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Lipotoxicity in the Heart

Adam R. Wende and **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

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 alters 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 the 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,

*Address correspondence to: E. Dale Abel, MD, PhD, Division of Endocrinology, Metabolism and Diabetes and Program in Molecular Medicine, 15 N 2030 E., Bldg # 533, Rm. 3110B Salt Lake City, Utah 84112, Phone: (801) 585-0727 Fax: (801) 585-0701, dale.abel@hmbg.utah.edu.

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 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 (Figure 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].

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 suggests 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 component of the adverse outcomes of obesity on cardiac function may result from decreased adiponectin signaling.

In contrast, obesity results in hyperleptinemia [64]. In addition to the known roles of leptin on satiety via its actions on the central nervous system, leptin has peripheral actions to increase fatty acid oxidation in adipose, liver [65], skeletal muscle [66], and heart [67]. It has recently been suggested that the leptin resistance that develops in obesity is specific for the metabolic actions of leptin [68]. Isolated skeletal muscle from obese subjects has a blunted response to leptin-dependent fatty acid oxidation [69]. Leptin-mediated hypertrophy in cultured neonatal cardiomyocytes is mediated by an endothelin-1 mediated increase in ROS [70]. By contrast treatment of cultured cardiomyocytes protects cells from H_2O_2-mediated apoptosis [71]. Thus leptin may mediate complex interactions between cellular redox state and cellular hypertrophy and apoptosis. Whether leptin action in the heart serves to modulate substrate utilization, or oxidative stress in the heart in obesity remains to be clarified and requires further study. Nevertheless, these findings support the notion that some of the cardiac changes in response to lipid excess could be indirectly regulated by signals that emanate from adipose tissue.

These *in vitro* studies provide evidence that excess lipid delivery can lead to cell death and although the exact mechanism has not been worked out, they provide a strong rationale for studies in animal models that seek to elucidate mechanisms and consequences of myocardial lipid accumulation *in vivo.*

2.2. Cardiac lipid accumulation in rodent models of obesity and diabetes

Short-term lipid-infusion enhances myocardial lipid accumulation and depresses cardiac function [72]. The role of nutrient excess and tissue lipid accumulation has been studied extensively *in vivo* in response to high fat diet (HFD) feeding. Multiple aspects of these dietary studies must be taken into consideration such as duration of the dietary intervention, the carbohydrate content and lipid saturation, if the diets are isocaloric or hypercaloric and the animal species studied. These variables mediate disparate effects on the development of obesity and their related comorbidities. For example, 2 wk of HFD feeding of C57BL/J6 mice alters cardiac metabolism by increasing fatty acid oxidation independently of changes in the expression of gene targets of the transcriptional regulator peroxisome proliferator activated receptor-α (PPARα) [73]. This metabolic switch precedes contractile dysfunction which does not develop until after 20 wk of HFD feeding [74]. In contrast, rats fed HFD for 7–8 wk, exhibit mild LVH, triglyceride accumulation, and contractile dysfunction associated with reduced phosphorylation of phospholamban [75] and increased membrane localization of CD36, which was postulated to increase myocardial lipid uptake [76]. These differences in the time to the development of contractile dysfunction in mouse and rat studies likely reflect genetic differences in myocardial susceptibility to lipotoxicity. The caloric content of HFD feeding may also lead to divergent outcomes in response to lipid excess. Specifically, isocaloric HFD attenuates development of diabetes compared to ad libitum HFD feeding, despite an increase in percent body fat compared to animals on a low-fat diet (LFD) [77].

Dietary lipid composition (e.g. saturated versus unsaturated or long-chain versus medium and short chain) also influences the development of lipotoxicity [11,78]. A number of studies have tested the hypothesis that mono- or polyunsaturated FA may play a protective role in lipotoxicity [79–81]. C57BL/J6 mice fed diets containing fish oil derived ω-3 FA versus soy oil-based diets had lower plasma triglyceride [79], although cardiac function and tissue triglyceride content were not reported. Studies specifically examining the role of diets rich in polyunsaturated FA (PUFA) in the hearts of rats found that a diet high in fish oil ω-3 FA prevented cardiac remodeling and dysfunction following aortic banding-induced pressure overload [80]. Additionally, in mice with pathological cardiac hypertrophy and lipid accumulation resulting from systemic carnitine deficiency, fish oil containing diets reversed

LV dysfunction through a proposed mechanism of altered diacylglycerol (DAG) composition and protein kinase c (PKC) redistribution [82]. However, diets rich in ω-6 PUFA, fed to diabetic rats resulted in increased cardiac necrosis [83]. Additional studies are needed to clarify the mechanism for the differences between ω-3 and ω-6 FAs in modulating cardiac remodeling.

