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Review

Lipotoxicity in the heart

Adam R. Wende, E. Dale Abel *

Program in Molecular Medicine and Division of Endocrinology, Metabolism, and Diabetes; University of Utah, School of Medicine, Salt Lake City, UT 84112, USA

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ABSTRACT

Obesity and insulin resistance are associated with ectopic lipid deposition in multiple tissues, including the heart. Excess lipid may be stored as triglycerides, but are also shunted into non-oxidative pathways that disrupt normal cellular signaling leading to organ dysfunction and in some cases apoptosis, a process termed lipotoxicity. Various pathophysiological mechanisms have been proposed to lead to lipotoxic tissue injury, which might vary by cell type. Specific mechanisms by which lipotoxicity alter cardiac structure and function are incompletely understood, but are beginning to be elucidated. This review will focus on mechanisms that have been proposed to lead to lipotoxic injury in the heart and will review the state of knowledge regarding potential causes and correlates of increased myocardial lipid content in animal models and humans. We will seek to highlight those areas where additional research is warranted.

1. Introduction

It has been suggested that the dramatic increase in the prevalence of obesity and cardiovascular disease worldwide, termed the metabolic syndrome pandemic [1], may result in a decline in the life expectancy of the current generation [2,3]. Obesity also increases the susceptibility to diabetes, which not only increases atherosclerotic heart disease but also increases the risk of developing heart failure [4]. The metabolic syndrome, which is in essence caused by an imbalance between nutrient uptake and energy expenditure, is associated with ectopic deposition of lipid (steatosis) in non-adipose tissue such as pancreas, kidneys, blood vessels, liver, skeletal muscle, and heart. Although these organs can initially store some of this surplus as triglycerides, excess lipids are eventually shunted into non-oxidative pathways resulting in the accumulation of toxic lipid species which alter cellular signaling [5], promote mitochondrial dysfunction [6], and increase apoptosis [7]. However, the order, progression and role of each of these cellular changes in the ensuing lipotoxicity have not been clearly defined, depend on lipid composition and differ between cell types [8].

Hypertriglyceridemia and increased circulating free fatty acids (FFA) are correlated with lipotoxicity in many tissues such as the liver and β-cell but not necessarily in the heart [9,10]. In addition to increased circulating lipids, co-existent hyperglycemia and increased inflammatory cytokines may accelerate progression of cellular dysfunction and death, leading to the concept of glucolipotoxicity [11,12]. Thus multiple mechanisms may lead to cardiac dysfunction in obesity and diabetes and these have been recently exhaustively reviewed [4,12–14] and will not be covered in detail here. Instead we will focus specifically on mechanisms by which increased cellular lipid impairs cardiomyocyte structure and function.

Obesity affects cardiac structure and function in various ways [4,14,15]. Cardiac triglyceride positively correlates with both body mass index and left-ventricular (LV) mass in subjects with impaired glucose tolerance or obesity and inversely with systolic function [10,16]. Obesity has been linked to both structural and functional changes of the heart including LV hypertrophy (LVH), contractile dysfunction, apoptosis, fibrosis, lipid accumulation, and metabolic substrate switching and this topic has also been recently reviewed [4,15].

Disturbances in various cellular pathways such as endoplasmic reticulum (ER) stress [17] and mitochondrial dysfunction [18], both of which may increase apoptosis have been implicated in lipid-induced cardiac dysfunction. Multiple molecular mediators have been proposed to promote these lipotoxic effects, such as reactive oxygen species (ROS) [19–26], nitric oxide (NO) [27–29], ceramide [30–33], phosphatidylinositol-3-kinase [34,35], ligands of PPAR nuclear receptors [36–38], leptin [39–41], and other adipokines [25,42]. Evidence for these mechanisms will be reviewed.

