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REVIEW ARTICLE

Lipotoxicity and cardiac dysfunction in mammals and *Drosophila*

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Abstract

The lipotoxic effects of obesity are important contributing factors in cancer, diabetes, and cardiovascular disease (CVD), but the genetic mechanisms, by which lipotoxicity influences the initiation and progression of CVD are poorly understood. Hearts, of obese and diabetic individuals, exhibit several phenotypes in common, including ventricular remodeling, prolonged QT intervals, enhanced frequency of diastolic and/or systolic dysfunction, and decreased fractional shortening. High systemic lipid concentrations are thought to be the leading cause of lipid-related CVD in obese or diabetic individuals. However, an alternative possibility is that obesity leads to cardiac-specific steatosis, in which lipids and their metabolites accumulate within the myocardial cells themselves and thereby disrupt normal cardiovascular function. *Drosophila* has recently emerged as an excellent model to study the fundamental genetic mechanisms of metabolic control, as well as their relationship to heart function. Two recent studies of genetic and diet-induced cardiac lipotoxicity illustrate this. One study found that alterations in genes associated with membrane phospholipid metabolism may play a role in the abnormal lipid accumulation associated with cardiomyopathies. The second study showed that *Drosophila* fed a diet high in saturated fats, developed obesity, dysregulated insulin and glucose homeostasis, and severe cardiac dysfunction. Here, we review the current understanding of the mechanisms that contribute to the detrimental effects of dysregulated lipid metabolism on cardiovascular function. We also discuss how the *Drosophila* model could help elucidate the basic genetic mechanisms of lipotoxicity- and metabolic syndrome-related cardiomyopathies in mammals.

Keywords: Obesity, diabetes, lipid metabolism, heart function, cardiovascular disease

Introduction

Obesity has grown to epidemic proportions globally; more than 1.5 billion people worldwide are overweight and 400 million are clinically obese. It has become clear that the excess lipid accumulation that characterizes obesity is detrimental to normal physiological function, and there is growing evidence of a link between obesity, type-2 diabetes (T2D) and cardiovascular disease (CVD). Obese people and T2D patients exhibit several progressively deteriorating cardiac conditions, including ventricular remodeling, more frequent diastolic and/or systolic dysfunction, decreased fractional shortening, and prolonged QT intervals (Christoffersen et al., 2003; van Herpen and Schrauwen-Hinderling, 2008; Unger, 2002; Lopaschuk et al., 2007; Zhang and Ren, 2011; Heather and Clarke, 2011). In addition, several studies have shown that increased lipid deposition in non-adipose tissues, such as skeletal muscle, liver, and heart, can lead to T2D and CVD in humans and other mammals.(Forouhi et al., 1999; Hulver et al., 2003; Browning and Horton, 2004; Yki-Jarvinen, 2005; Kotronen et al., 2008; Jimba et al., 2005; Sharma et al., 2004; Fujita et al., 2011) However, it remains unclear whether systemic accumulation of lipids is indirectly detrimental to heart function, or if accumulation of excess lipid in the heart plays a more direct role. Several epidemiological studies have addressed this question, and found a correlation, between increased deposition of visceral fat and the incidence, of both T2D and CVD (Phillips and Prins, 2008; Mathieu et al., 2008; Despres, 2007). Under normal physiological conditions cardiomyocytes generate the majority of adenosine triphosphate (ATP) through β-oxidation of free fatty

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acids (FFA) (Lopaschuk et al., 2007; Peura et al., 2007). Cardiomyocytes have a limited ability to synthesize FFA *de novo* or to form storage depots, and therefore have developed tightly regulated mechanisms for importing and metabolizing FFA. Dysregulation of this system has been shown to cause cardiovascular dysfunction. For example, cardiac-specific overexpression of the FFA transporter FATP1 in transgenic mice has been shown to increase FFA transport into cardiomyocytes and cause severe cardiac dysfunction (Chiu et al., 2005). Similarly, several studies have shown a correlation between ectopic lipid accumulation within cardiomyocytes and increased cardiovascular dysfunction (Christoffersen et al., 2003; Lopaschuk et al., 2007; Stanley and Recchia, 2010).