Not all HFDs lead to cardiac dysfunction. This seems to be particularly true when isocaloric HFDs are used, which do not precipitate insulin resistance or hyperglycemia. It has also been suggested that certain molecular changes that occur in response to lipid overload may be deleterious under non-stressed conditions but could be protective in the face of additional pathological insults. In a growing number of studies, high-fat feeding has been shown to attenuate some of the defects associated with pressure-overload and ischemic injury. In hypertensive rats fed an isocaloric HFD compared to a LFD, there was reduced LVH and improved contractile function [84,85]. Additionally, isocaloric HFD feeding for 8 wk following myocardial infarction (MI)-induced heart failure resulted in increased mitochondrial respiration, despite elevated ceramide levels and modest attenuation of contractile dysfunction [86]. Isocaloric HFD feeding for 16 wk post-MI increased myocardial tissue triglyceride accumulation, but did not alter mitochondrial function and increased cardiac function as assessed by fractional shortening. Interestingly, sham-operated animals exhibited decreased mitochondrial function in response to HFD [87]. Epidemiological studies in humans have also suggested the existence of an obesity paradox (described below), but whether or not similar mechanisms account for the potential beneficial effects of high-fat feeding observed in the animal models described above is currently not known.

Rodents with mutations that impair leptin signaling have been extensively studied and have shed important insights into potential mechanisms and consequences of myocardial lipotoxicity. *Db/db* mice harbor a mutation in the long form of the leptin receptor. In the C57BL6/KsJ background *db/db* mice develop diabetes by 5 wk of age [18]. *Ob/ob* mice lack the leptin gene, and on the C57BL/6J background they develop diabetes by ~10–15 wk of age [88]. *Db/db* mice on the C57BL/KsJ background develop a 2–3 fold increase in myocardial triglyceride accumulation, which is associated with LV contractile dysfunction [89]. Interestingly, myocardial steatosis and increased rates of FA oxidation could be reversed by treatment of mice with a PPARα ligand that normalized serum glucose and lipid concentrations. However, LV contractile dysfunction was not improved. In contrast, perinatal expression of the glucose transporter GLUT4 rescued contractile dysfunction and lowered the increased rates of FA oxidation in *db/db* mice [90,91]. It is likely that the inability of PPARα agonist treatment to normalize cardiac function might reflect cellular consequences of lipotoxicity or diabetes, which were not reversible with short-term normalization of systemic metabolism, whereas transgenic GLUT4 upregulation might have prevented cardiac dysfunction because it occurred prior to the onset of obesity and diabetes. The *ob/ob* mouse model also shows increased myocardial triglyceride content and diastolic dysfunction that is evident as early as 10 wk of age [92]. In a study directly comparing the development of cardiac dysfunction in these two mouse models it was found that metabolic dysfunction and myocardial triglyceride accumulation precedes the onset of contractile dysfunction and hyperglycemia [18]. Taken together, these studies suggest that metabolic dysfunction may precipitate cardiac dysfunction.

Zucker rats have been an extensively studied model of obesity and cardiac lipotoxicity [30]. The Zucker fatty rat (*fa/fa*) [93–95] has a mutation in the leptin receptor and impaired leptin signaling leads to obesity. In Zucker diabetic fatty rats (ZDF) a defect in β-cells leads to early development of severe diabetes [96]. Because obesity precedes diabetes by variable intervals in these rats, comparisons of these two rat strains have identified cardiac changes that can be attributed to obesity in the presence or absence of diabetes [30,97–99]. ZDF rats have increased myocardial triglycerides, increased ceramide levels, increased iNOS expression, increased apoptosis, decreased contractile function and decreased PPARα expression [30]. Studies

