recruitment of this pathway may in fact limit the effects of excessive calories on ectopic lipid deposition and glucose intolerance by a number of mechanisms. We also propose that reactivation of DNL in adipose tissue of obese people could be a promising strategy for the treatment of obesity-driven diseases.

2. THE DNL ROAD TO ECTOPIC LIPIDS

2.1. Contribution of DNL to fatty liver disease

Intracellular lipids can accumulate from dietary lipid influx or can be synthesized de-novo from Acetyl-CoA and Malonyl-CoA produced from the catabolism of different substrates (Figure 1A). For conditions in which lean body mass is not increasing, excess calories from positive energy balance are stored as triglycerides in white adipocytes. Triglycerides are energy dense and chemical stable compounds, and the adipocyte is a specialized cell type, which can safely store large amounts of triglycerides in a monolocular lipid droplet [4]. However, this system has a saturation limit, and excessive calories over a long period may lead to the deposition of triglycerides and other more toxic lipids in non-adipose tissues, leading to lipotoxicity and inflammation [2,3,5–7]. Hence, ectopic lipid deposition is considered a major source of metabolic stress and a major pathogenic factor in obesity-associated diseases. In humans, DNL can be an important contributor to adipose tissue and ectopic lipid accumulation [8,9], and several cell types express the enzymes implicated in this pathway. Because the hepatocyte is the non-adipose cell type displaying the highest lipogenic capacity, NAFLD is an ideal model to investigate the role of DNL in ectopic lipid deposition. The contribution of DNL to fatty acids

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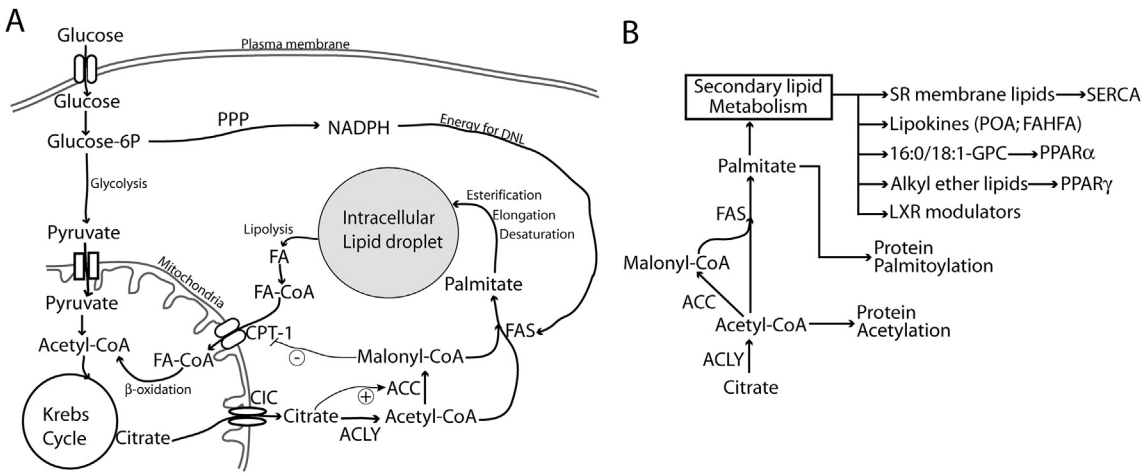

Figure 1: Energetic and biosynthetic functions of de novo lipogenesis (DNL) in the control of metabolic homeostasis. (A) DNL produces lipids by disposing of glucose and calories. Whereas lipids can be directly incorporated into intracellular stores in an energetically efficient manner, the conversion of glucose into intracellular lipids via DNL is a costly process. Glucose enters the cell via specific glucose transporters. It is converted to pyruvate via glycolysis and, in this form, enters the mitochondria where it is converted to acetyl-CoA in order to enter the Krebs cycle. In the presence of excessive glucose and calories, citrate from the Krebs cycle is exported to the cytoplasm via the citrate carrier (CIC). The latter is the first committed step of DNL. Indeed, citrate is a powerful inducer of acetyl-CoA carboxylase (ACC) activity, which produces malonyl-CoA, a major intermediate of fatty acid synthesis and an inhibitor of the fatty acid transporter CPT-1. However, it is important to consider that fatty acid synthase (FAS) consumes malonyl-CoA, limiting its accumulation and consequent inhibition of CPT-1. Because DNL and β-oxydation of fatty acids are distinct pathways, fatty acid synthesis and β-oxidation can occur simultaneously, creating futile cycles as described during brown adipose tissue activation and browning of white adipose tissue. The pentose phosphate pathway (PPP) is an important intracellular source of NADPH, which provides energy for DNL. Altogether DNL is an energetically inefficient way to form intracellular lipids and, in specific circumstances, can act as a considerable sink for calories and glucose. (B) DNL was also proposed to support the synthesis of several signaling molecules implicated in the control of metabolic homeostasis. These include specific lipids of the sarcoplasmic reticulum (SR) membrane controlling SERCA function and intracellular calcium; secreted lipids with cytokine-like activity supporting metabolic homeostasis "lipokines", such as palmitoleic acid (PAO) and branched fatty acid esters of hydroxy fatty acids (FAHFA); endogenous ligands of nuclear receptors including PPARα (16:0/18:1-GPC), PPARγ (alkyl ether lipids), and possibly LXR. DNL was also implicated in the palmitoylation and acetylation of specific proteins.