Although these studies show that excessive FFA transport into cardiomyocytes and subsequent cardiac-specific lipid accumulation are detrimental to normal cardiac function, the underlying cause of the associated heart dysfunction remains unknown. Traditionally, an increase in the total systemic fat has been considered the major cause of cardiovascular dysfunction in obese or T2D animals. However, an alternative possibility is that obesity leads to cardiac-specific steatosis, in which lipids and their metabolites accumulate in the cardiomyocytes themselves, and thereby disrupt normal cellular function (Fujita et al., 2011; Stanley and Recchia, 2010; Glenn et al., 2011; Chiu et al., 2001; Brindley et al., 2010; Li, Klett, and Coleman, 2010). A recent study using the *Drosophila* model of genetic cardiac lipotoxicity, showed that alterations in genes associated with membrane phospholipids may also play a role in cardiac lipid accumulation and consequent heart dysfunction (Lim et al., 2011). Studies in our laboratory have shown that *Drosophila* fed a high fat diet (HFD) develop obesity, dysregulated insulin and glucose homeostasis, and severe cardiac dysfunction (Birse et al., 2010). In this review we address the subject of cardiac lipotoxicity and reflect on the possible determining factors involved in the development of lipid-associated cardiomyopathies. In addition, we discuss how the *Drosophila* model can aid in further understanding the basic genetic mechanisms involved in lipotoxic cardiac dysfunctions.

The effects of systemic obesity

The wealth of accumulated data leaves little doubt that a causal link exists between obesity and the disruption of normal physiological functions, in particular heart dysfunction. One theory proposes that aspects of the metabolic syndrome, such as dyslipidemia, hyperglycemia, and insulin resistance, play a role in obesity-associated dysfunctions such as atherosclerosis, cardiac hypertrophy, and ventricular remodeling (Lopaschuk et al., 2007; Phillips and Prins, 2008; Mathieu et al., 2008; Despres, 2007; Van Gaal, Mertens, and De Block, 2006). In addition, the presence of one or more symptoms of the metabolic syndrome can adversely affect other metabolic pathways, thereby inducing both systemic and tissue-specific changes in glucose and lipid metabolism, and in the transport, storage, and oxidation of FFA. Therefore, it is possible that obesity might affect one organ or tissue primarily, which then indirectly affects the function of other organs.

Peripheral insulin resistance, which is largely dependent on skeletal muscle homeostasis, is closely linked to the development of cardiovascular disease (van Herpen and Schrauwen-Hinderling, 2008; Schrauwen-Hinderling et al., 2008; Chow, From, and Seaquist, 2010; DeFronzo and Tripathy, 2009). To function normally, skeletal muscle must have a degree of regulatory flexibility to shift rapidly between lipid and glucose metabolism. If this flexibility is removed or constrained, as is the case in obese and insulin-resistant individuals, skeletal muscle may concomitantly increase lipid storage and reduce glucose metabolism, which in turn may lead to systemic metabolic dysregulation (Chow et al., 2010; DeFronzo and Tripathy, 2009; Bouzakri et al., 2005). Each of these factors can alter cardiac metabolism through mechanisms that are not yet fully understood. For example, insulin resistance in skeletal muscle is thought to initiate systemic insulin resistance, which induces increased FFA uptake and lipid accumulation in the heart, and ultimately leads to CVD (Figure 1)(Chow et al., 2010; DeFronzo and Tripathy, 2009; Bouzakri et al., 2005). However, this theory has yet to be rigorously investigated, and it is not yet known, if obesity contributes to CVD primarily through insulin resistance in skeletal muscle, or by lipid accumulation in the heart itself.

Just as obesity affects the normal functioning of skeletal muscle, overweight individuals tend to have higher occurrences of non-alcoholic fatty liver disease (NAFLD). NAFLD is commonly defined as alcohol-independent fat accumulation in excess of 5% to 10% of the liver by wet weight. NAFLD has been strongly associated with the metabolic syndrome; however, recent epidemiological studies suggest an additional and independent link between NAFLD and an increased risk of CVD (Figure 1) (Feldstein, 2010; Perseghin, 2010; Fabbrini et al., 2010). These findings suggest that NAFLD is not merely a consequence of obesity and T2D, but may also be actively involved in the initiation of CVD. One mechanism by which the liver may achieve this is through molecular signals such as the release of the coagulant protein, fibrinogen, which is known to be correlated with risk factors for cardiovascular disease (Meade et al., 1986; Kannel et al., 1987; Stec et al., 2000). In addition, the liver can release inflammatory cytokines during NAFLD. Increases in inflammatory cytokine levels have been shown to play a pathogenic role in CVD by influencing heart contractility, thereby inducing hypertrophy and apoptosis, which in turn contributes to myocardial remodeling (Goldberg, 2009; Picano et al., 2010).