examining non-diabetic *fa/fa* rats also show higher cardiac triglyceride content compared to lean controls. PPARα expression has been reported to increase or be unchanged in ZDF rats or *fa/fa* rats [97–99]. However, expression of PPARα targets uniformly increased, implying increased activation by FA ligands. Of interest, many of the transcriptional changes seen in the ZDF rat heart, including increased expression of the β-oxidation genes, MCAD and mCPT1, parallel those found in human failing hearts with intramyocardial lipid accumulation versus failing hearts with no lipid accumulation [98]. Additionally, in response to fasting, obese *fa/fa* rats show an inability to increase oxidation of exogenous fatty acids and have reduced cardiac function [99]. Oxidation of endogenous FAs was not determined in these experiments. Thus studies in these models provided evidence for a close relationship between cardiac steatosis and cardiac dysfunction in obesity and diabetes.

2.3. Mitochondrial dysfunction and lipotoxicity

Obesity is associated with changes in mitochondrial number and morphology. Despite the observed increases in mitochondrial number in *ob/ob* and *db/db* mice [6], recent evidence has suggested that these two models exhibit decreased mitochondrial function [100,101]. The increase in mitochondrial number occurred without a concomitant increase in the expression of nuclear-encoded genes that encode oxidative phosphorylation subunits. These mitochondria showed reduced oxidative capacity for glucose and although fatty acid utilization was increased, ATP generation was reduced suggesting that the mitochondria were uncoupled. Measurement of reactive oxygen species in *db/db* mice revealed increases in ROS which was proposed to lead to activation of uncoupling proteins as no increase in uncoupling protein 3 (UCP3) expression was observed [101]. Although changes in substrate utilization occur early in course of obesity in these models [18], mitochondrial dysfunction might represent a later change. This was recently substantiated in a study that examined mice following short-term HFD feeding [73]. Wright et al. found that decreased glucose utilization and increased FA utilization occurred following as little as 2 wk of HFD feeding and these metabolic changes preceded impaired insulin signaling, changes in PPAR gene expression, mitochondrial uncoupling, ROS production or myocardial triglyceride accumulation. Thus altered myocardial substrate utilization represents the earliest change that develops in response to an increase in caloric intake and precedes mitochondrial and contractile dysfunction and cardiac steatosis.

2.4. Myocardial lipid accumulation in humans with obesity and diabetes

Correlations between myocardial lipid accumulation and cardiac dysfunction have been noted in humans for >150 yr [102]. However, only recently has there been renewed interest in the link between lipid accumulation and cardiac dysfunction [15]. Studies of lipid content and substrate utilization, which have long been conducted in rodent models of obesity, are now being extended to humans. Indeed intramyocardial lipid accumulation in the failing heart shares many similarities with that seen in the lipotoxic rat heart [16,98]. When comparing healthy lean individuals to those with moderate obesity (body mass index (BMI), 28–33 kg/m^2), an increase in triglyceride accumulation with increasing body mass appears to precede LVH [103]. To begin to evaluate the relationship between cardiac steatosis and cardiac function, McGavock et al. compared lean normoglycemic individuals, individuals with obesity, impaired glucose tolerance and type 2 diabetes [10]. They found that myocardial lipid accumulation was increased in all groups (obese, IGT and diabetic), preceded the development of diabetes, LVH and systolic dysfunction, but was associated with diastolic dysfunction [104].

The myocardial triglyceride pool is highly dynamic and can increase 3-fold following a 48 h fast in healthy individuals [105], increase 4-fold following a 3 d fast [106], or 55%-2-fold following 3 d of caloric restriction in healthy individuals [106,107]. However, in healthy individuals no increase in cardiac lipid accumulation was seen following a single high fat meal, despite a 2-fold increase in serum triglyceride content [105] or following 3 d of a high fat/high

energy diet [108]. In some of these short-term studies triglyceride accumulation was associated with diastolic dysfunction [106,107]. Thus in lean subjects fasting or caloric restriction increases cardiac triglyceride, whereas short-term lipid excess does not. In individuals with type 2 diabetes, 3 d of calorie restriction also increased myocardial triglyceride and decreased LV diastolic function [109]. However, after 16 wk of calorie restriction, myocardial triglyceride levels fell and LV diastolic function improved in diabetic subjects in parallel with normalization of glucose tolerance [110]. In contrast, treatment of relatively lean diabetics with metformin and the thiazolidinedione, pioglitazone, improved cardiac function without clearly changing cardiac metabolism or triglyceride content [111]. Taken together, these studies illustrate that the myocardial triglyceride pool in humans is dynamic and can clearly be manipulated by dietary intervention, but do not prove that triglyceride accumulation per se directly influences cardiac function, but might be a biomarker for additional underlying defects.