2. Lipid accumulation and cardiac dysfunction

This section will review data obtained in cell culture, animal and human studies that link excess lipid delivery and accumulation to cellular apoptosis, contractile and metabolic dysfunction. Cell culture experiments have defined potential mechanisms for lipid-induced cell death [43]. Studies in animal models of obesity have demonstrated triglyceride accumulation in the heart and correlated these changes with potential mechanisms such as mitochondrial dysfunction or

* Corresponding author. Division of Endocrinology, Metabolism and Diabetes and Program in Molecular Medicine 15 N 2030 E., Bldg. # 533, Rm. 3110B Salt Lake City, Utah 84112, USA. Tel.: +1 801 585 0727; fax: +1 801 585 0701.
E-mail address: dale.abel@hmbg.utah.edu (E.D. Abel).

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apoptosis [30]. Recently, the ability to assess lipid content in the human heart has been enhanced by use of ^{1}H-NMR, allowing for the measurement of triglyceride in the hearts of healthy, obese, and diabetic subjects [10,16]. By examining lipid accumulation in these different contexts and correlating these measures with contractile function, we now have obtained some insight into the relationship between lipid accumulation and cardiac function. These studies also highlight the dynamic nature and complex molecular interplay between lipid metabolites and normal cellular function (Figs. 1 and 2).

2.1. Mechanisms and consequences of lipotoxicity: insights from cell culture experiments

It has long been known that exposure to saturated fatty acid (SFA) but not to unsaturated fatty acid (UFA) precipitates apoptosis in cell culture [43]. These early studies in fibroblasts provided evidence that lipid accumulation in the ER may lead to the toxic effects of the SFA, and that UFA leads to an increase in cytoplasmic lipid droplets but with maintenance of cell viability. In response to a number of stimuli associated with obesity and increased lipid delivery, there is increased protein flux through the ER. Initially, the influx of unfolded proteins is regulated by increased expression of chaperone proteins, referred to as the unfolded protein response (UPR). When there is a mismatch between the UPR and protein translation, ER stress ensues and may ultimately lead to cell death [44]. ER stress has been suggested as a potential mechanism linking obesity and the development of diabetes by increasing β-cell dysfunction and apoptosis, and has recently been reviewed in detail [45]. When treated with FFA, β-cells in culture exhibit increased levels of known ER stress response proteins in a cytokine-independent manner, suggesting that lipids play a direct role in initiating the ER stress response [46]. Additionally, high-fat diet feeding was shown to increase ER stress in liver and adipose, but not muscle [47]. Though the specific mechanism(s) by which obesity leads to ER stress and ultimately cell death remains undefined, ER stress enhances calcium release and signaling to the mitochondria, altering function of the proapoptotic BCL-2 family members, BAX and BAK, resulting in increased apoptosis [48]. The molecular pathways linking ER dysfunction and mitochondria to the ensuing cell death has recently been reviewed [49]. Studies to define the molecular mechanism of lipid-induced cell death in β-cells, found that apoptosis was enhanced when mitochondrial lipid uptake was inhibited by decreasing carnitine palmitoyltransferase 1 (CPT1) activity [50]. Studies by Paumen et al. also found that *de novo* ceramide synthesis, resulting from increased cytoplasmic FA accumulation, enhances rates of apoptosis. A similar role for ceramide was also found in skeletal muscle cell culture [31]. However, studies in Chinese hamster ovary (CHO) cells suggest that, unlike in β-cells and skeletal muscle cells, a ceramide-independent mechanism involving increased ROS, may be involved [20]. These observations in various cells and tissues raise the possibility that consequences of lipotoxicity in the heart may differ in myocytes [51–53] and non-myocyte cells [11].