Recent epidemiological studies have shown that patients with chronic kidney disease (CKD) have a high risk for developing CVD, and that most CKD patients die, not from kidney failure but from CVD (Sarnak et al.,

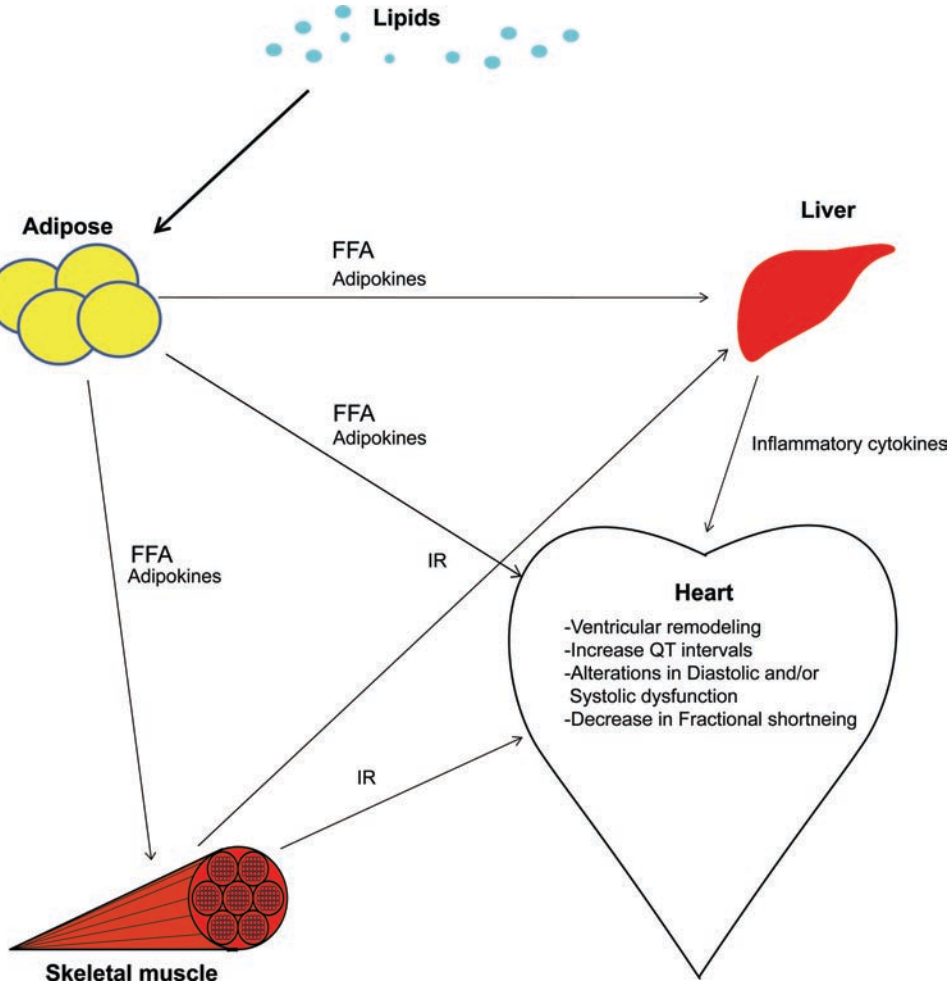

Figure 1. Schematic of the effects of lipid accumulation in non-adipose tissues. When overwhelmed with lipids, the adipose tissue will begin transporting excess free fatty acids (FFA) to non-adipose tissues such as the skeletal muscle, liver, and heart. Adipose tissue will also release adipokines (leptin, adiponectin, and inflammatory cytokines), while the liver will release inflammatory cytokines, and skeletal muscle may induce insulin resistance (IR). This may lead to heart problems, including ventricular remodeling, increased QT interval (arrhythmias), alterations in diastolic and systolic dysfunction, and lower fractional shortening.

2003; Go et al., 2004; Chen et al., 2004; Vaziri and Norris, 2011; Sowers, 2007; Schiffrin et al., 2007). Recently, an epidemiological correlation was made between metabolic syndrome, and the incidence of kidney failure and CVD. These findings suggested that excess dietary lipids may affect kidney function, which in turn influences heart function (Figure 1) (Sarnak et al., 2003; Go et al., 2004; Chen et al., 2004; Vaziri and Norris, 2011; Sowers, 2007; Schiffrin et al., 2007). In addition, patients with CKD exhibit high blood pressure and a higher incidence of atherosclerosis (Chen et al., 2004; Sowers, 2007; Vanholder et al., 2005).Taken together, these findings suggest, a causative relationship exists between CKD and CVD. However, further mechanistic research will be necessary to substantiate such a connection.