Obesity has not been linked to increased mortality in all cases. In fact, a number of reports have described a survival benefit for overweight patients, termed the “obesity paradox” (reviewed in [4,112]). Specifically, in studies examining survival rates in patients post-MI, higher BMI was associated with greater survival [113] and smaller infarct size [114]. Additionally, in hypertensive patients, overweight individuals had lower mortality, stroke risk, and cardiovascular events compared with lean patients [115–117]. These findings bear similarity with rodent studies showing that high-fat diet feeding is protective post-MI or in models of hypertension [84–87]. It is important to note that in some of these studies, both underweight and the most obese individuals had increased mortality [116] while in others the increased mortality in the underweight group was more closely linked to lifestyle (such as alcohol consumption and smoking) than BMI [117]. In either case these reports suggest that there might be some attribute to mild obesity (or high-fat feeding in rodents) that may confer a protective effect against adverse cardiovascular outcomes once they occur. It is important to emphasize though that modest degrees of obesity will increase the risk for developing cardiovascular disease such as heart failure, atherosclerosis, myocardial ischemia and stroke [4]. Therefore from the standpoint of prevention, reducing levels of obesity should reduce the overall burden of cardiovascular disease in terms of prevalence and outcomes. Moreover, given that most of the studies that suggest an “obesity paradox” have been retrospective and cross-sectional, a direct mechanistic link between obesity and improved myocardial outcomes following acute cardiovascular events remains to be elucidated.

The majority of reports describing the effects of obesity on mortality stratified their patient populations based on BMI, as defined by the World Health Organization. Use of BMI to predict the development of cardiovascular disease is commonly used, however it is likely that the distribution of fat might more accurately predict outcome, and consensus regarding the most suitable measure of obesity for epidemiological studies has not yet been obtained [118]. Finally, the epidemiological studies describing the obesity paradox do not directly address the relationship between cardiac steatosis and clinical outcome.

With the development of technologies, such as magnetic resonance spectroscopy (MRS) [119], it is now possible to quantify myocardial triglyceride content as described above [104]. Positron emission tomography (PET) has been used to address changes in cardiac metabolic flux rates and MVO_2 in obese and diabetic subjects and in response to changes in circulating FA concentrations or following various therapeutic interventions [4]. For example, examination of patients with type 1 diabetes, found that glucose utilization increased when FFA levels were decreased and fat oxidation increased with increasing FFA levels [120]. Additionally, use of phosphorus 31 (^{31}P) magnetic resonance spectroscopy, has been used to measure high-energy phosphate metabolite levels (phospho-creatine (PCr) and ATP) and found that in the absence of structural and contractile dysfunction, type 2 diabetic patients have a decrease in the PCr/ATP ratio [121]. A recent study of well-controlled type 2 diabetic patients

suggested that contractile function could be improved with anti-diabetic drugs in the absence of any change in substrate metabolism or triglyceride content [111]. These studies define new techniques that extend the findings in rodent models to humans by confirming similar patterns of substrate utilization and lipid accumulation. Moreover they suggest that increased triglyceride storage or FFA delivery may reduce cardiac energetics via mechanisms that may be related to FA induced mitochondrial uncoupling or obesity and diabetes-associated reductions in mitochondrial metabolic capacity. These studies indicate a correlation between cardiac function and triglyceride content but do not necessarily prove that changes in triglyceride content directly cause cardiac dysfunction. However, it may be reasonable to conclude that myocardial triglyceride content represents a biomarker for obesity or diabetes-related cardiac dysfunction. In the future it will be important to determine if changes in cardiac lipid or high-energy phosphate content influences or predicts clinical outcome.

3. Transgenic models of lipotoxicity and its reversal

Although diet-induced obesity, or rodents that develop obesity because of impaired leptin signaling develop evidence of lipotoxicity in the heart, analysis of pathophysiological mechanisms are confounded by systemic disturbances, such as hyperglycemia. This section will focus on mouse models that attempt to directly address the role of lipid in the heart in the absence of changes in systemic metabolism in an attempt to elucidate molecular mechanisms leading to lipotoxicity (Fig. 2).