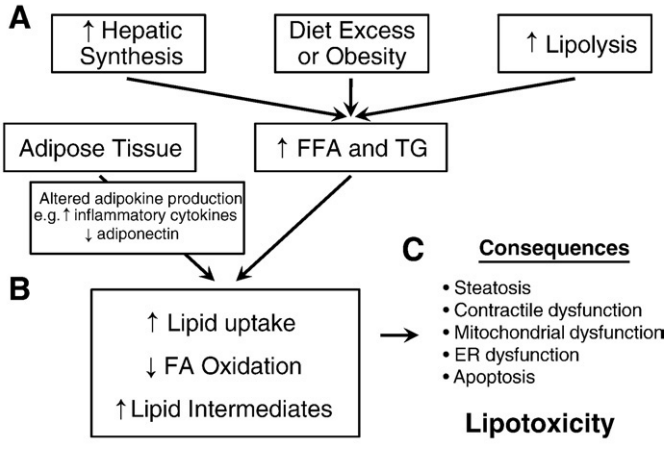

Fig. 1. Pathophysiological mechanisms leading to cardiac lipotoxicity. (A) Increased dietary fat intake, hepatic lipogenesis, and lipolysis lead to increased levels of circulating free fatty acids (FFA) and triglycerides (TG). Obesity and insulin resistance also alter adipokine signaling. (B) Changes in circulating FFA and signaling molecules lead to increased FA uptake, decreased FA oxidation, and increased synthesis of toxic lipid intermediates within the heart. (C) These molecular changes ultimately contribute to cardiac steatosis, contractile dysfunction, mitochondrial dysfunction, endoplasmic reticulum (ER) dysfunction and apoptosis.

Studies examining the role of SFA versus UFA in primary cardiac myocytes found that C16:1 (palmitoleate) or cis-C18:1 (oleate) FA treatment did not alter cell viability, while 24 h of treatment with C16:0 (palmitate) or C18:0 (stearate) precipitated apoptosis as evidenced by DNA-laddering [52]. Similar to studies with β-cells, treatment of primary adult cardiac myocytes with excess SFA leads to ceramide accumulation and cell death [51]. Dyntar et al. further found that increased ceramide levels mediated apoptosis through a mitochondrial-dependent pathway of cytochrome *c* release [51]. Direct application of ceramide or increased ceramide synthesis by cytokine-mediated activation of sphingolipid metabolism can induce apoptosis in cardiac myocytes [53] and cytochrome *c* release from mitochondria [54], supporting a mitochondria-dependent role for ceramide-induced apoptosis.

Mitochondrial dysfunction, ceramide synthesis and apoptosis are not completely separable effects. Moreover, the progression of this pathway has been called into question because careful time course analyses following palmitate treatment suggest that in primary neonatal cardiac myocytes cytochrome *c* release and mitochondrial dysfunction precede ceramide accumulation [55]. Although ceramide treatment is sufficient to induce apoptosis, additional studies of immortalized cardiac cells (H9c2) treated with palmitate found that increased cellular ROS accumulation and ER stress precede apoptosis [17,19], however the contribution of ROS versus ceramide and the source of the ROS was not determined. These *in vitro* studies also provide evidence for a mechanism of rapid incorporation of excess lipid into the rough ER membrane, ultimately compromising the structure and integrity of the ER, further enhancing ER stress. These observations support a mechanism of altered membrane composition as a proximal step in the pathogenesis of lipotoxicity [17]. Mitochondria are the primary source of cellular ROS production [6]. When mitochondrial dysfunction was induced by reducing CPT1 activity, the availability of palmitoyl-CoA for ceramide synthesis was increased [50]. Thus a primary defect in mitochondrial function could precipitate ceramide accumulation. For this reason it is difficult to dissect if mitochondrial dysfunction precedes or results from ER stress and/or ceramide accumulation. Additional studies will be required to clarify this issue.

It has recently been shown that circulating factors, such as adipokines may elicit cardiac-specific effects. Adiponectin and leptin are adipose-derived signaling molecules that are important regulators of cardiac energy metabolism. Adiponectin treatment is sufficient to increase fatty acid oxidation in the intact neonatal heart [56] and in cardiomyocytes in cell culture [57]. A potential cardiac-specific role for adiponectin is further supported by the finding that adiponectin accumulates in myocardial tissue following ischemic injury [58]. Shibata et al. concluded that this increase results from leakage from the vascular compartment and increased protein stability as opposed to increased local expression. This accumulation may play a cardioprotective role via inhibition of inducible nitric oxide synthase (iNOS) and NADPH-oxidase-expression, leading to decreased oxidative stress [59]. Low levels of plasma adiponectin in diabetics [60], patients with coronary artery disease [61], and in patients following myocardial infarction [62] correlate with increased cardiovascular risk. Obesity in both animals and humans is associated with hypoadiponectinemia [63]. Together these findings suggest that a