Obesity and the metabolic syndrome may also affect cardiovascular metabolism and function, through products secreted by adipose tissue. When excess lipid accumulates, adipose tissue secretes several adipokines such as leptin, adiponectin (APN), and inflammatory cytokines, which can increase systemic oxidative stress and promote inflammation (Figure 1). The mammalian heart expresses three APN receptors, AdipoR1, AdipoR2, and T-cadherin (T-cad), suggesting that APN may be important to heart function (Denzel et al., 2010; Hug et al., 2004; Yamauchi et al., 2003). Consistent with this possibility, APN knockout mice exhibit left ventricular hypertrophy and a tendency to develop larger infarcts (Lopaschuk et al., 2007; Denzel et al., 2010; Lopaschuk et al., 2010). Moreover, in the recent study by (Denzel et al., 2010) it was found that T-cad knockout mice have a similar cardiac phenotype to that of APN mutant mice. These data confirm the role of APN in cardiac stress responses, and show that T-cad plays a protective role in cardiac remodeling by reducing hypertrophy and decreasing infarct size (Denzel et al., 2010).

The adipose-derived hormone leptin was initially thought to serve only as a neuronal signal that helped regulate feeding behavior and metabolism. However, leptin receptors were later shown to be expressed in several

peripheral tissues, including the heart (Lollmann et al., 1997). These observations suggest that the heart may receive signals directly from adipose tissue to alter its function, and raise the possibility that adipose-derived signals may be involved in the development of lipotoxic cardiomyopathies. Further research will be necessary to identify the effects of leptin on heart function in obese individuals or T2D patients, and the effects on lipid metabolism within the heart.

The adverse effects of a HFD on heart function may be evolutionarily conserved, as simple organisms such as the fruit fly (*Drosophila melanogaster*) exhibit cardiac dysfunction that is reminiscent of lipotoxic cardiomyopathy observed in mammals fed with HFD (Birse et al., 2010). These phenotypes include increased heart rate, decreased fractional shortening, and morphological remodeling. The *Drosophila* model system has emerged as a powerful tool for studying not only the conserved genetic network of cardiogenesis, but also the control mechanisms that establish and maintain heart function (Birse et al., 2010; Bodmer and Venkatesh, 1998; Cripps and Olson, 2002; Qian et al., 2008; Zaffran and Frasch, 2002; Ocorr et al., 2007a; Neely et al., 2010). Similarly, *Drosophila* provides an excellent model to study the genetic mechanisms of metabolism and obesity, and their relationship to heart function (Birse et al., 2010; Oldham and Hafen, 2003; Baker and Thummel, 2007; Kim and Rulifson, 2004). We have recently shown that *Drosophila* fed with a HFD exhibit dysregulated insulin and glucose homeostasis, increased triacylglyceride (TG) levels, decreased activity levels, and cardiac remodeling and heart dysfunction (Birse et al., 2010). Collectively, these data support the emerging concept that TG accumulation and homeostasis is evolutionarily conserved, and that excess lipid accumulation may cause heart dysfunction.

Heart-specific lipid accumulation

When fat levels exceed the storage capacity of adipocytes, lipids are released from the cells and accumulate in other cells and tissues, including the heart (van Herpen and Schrauwen-Hinderling, 2008). Cardiomyocytes require a constant supply of energy in the form of ATP, and under normal circumstances, this need is satisfied by a well-regulated balance between the metabolism of FFA and glucose. However, the onset and development of obesity, and T2D can increase the availability of FFA, which in turn accelerates fatty acid oxidation. The high level of FFA uptake in the cardiomyocyte often exceeds its mitochondrial oxidative capacity, and cardiac steatosis ensues (Lopaschuk et al., 2007). Thus, although tissue-derived systemic endocrine signals may contribute to heart dysfunction, it is also possible that the heart phenotypes seen in obese animals could be caused by the accumulation of lipids or their metabolites within the heart itself.

