METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 1049–1061

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease☆

Manoela Mota, Bubu A. Banini, Sophie C. Cazanave, Arun J. Sanyal**

Department of Internal Medicine, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

ARTICLE INFO

Article history:
Received 15 September 2015
Accepted 23 February 2016

Keywords:
NASH
CHOP
JNK
Lipid
Oxidative stress

ABSTRACT

The exposure of hepatocytes to high concentrations of lipids and carbohydrates and the ensuing hepatocellular injury are termed lipotoxicity and glucotoxicity, respectively. A common denominator is metabolic derangement, especially in regards to intracellular energy homeostasis, which is brought on by glucose intolerance and insulin resistance in tissues. In this review, we highlight the lipids and carbohydrates that provoke hepatocyte injury and the mechanisms involved in lipotoxicity and glucotoxicity, including endoplasmic reticulum stress, oxidative stress and mitochondrial impairment. Through upregulation of proteins involved in various pathways including PKR-like ER kinase (PERK), CCAAT/enhancer-binding homologous protein (CHOP), c-Jun NH2-terminal kinase-1 (JNK), Bcl-2 interacting mediator (BIM), p53 upregulated modulator of apoptosis (PUMA), and eventually caspases, hepatocytes in lipotoxic states ultimately undergo apoptosis. The protective role of certain lipids and possible targets for pharmacological therapy are explored. Finally, we discuss the role of high fructose and glucose diets in contributing to organelle impairment and poor glucose transport mechanisms, which perpetuate hyperglycemia and hyperlipidemia by shunting of excess carbohydrates into lipogenesis.

© 2016 Elsevier Inc. All rights reserved.

Abbreviations: ALA, alpha-linolenic; ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; ATF, activating transcription factor; AP-1, activator protein-1; BAs, bile acids; BH3, Bcl-2 homology 3; BIM, Bcl-2 interacting mediator; CHOP, CCAAT/enhancer-binding homologous protein; ChREBP, carbohydrate responsive element binding protein; CYP2E1, cytochrome P450 2E1; DAG, diacylglycerides; DR, death receptor; ER, endoplasmic reticulum; ERAD, ER-assisted degradation; FAS, fatty acid synthase; FAT, fatty acid translocase;; FATP, fatty acid transport protein; FC, free cholesterol; FFAs, free fatty acids; FXR, farnesoid X receptor; GLUT2, glucose transporter 2; HMGB1, high mobility group box 1 protein; HMGCo-A, hydroxymethylglutaryl-Co-A; HSCs, hepatic stellate cells; GSK3, glycogen synthase kinase 3; IRE1α, inositol-requiring enzyme-1α; IRS – 1, insulin receptor substrate-1; JNK, c-Jun. NH2-terminal kinase; Keap1, Kelch-like ECH-associated protein; LPC, lysophosphatidyl Choline; LDL, low density lipoprotein; MUFA, monounsaturated fatty acid; NF-kB, nuclear factor-kappaB; MCD, methionine choline deficient; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; N-SMase, neutral sphingomyelinase; PA, palmitate; PERK, PKR-like ER kinase; PLA2, phospholipase A2; PO, palmitoleate; PTA, p53 inhibitor pifithrin-alpha; PTP1B, protein-tyrosine phosphatase 1B; PUFA, polyunsaturated fatty acid; PUMA, p53 upregulated modulator of apoptosis; OA, oleate; ROS, reactive oxygen species; SA, stearate; SCD-1, stearoyl-CoA desaturase-1; SOCS, suppressor of cytokine signaling; SREBP-2, sterol regulatory-element binding protein 2; StAR, steroidogenic acute regulatory protein; STAT5, signal transducer and activator of transcription 5; SIRT1, JNK-1/p-53/miR 34a sirtuin 1; T2DM, type 2 diabetes mellitus; TAG, triacylglycerides; TG, triglycerides; TGF beta, transforming growth factor beta; TLR4, toll like receptor 4; TNF, tumor necrosis factor; TRAIL, TNFα-related apoptosis-inducing ligand; UFA, unsaturated fatty acid; UPR, unfolded protein response; VDAC, voltage dependent anion channel; VLDL, very low-density lipoprotein particles.

☆ This work was supported, in whole or in part, by NIH Grants R01 DK081450 and T32 07,150 (AJS).

* *Corresponding authors at:* Virginia Commonwealth University Medical Center, 1220 E. Broad Street, Richmond, VA, 23219. Tel.: +1 804 828 6314; fax: +1 804 828 5348.

E-mail addresses: manoela.mota@vcuhealth.org (M. Mota), asanyal@mcvh-vcu.edu (A.J. Sanyal).

http://dx.doi.org/10.1016/j.metabol.2016.02.014
0026-0495/© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Lipotoxicity refers to the harmful effects of high concentrations of lipids and lipid derivatives to cells. Hyper-alimentation with diets rich in lipids and carbohydrates is associated with the development of one of two clinical-histopathological phenotypes of liver fatty accumulation: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Clinically, NASH is associated with obesity, metabolic syndrome, insulin resistance and dyslipidemia. Histological features of NASH include hepatic macrovesicular lipid accumulation, chronic inflammation, hepatocyte ballooning, interstitial fibrosis and necro-apoptosis [1]. The mechanisms involved in lipotoxicity include endoplasmic reticulum (ER) stress, c-Jun. NH2-terminal kinase (JNK)-induced toxicity and Bcl-2 Homology 3 (BH3)-only protein-induced mitochondrial and lysosomal dysfunction [2–6].