stored in the liver of patients with NAFLD has been quantified in an elegant study using multiple stable isotopes to trace the different sources of liver fat [10]. DNL contributed about 26% of fatty acids in livers of NAFLD patients, free fatty acids from adipose tissue and from the diet contributed 59% of liver lipids, and dietary triglycerides associated with chylomicrons contributed 15% of liver fat. Hence, DNL can contribute about a quarter of the liver lipids in patients with NAFLD. A more recent study from the same laboratory investigated the contribution of the different lipid sources above to liver fat of human subjects with either low or high liver lipid content but with similar adiposity [11]. The results show that DNL was the only source of lipids displaying a statistically significant increase in subjects with high liver lipid content, compared to those with lower liver lipid content but comparable adiposity [11]. From these results it can be concluded that DNL is specifically recruited during the development of fatty liver. These findings led the authors to suggest that DNL plays a causative role in the pathogenesis of NAFLD and that suppression of DNL by carbohydrate restriction may be a valuable approach for the treatment of NAFLD [11]. In support of the latter concept, it has been reported that carbohydrate restriction clears liver lipids faster than lipid restriction in NAFLD patients [12]. However, no difference in liver lipids was observed between carbohydrate-restricted or fat-restricted patients after a weight loss of about 7% of the starting body weight [12,13]. Furthermore, it is not known whether the faster clearance of hepatic lipids observed during carbohydrate restriction, compared to fat restriction, depends on differences in DNL. Indeed, it is likely that carbohydrate restriction, more than fat restriction, will lead to increased hepatic glucose production, an important caloric output from the liver, which could further promote hepatocyte negative energy balance. Additional evidence to support a role for carbohydrate and DNL in human NAFLD comes from fructose overfeeding studies. Healthy men fed a 35% caloric surplus as fructose for seven days showed significantly elevated intrahepatocellular lipids compared to control subjects not receiving the fructose caloric surplus [14]. Furthermore, extra calories from fructose synergize with extra calories from fat to promote fatty liver [14]. Importantly, it was shown that an extra 25% calories in the form of fructose fed to healthy men for six days is sufficient to cause a marked increase of fractional DNL [15]. Taken together, these studies demonstrate that DNL is a significant source of intrahepatocellular lipid in fatty liver disease, and many have proposed that DNL is a major pathway in the pathogenesis of NAFLD. However, It is important to note that these studies are correlative and do not establish whether the specific recruitment of DNL in people with high-liver lipids is a promoting or a protecting factor in the progression of NAFLD.

2.2. DNL is the most "energetically costly" road for extra calories to ectopic lipid deposition

The studies described above demonstrate that DNL is specifically recruited during the development of NAFLD in humans, and that it significantly contributes to ectopic lipid accumulation. However, it could be argued that the specific recruitment of DNL in people accumulating liver lipids may offer some protection from NAFLD (and ectopic lipid deposition) progression, by minimizing the conversion efficiency of extra calories from positive energy balance to lipids. Indeed, among all the possible sources of ectopic lipid deposition DNL is by far the one that costs the most calories (Figure 1A). Based on stoichiometry, the synthesis of one molecule of palmitate from acetyl-CoA costs 7 molecules of ATP and requires the conversion of 14 high-energy NADPH molecules to $NADP^+$. Different studies evaluating feeding efficiency in pigs consistently indicate an energetic cost for storing fat via DNL of 20%—25% of metabolizable energy intake