Recently, several studies have begun to address this complex issue by using genetically manipulated mice, in which components of lipid transport, storage, and metabolism pathways are altered specifically in the heart ((Chiu et al., 2005; Stanley and Recchia, 2010; Glenn et al., 2011; Chiu et al., 2001; Li, Klett, and Coleman, 2010; Duncan et al., 2010; Son et al., 2010; Liu et al., 2011; Hoy et al., 2011; Summers, 2006). Many of these studies employed the alpha-myosin heavy chain promoter to investigate heart-specific effects of genetic modification. The studies have focused on manipulating the expression of genes implicated in FFA uptake and metabolism, such as cardiac-specific lipoprotein lipase (LpL), acyl-CoA synthetase and the FA transporter FATP1 (Chiu et al., 2005), or involved in lipid utilization, such as adipose triglyceride lipase (ATGL)(Hoy et al., 2011; Haemmerle et al., 2006; Hirano et al., 2008). The studies have revealed that cardiomyocyte-specific lipid deposition is strongly associated with heart dysfunction. In one study, the effect of heart-specific lipid accumulation was investigated by overexpressing LpL, an enzyme that hydrolyzes circulating TG and liberates FFA (Yagyu et al., 2003). These mice had dilated hearts that exhibited systolic dysfunction, even when the animals were maintained on a normal diet. In another study, FATP1 was overexpressed in the heart to investigate the effect of increased FFA uptake. These animals showed rapid cardiomyocyte lipid accumulation and developed cardiac phenotypes reminiscent of those seen in T2D and obese animals (Chiu et al., 2005). Collectively, these studies demonstrated that increased FFA uptake by cardiomyocytes correlated directly with the progression of heart dysfunction.

The *ATGL* gene encodes a triacylglycerol lipase that is required for the breakdown of lipid droplets, and is conserved from nematodes to mammals (Birse et al., 2010; Gronke et al., 2005; Gronke et al., 2007). Previous studies in mice and humans have shown that mutations in *ATGL* increase lipid accumulation in the heart and elicit cardiac phenotypes similar to those of obese or T2D hearts (Hoy et al., 2011; Haemmerle et al., 2006; Hirano et al., 2008). To investigate this issue further, we asked if the *Drosophila* heart could be protected from the detrimental effect of increased systemic TG by inhibiting either the Target of Rapamycin (TOR) pathway, or by overexpressing *Brummer* (Bmm), the *Drosophila* homolog of the mammalian *ATGL* gene, specifically in the heart. The nutrient sensing TOR pathway is well known for its function in regulating metabolism. Although the molecular basis of metabolic processes are far from being understood, manipulation of TOR can dramatically influence metabolic responses in species ranging from yeast to humans (Arking et al., 2005; Saltiel and Kahn, 2001; Tatar, Bartke, and Antebi, 2003; Vellai et al., 2003; Wang, Bohmann, and Jasper, 2005). We found that the adverse effects of a HFD and the ensuing accumulation of TG were ameliorated by either inhibition of the TOR pathway or by overexpression of Bmm lipase in adipose tissue or in the heart itself (Birse et al., 2010). The protective effects of Bmm may stem from a change in lipid utilization by the mitochondria. Alternatively, lipid droplet lipolysis may liberate fatty acid ligands for nuclear receptors, which may contribute

to changes in mitochondrial biogenesis, or may simply decrease overall lipid accumulation (Palanker et al., 2009; Park et al., 2005). Changes in insulin-TOR signaling are likely to increase activity of translation factors involved in mitochondrial function (Zid et al., 2009). Lastly, increases in autophagy have been implicated in the regulation of lipid metabolism by promoting the breakdown of lipid droplets (Kovsan et al. 2009). Thus, a reduction of insulin-TOR signaling, can lead to coordinate changes in lipid metabolism, which in turn may profoundly affect the organism's physiology under different dietary conditions. These effects are also observed in mammalian hepatocytes, where TOR function is required for activation of the sterol regulatory element-binding protein (SREBP), and it has been proposed that TOR serves a key role in diabetic insulin resistance by separating gluconeogenesis from lipogenesis) (Laplante and Sabatini, 2010; Laplante and Sabatini, 2009). Collectively, these data support the idea that TOR is evolutionarily conserved, and mediates HFD-induced obesity and its associated cardiac defects through multiple mechanisms.