3.1. Mouse models of lipotoxicity via increased lipid uptake and oxidation or reduced turnover

To directly address the role of increased delivery of myocardial fatty acids, a number of groups have generated cardiac-specific models of increased lipid uptake and delivery. One such model is cardiac-specific overexpression of acyl-CoA synthase (ACS), which leads to the accumulation of triglyceride in the heart that is associated with LVH, LV dysfunction and cytochrome c release [122]. The severity of the cardiac phenotypes and mortality rates were directly proportional to the degree of ACS overexpression in the three lines of animals examined. In the highest expressing line, there was a 3.3-fold increase in ceramide levels, increased cardiomyocyte apoptosis, and all animals died by 4-months of age [122]. A second model evaluated the consequence of cardiac-specific overexpression of the fatty acid transport protein (FATP1). These mice had a less severe phenotype, but manifested diastolic dysfunction that was associated with a ~2-fold increase in cardiac FA moieties with no change in triacylglycerols [123]. FATP1 overexpressing mice exhibited increased fatty acid uptake that was accompanied by increased fatty acid oxidation and reduced glucose oxidation.

Overexpression of a membrane anchored lipoprotein lipase (LpL) in cardiomyocytes also induced a lipotoxic cardiomyopathy that was associated with increased myocardial accumulation of various lipid moieties, including ceramide and cholesterol. LpL transgenic animals also exhibited mild LVH, increased PPARα expression, and increased mortality from a dilated cardiomyopathy [124]. These studies are also significant because they underscore that *in vivo*, lipolysis of triglyceride-rich lipoprotein particles represent an important source of myocardial lipid [125] and that exposure to triglyceride (TG) rich particles recapitulate metabolic abnormalities associated with lipotoxic cardiomyopathy [126]. It is important to note that under physiological circumstances, LpL mediated lipolysis of TG-rich particles represents an important route of substrate delivery to the heart, as evidenced by impaired cardiac contractile function and perivascular fibrosis, despite a compensatory increase in glucose oxidation in mice with cardiomyocyte-restricted deletion of LpL [125]. Germline deletion of adipose tissue triglyceride lipase (ATGL), resulted in dramatic cardiac lipid accumulation, contractile dysfunction and premature death [127]. However, in contrast to models with increased myocardial lipid uptake, ATGL KO mice represent a model with decreased

myocardial lipid pool turnover. Taken together, these studies support the hypothesis that increased myocardial lipid delivery, uptake or decreased turnover may impair cardiac contractile function and alter cardiac metabolism.

A number of studies have provided evidence that activation of transcriptional pathways that regulate the expression of FA oxidation enzymes might be sufficient to induce lipotoxicity [128]. Thus activation of PPAR increases the uptake and oxidation of fatty acids by regulating the expression of fatty acid transporters and mitochondrial genes that regulate FA oxidation. Mice with cardiac-specific overexpression of PPARα develop LVH, increased rates of FA oxidation and decreased rates of glucose oxidation [36]. These animals develop increased myocardial lipid triglyceride content, suggesting mismatch between FA uptake and mitochondrial FA oxidative capacity. Consistent with this hypothesis, HFD exacerbated cardiac dysfunction in PPARα overexpressors [33]. Cardiac-specific expression of the related transcription factor PPARγ, also resulted in cardiac dysfunction and increased lipid stores though, the changes in gene expression differed from PPARα overexpressing transgenic mice [129]. Interestingly, cardiac expression of PPARβ/δ preferentially increased glucose utilization without increasing myocardial lipid accumulation and these mice were protected from ischemia [130]. In contrast, PPARβ/δ-null animals developed cardiac dysfunction and myocardial lipid accumulation with reduced survival that likely developed on the basis of reduced mitochondrial FA oxidative capacity [131]. Thus modulation of fuel utilization at the level of mitochondrial oxidation could represent a mechanism for cardiac dysfunction in lipotoxic cardiomyopathies.