Glucotoxicity refers to the toxic effects of hyperglycemia and excess carbohydrate intake on cells and tissues. Glucotoxicity is intrinsically linked to insulin resistance, which facilitates hyperglycemia. Excess carbohydrates can be converted into free fatty acids (FFA) and triglycerides (TG), and subsequently hepatotoxic lipids such as lysophosphatidyl choline (LPC), ceramides, free cholesterol and bile acids (BA) may accumulate. High carbohydrate diets activate several lipogenic enzymes such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) or stearoyl-CoA desaturase-1 (SCD-1), inducing lipogenesis and steatosis. Recent data indicate that glucotoxicity can be injurious to liver cells by inducing ER stress and hepatocyte cell death. In this review, we explore some of the organelle dysfunction and molecular pathways activated by excessive consumption of carbohydrates and lipids fats, leading to hepatotoxicity.

2. Hepatotoxic Lipids

Several members of the lipid family have been shown to mediate hepatic lipotoxicity. These include free fatty acids (FFA), triglycerides (TG), lysophosphatidyl choline (LPC) and ceramides, free cholesterol (FC), and bile acids (BA).

2.1. Free Fatty Acid and Triglycerides

2.1.1. Free Fatty Acid

FFA with double bonds are referred to as “unsaturated” while those without double bonds are called “saturated”. Palmitate (PA; C16:0), the most common saturated FFA found in animals and plants, is ingested as part of the diet or can be produced by *de novo* lipid synthesis from excess carbohydrate consumption. Oleate (OA; C18:1), an unsaturated FFA, is commonly present in the Western diet. Several in vitro studies have demonstrated the toxic effects of unsaturated FFA such as PA or stearate on liver cells by inducing apoptosis (vide infra).

Hepatocytes exposed to high circulating FFAs increase uptake in order to clear the FFAs in the blood. FFAs entering the liver are mostly derived from lipolysis of adipose tissue triglyceride in the fasting state (constituting 60% of liver FFAs in NAFLD subjects), *de novo* lipogenesis (26%) and from hydrolysis of dietary triglycerides (15%) [1]. Although the precise mechanisms regulating increased hepatic FFA uptake are unclear, it seems to involve a tetrameric plasma membrane protein complex that comprises plasma membrane fatty acid-binding protein (FABP), caveolin-1, fatty acid translocase (FAT/CD36) and calcium independent membrane phospholipase A2 (iPLA2β) [2]. FAT/CD36-mediated incorporation of circulating FFA into hepatocyte vacuoles causes these hepatocytes to resemble adipocytes [3]. In the liver of mice and humans with insulin resistance, steatosis and NASH, CD36 is overexpressed via transcriptional regulation by the transcription factor PPARγ. Hepatocytes exposed to PA and OA display increased expression of FAT/CD36 and fatty acid transport protein (FATP)-2 leading to accumulation of diacylglycerol (DAG) or ceramides in the cells [4].

2.1.2. Triglycerides

Triglycerides are composed of a glycerol molecule with three free fatty acids and represent a form of energy storage. Studies performed in humans have shown that accumulation in excess of hepatic TG is mainly the result of increased delivery of adipose-derived FFAs to the liver and enhanced *de novo* lipid synthesis in the liver [1]. In contrast hepatic steatosis is only modestly affected by lipid disposal via β-oxidation or very low density lipoproteins (VLDL) export [5]or directly by increased dietary lipids [1]. Also, consumption of large amounts of carbohydrates can contribute to hepatic steatosis by facilitating lipogenesis and lipid storage as TG. Indeed, rat pups fed a 60% fructose rich diet showed altered lipid profile with increased TG, cholesterol, VLDL and low density lipoproteins (LDL) which was reversed when fed a standard diet [6].

2.1.3. Unlike TG, Saturated FFA are Toxic to Hepatocytes

Treatment of hepatocyte cell lines with OA versus PA showed that while OA generated more hepatocyte steatosis, PA was responsible for higher rates of apoptosis. PA was associated with PPARα activation and impairment of insulin signaling. In addition, PA triggered cell death via JNK-dependent mitochondrial dysfunction and caspase activation [7] (Table 1). OA, on the other hand, generated higher formation of TG [7]. It appears that TG represent a defense system against the pro-apoptotic effects of large loads of FFA in cells [7,8]. Yamaguchi et al. confirmed the protective role of TG by showing that inhibition of dyacylglycerol acetyltransferase 2 (DAGT2), the final catalyst in hepatocyte TG synthesis, generated increased necro-inflammation, increased peroxidation and oxidative stress [9] (Table 1).

2.2. Lysophosphatidyl Choline

LPC is a class of lipids derived from phosphatidylcholine by partial hydrolysis mediated by phospholipase A2 (PLA2). LPCs have been implicated in phagocyte chemotaxis and are released secondary to activation of calcium independent PLA2 by caspase 3 when cells undergo apoptosis [10]. LPC levels are increased in the liver or plasma of both human NASH patients [11] and animal models of NASH [12,13]. Furthermore, treatment of liver cells with PA results in increased intracellular LPC concentration and cell toxicity [14]. LPC appears to be a key instigator of lipotoxicity by triggering an ER stress and inducing apoptotic pathways downstream of JNK or glycogen synthase kinase 3 (GSK3)

Download English Version:

https://daneshyari.com/en/article/5902984

Download Persian Version:

https://daneshyari.com/article/5902984

Daneshyari.com