Overexpression of the transcription factor peroxisome proliferator-activated receptor (PPARα) specifically in the mouse heart has been shown to induce overt cardiac lipid accumulation and cardiomyopathy (Son et al., 2010). Moreover, (Duncan et al., 2010) found that the detrimental effects of heart-specific PPARα overexpression could be reduced by decreasing levels of CD36, which is a sarcolemmal protein required for FFA uptake into the cardiomyocyte. Moreover, a recent study found that palmitate-induced TG accumulation in cardiomyocytes was accompanied by increased translocation of CD36 to the plasma membrane (Puthanveetil et al., 2011). These data favor the notion that cardiac steatosis affects heart function independently of systemic increases in adiposity, dyslipidemia, and insulin resistance. However, it remains unclear if the steatosis-induced cardiac dysfunction is due to cardiomyocyte accumulation of lipids or of lipid intermediates. (Son et al., 2010) found that overexpression of PPARγ in the heart of PPARα mutant mice increased the TG content of cardiomyocytes while preserving heart function. Conversely, the ATGL knockout mouse also displays TG accumulation in the heart, but exhibits rather extreme heart dysfunction (Hoy et al., 2011; Haemmerle et al., 2006). One possible explanation is the existence of a threshold for accumulation of TG and lipid metabolites within the cardiomyocyte; if lipids accumulate above this threshold then cardiac-specific dysfunction will occur. It will be of interest to ectopically increase the lipid levels in *Drosophila* heart as a model system to elucidate the genetic mechanisms that regulate lipid metabolism, and their relationship to heart function.

Possible reasons for cardiac-specific dysfunction.

FFA are stored as TG during times of nutritional excess and are mobilized when exogenous energy substrates are in short supply. TG are primarily stored in the adipose tissue, and it is thought that adipose tissue plays a key role in preventing excess lipid accumulation in other organs such as skeletal muscle, liver, and heart. TGs are thought to be relatively harmless when stored within the cells as lipid droplets. However, both lipolysis and synthesis of TG produce lipid intermediates that can have deleterious effects on cell and tissue function. The coenzyme acyl-CoA plays a critical role in lipid synthesis and metabolism; although FFA levels are diminished during formation of long-chain acyl-CoAs, the acyl-CoAs themselves are thought to affect signaling pathways, and could lead to the accumulation of ceramide and diacylglycerols (DAG) (Chiu et al., 2001; Li, Klett, and Coleman, 2010) (Figure 2). Recently, a growing body of evidence has implicated long-chain acyl-CoA synthetase (ACSL) in the functional disturbances caused by lipotoxicity. Increased synthesis of TGs has been closely linked with the detrimental effects of lipotoxicity (Chiu et al., 2001; Li, Klett, and Coleman, 2010). ACSL is involved in a wide range of functions including oxidation of FFA and synthesis of complex lipids such as phospholipids, ceramide, DAG and TG. ACSL exists as several isoforms, one of which (ACSL1) has been closely linked to increases in TG and to heart dysfunction (Chiu et al., 2001). Transgenic overexpression of the ACSL1 isoform in the heart caused significant accumulation of TG within the heart and resulted in cardiac hypertrophy and ventricular dysfunction. This study also reported a 3-fold increase in levels of ceramide, which is thought to be involved in heart dysfunction and insulin resistance. Cardiac overexpression of FATP1 in transgenic mice also results in a significant increase in ACSL1 transcripts, and the mice suffer from heart defects similar to those observed in ASCL1 overexpressing mice (Chiu et al., 2005). These findings provide further evidence of the contribution of excess ACSL activity to lipid-associated heart dysfunction.

Ceramides are composed of sphingosine and a FA, and are generally found at high concentrations in cell membranes and may be critically involved in the lipotoxic deterioration of heart function (Figure 2). They are also present in sphingomyelin, a major component of lipid bilayers. Ceramide has been implicated in a variety of physiological functions including apoptosis, cell development, and growth (Hannun and Obeid, 2008; Zeidan and Hannun, 2007; Wu et al., 2007). Ceramide and its downstream metabolites have also been linked to diabetes, inflammation, obesity, and the cellular response to changes in nutrient availability (Summers, 2006). These observations suggest that ceramides may be involved in mediating heart dysfunction due to excess lipid metabolism. (Turinsky et al., 1990) first showed that plasma ceramide levels are increased by 26 to 52% in obese insulin-resistant mice. Later, (Gorska et al., 2004) reported a 78% increase in ceramide levels in streptozotocin-induced diabetic rats. (Straczkowski et al., 2004) found similar results, and demonstrated an inverse correlation between insulin sensitivity and ceramide levels.