3.2. Reversal of lipotoxic phenotypes

Adenoviral overexpression of leptin in liver resulted in hyperleptinemia that rescued the contractile dysfunction observed in the cardiac-specific ACS overexpressing mice, via mechanisms that presumably result from increased myocardial FA oxidation or increased peripheral oxidation of lipids [39]. α-Lipoic acid (α-LA) treatment also normalized LVH, cardiac contractility and triglyceride content in ACS transgenic mice [40]. Treatment with α-LA resulted in a 6-fold increase in the activation of the energy sensing kinase, AMPKα, which is known to increase myocardial FA oxidation. Thus therapeutic strategies that increase myocardial FA oxidation might have utility in treating lipotoxic cardiomyopathies. Strategies that promote triglyceride export from the heart might represent an alternative aproach to combat lipotoxicity. For example, overexpression of apolipoprotein B (apoB) reversed lipotoxic cardiomyopathy in LpL overexpressing transgenic mice and attenuated cardiac dysfunction following high-fat feeding, presumably by increasing export of TG-rich particles from the heart [132,133].

A direct role for ceramide accumulation in cardiac contractile and metabolic dysfunction was shown in studies examining the cardiac-specific LpL overexpression model of lipotoxicity [32]. Park et al. found that either pharmacologic or genetic inhibition of ceramide synthesis normalized myocardial substrate utilization and improved systolic function. These results underscore the important role of *de novo* ceramide synthesis in contributing to cardiac dysfunction in lipotoxic cardiomyopathy.

PPARα signaling affects the uptake and utilization of fatty acids. Of interest, ablation of the fatty acid transporter, CD36, was sufficient to rescue the dysfunction observed following PPARα overexpression [134]. CD36 ablation was also shown to protect against age related decreases in cardiac function that are associated with increased intramyocardial lipid accumulation [135]. Thus in addition to its role in the regulation of mitochondrial function, PPAR-mediated regulation of fatty acid uptake pathways are also critical in the development of lipotoxicity in the heart.

Activation of PPARγ receptors in adipose tissue, using the agonist troglitazone, in ZDF rats lowered cardiac triglyceride and ceramide levels, which was associated with prevention of apoptosis and improved cardiac function [30]. It is likely that these effects were secondary to the troglitazone-mediated improvement in glucose homeostasis and insulin resistance. Additionally, troglitazone-treatment of either ZDF rats or *ob/ob* mice was associated with increased phosphorylation of AMPKα, via a proposed mechanism involving reduced protein phosphatase 2C (PP2C) expression [136]. Palmitate treatment decreases AMPKα phosphorylation in H9c2 cells [136] and red wine polyphenol-treatment of HepG2 hepatocytes has been shown to activate AMPKα [137]. It was recently shown that *fa/fa* rats fed a diet supplemented with polyphenols had increased cardiac function, potentially through enhanced NO signaling, reduced triglyceride accumulation, and improved glucose metabolism [28]. Together these studies suggest that reversal of triglyceride accumulation and rescue of cardiac contractile dysfunction either via PPAR agonist treatment or polyphenol supplementation may work through a molecular mechanism involving AMPKα.

4. Concluding remarks

Recent advances in imaging technology now make it possible to directly measure human cardiac lipid content and flux providing a novel biomarker that may provide insight into the progression and correlates of lipotoxic heart disease. Although studies in cell culture and animal models have suggested potential mechanisms either associated with or that might link triglyceride accumulation with cardiac dysfunction, more studies are required to determine if these mechanisms also exist in humans. Animal studies that have taken advantage of dietary manipulations, spontaneously occurring mutations, or cardiomyocyte-restricted transgenes, support a causative relationship between lipid accumulation and metabolic and contractile dysfunction. However, differences in the models and the severity of the dysfunction makes the identification of unifying underlying pathophysiological mechanisms a challenge to achieve. The sum of existing evidence suggests that lipid-induced apoptosis, ceramide accumulation, ROS overproduction, ER stress, and mitochondrial dysfunction might play independent and distinct roles in the pathogenesis of lipotoxic cardiomyopathy. However, all of these mechanisms do not necessarily need to be present in a given model. We are hopeful that research efforts in the next few years will further elucidate the pathophysiology of lipotoxic cardiomyopathy and importantly provide additional insights into therapeutic targets and strategies.