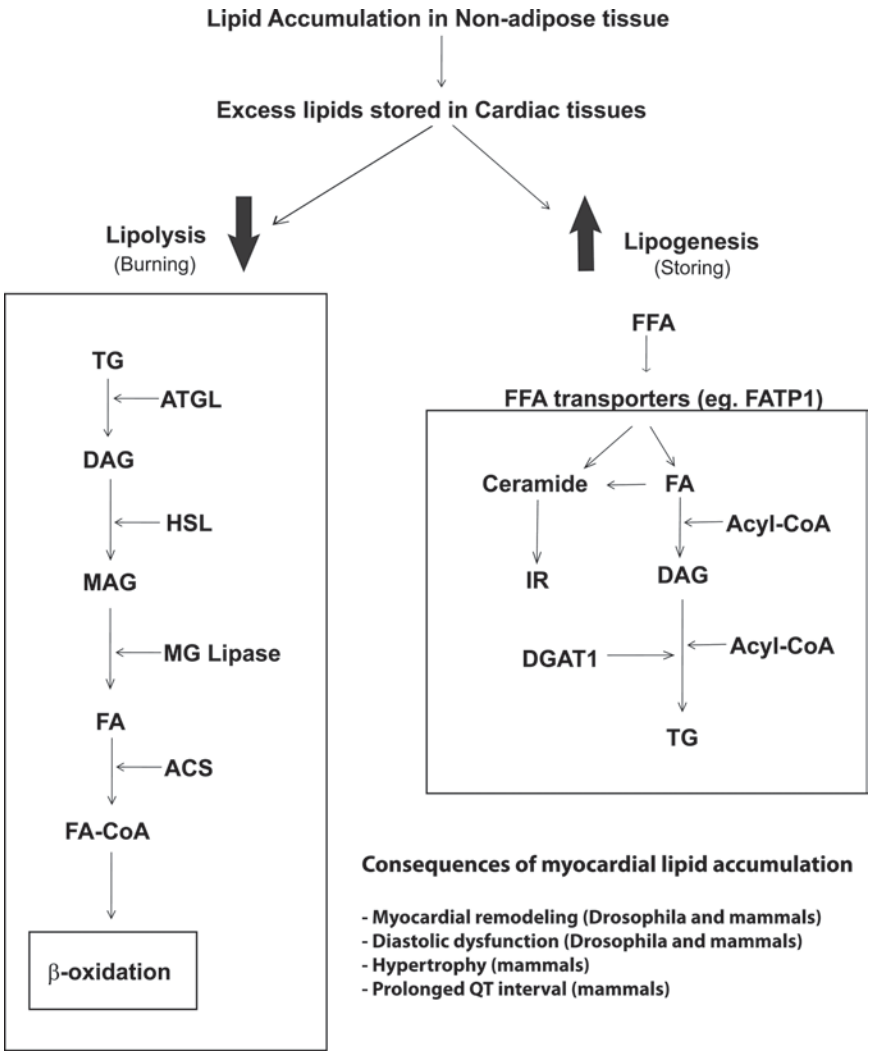

Figure 2. Schematic representation of excess lipid accumulation and possible effects on lipolysis and lipogenesis. In an obese and/or lipotoxic state, the heart accommodates excess fat by increasing either lipid breakdown (lipolysis) or storage as TG (lipogenesis). Lipolysis involves the progressive breakdown of triaclyglycerides (TG) by adipose triglyceride lipase (ATGL), sensitive lipase (HSL), and monoacylglyceride (MAG) lipase. This breakdown generates diacylglycerides (DAG) and MAG and liberates FFA, which can then be converted by Acyl-CoA synthase (ACS) to fatty acid CoAs (FA-CoAs), which are then transported into the mitochondria to undergo -oxidation. The heart may also reduce an excess lipid load by converting FFA to TG through lipogenesis. FFA are transported into the cell by the Fatty Acid Transport Protein 1 (FATP1) and other transport mechanisms. These FA can then be processed into ceramides, which may lead to insulin resistance. Acyl-CoA uses the FFA to produce DAG and, in combination with diacylglyceride transferase (DGAT1), to produce TG. When FFA levels in the cardiomyocyte exceed the mitochondrial capacity for oxidation, lipolysis is decreased and lipogenesis is increased. Collectively, these events can lead to cardiac steatosis and eventually, to cardiac dysfunction.

The same authors found that lipid infusion into the animals also increased ceramide levels. To probe further the relationship between cardiac dysfunction and FFA-induced ceramide synthesis, several groups have exposed isolated cardiomyocytes to a variety of FFA (Dyntar et al., 2001; Hickson-Bick et al., 2000; Sparagna et al., 2000). Interestingly, only the FFA that induced ceramide synthesis caused apoptosis and damaged myofibrils within the cardiomyocyte. Extending these observations, (Dyntar et al., 2001) showed that addition of ceramide analogs to cardiomyocytes mimicked the effects on cell function of palmitate, a ceramide-synthesizing FFA. They also found that inhibition of ceramide synthesis ameliorated palmitate-induced apoptosis and the detrimental effects on the myofibrils. Taken together, these data strongly suggest that ceramide may be a key regulator of cardiac lipotoxicity.