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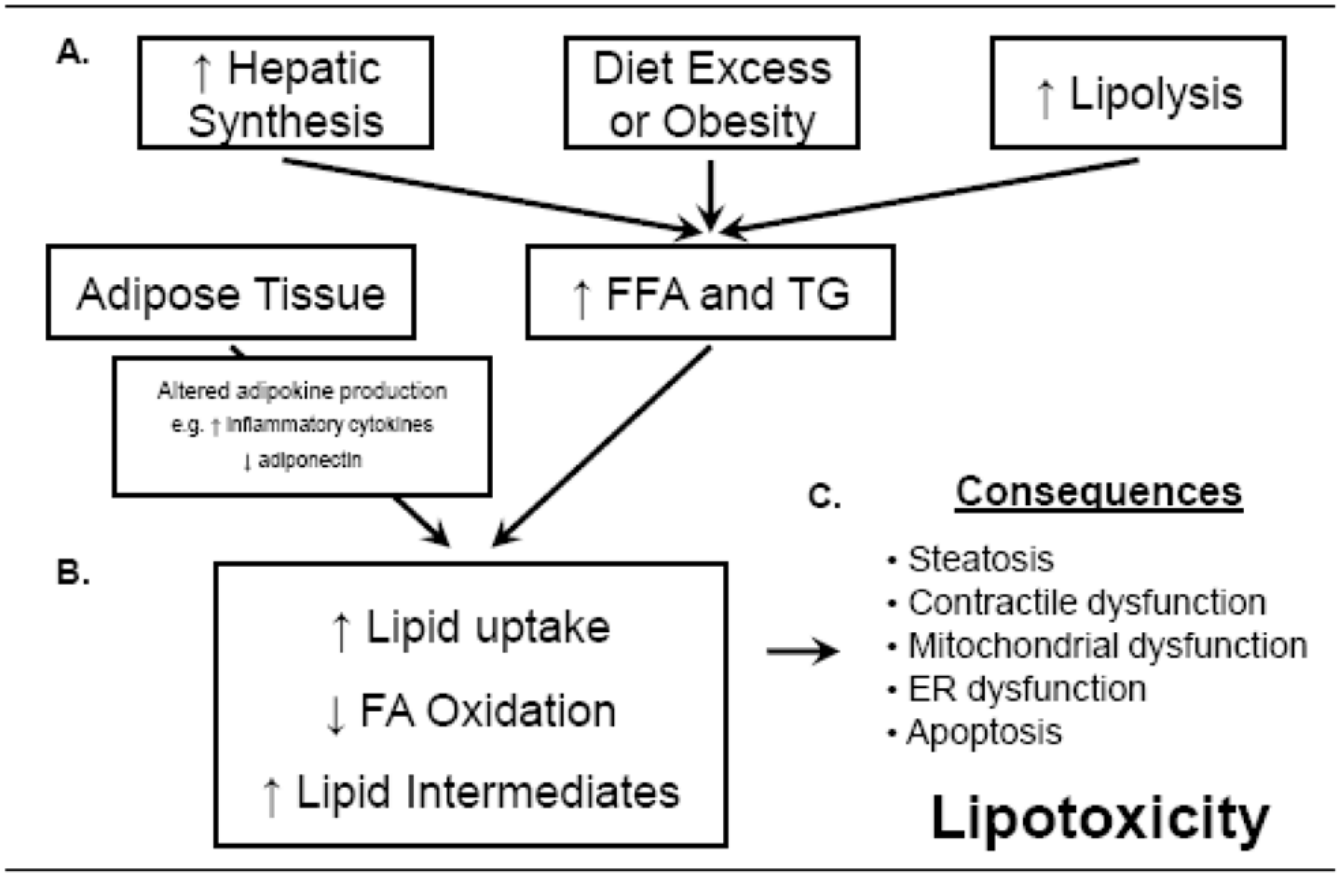

Fig. 1.

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.

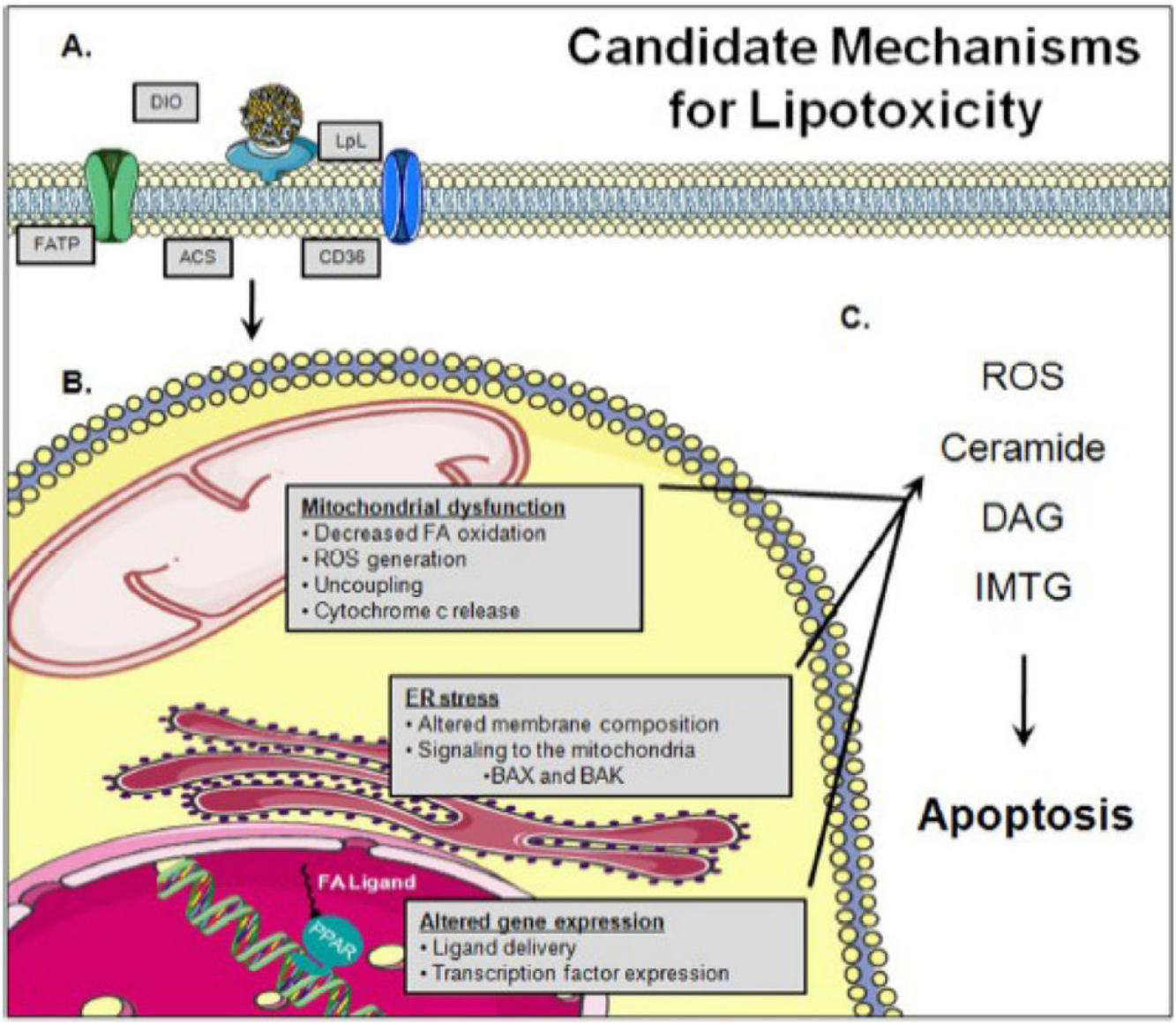

Fig. 2.

Schematic summary of mechanisms for lipotoxicity. (A) Transgenic models of increased lipid uptake and delivery as well as dietary studies have provided insight into a number of candidate molecular pathways that mediate cardiac lipotoxicity. (B) These include: decreased mitochondrial coupling and oxidative capacity, ER stress, altered membrane composition and function, and altered gene expression through enhanced ligand delivery to transcription factors (e.g. PPARs). However, the specific sequences with which these changes occur and the requirement for each of these pathways is not yet clearly defined. (C) Nevertheless, accumulation of toxic intermediates results in cell death. ACS, acyl-CoA synthase; FATP, fatty acid transport protein; LpL, lipoprotein lipase; DIO, diet-induced obesity; ROS, reactive oxygen species; DAG, diacylglyerol; IMTG, intramyocellular triglycerides; ER, endoplasmic reticulum; FA, fatty acid; PPAR, peroxisome proliferator-activated receptors. Figure was produced using Servier Medical Art (www.servier.com).