The final step of TG synthesis involves the conversion of DAG to TG, which is catalyzed by diacylglycerol transferase (DGAT) (Figure 2). DGAT has several isoforms and is expressed in most tissues, but is highly expressed in skeletal muscle, adipose, and cardiac tissues (Glenn et al., 2011; Liu et al., 2011). To study the effects of modulating DGAT1 levels *in vivo,* (Liu et al., 2011) generated mice overexpressing DGAT1 in skeletal muscle. The mice exhibited increased TG levels, but maintained insulin sensitivity. These findings appear to mirror the effects of the altered lipid storage observed in individuals with extensive athletic training. However, in an earlier paper (Liu et al., 2009) found that short term overexpression of DGAT1 in isolated

cardiomyocytes decreased levels of potentially toxic intermediate lipids such as DAG, ceramide, and FFA, and that expression of DGAT1 in ACSL knockout mice preserved normal heart function. Interestingly, (Liu et al., 2011) found that DGAT1-deficient and DGAT1-overexpressing mice did not exhibit opposite phenotypes. Instead, DGAT1-deficient mice were lean, insulin resistant, had decreased levels of DAG and ceramide, and did not show cardiac dysfunction. The authors then investigated these apparent discrepancies and found that the DGAT1 knockout mice had decreased mRNA levels for several proteins involved in cellular FFA uptake, including CD36 and LpL. Therefore, decreased DGAT1 expression may result in a feedback loop that prevents FFA from entering the cell, thereby decreasing the lipid pool available for TG synthesis. In another study, sustained overexpression of DGAT1 in cardiomyocytes resulted in excess fat accumulation in the cells, with progressive development of fibrosis, ventricular remodeling, contractile dysfunction, and decreased mitochondrial biogenesis. Moreover, these effects occurred in the absence of obesity, insulin resistance, or systemic dyslipidemia (Glenn et al., 2011). The results of this study suggest that while acute overexpression of DGAT1 can be protective, prolonged DGAT1 overexpression can cause cardiomyopathies, likely due to excessive accumulation of lipids.

In our recent study we showed that the detrimental effects of a HFD on *Drosophila* heart function could be counteracted by two heart-specific genetic interventions. In one, Bmm lipase was overexpressed, and in the second RNAi was used to decrease expression of fatty acid synthase (FAS), in the heart only (Birse et al., 2010). These experiments showed that increasing lipase activity or decreasing FA synthesis in the heart protected against damage from excess lipid buildup in a manner that was independent of systemic lipid accumulation. To investigate the effects on heart function of altered FA synthesis, another study determined the effects of reduced phosphatidylethanolamine (PE) synthesis on TG levels and heart function in *Drosophila* (Lim et al., 2011). It was found that mutants of ethanolamine kinase (encoded by the gene *easily shocked; eas*) had increased TG levels and considerable heart dysfunction. As expected, these mutants also exhibited reduced levels of PE, which is a major phospholipid component of most lipid membranes across species. In *Drosophila*, reduction in PE affects activation of SREBP, which regulates FA synthesis (Rawson, 2003). (Lim et al., 2011) found that elevated SREBP activity in *eas* mutants caused fat accumulation and heart dysfunction, and suppression of cardiac SREBP activity was found to ameliorate the detrimental effects of reduced PE levels. It has been shown previously that excess levels of FFA in rat cardiomyocytes induces breakdown of phospholipids and ultimately leads to cell death (Janero et al., 1988). However, one promising study has shown that the drug trimetazidine increases membrane phospholipid synthesis and has a cardioprotective affect in rats ((Sentex et al., 1997). There is also a growing body of work that implicates sarcolemmal phospholipid signaling as a source of increased lipid intermediates such as DAG that may contribute to heart dysfunction (Tappia and Singal, 2008). Collectively, these studies indicate that membrane composition as well as components of membrane biosynthesis and membrane phospholipid signaling can be of key importance in the regulation of cardiovascular function under obese conditions.

Conclusion

The study of diet-induced and genetic lipotoxicity has shed light on the underlying mechanisms that lead to dysregulated lipid metabolism, and their relation to the development of cardiomyopathy. It seems clear that adipose tissue can communicate with other organs through leptin and ANP, and that these organs then become susceptible to the effects of obesity. Although there is considerable evidence for a complex tissue-to-tissue communication system, the details of their relation to perturbed cardiac function has yet to be fully elucidated. One exciting area of research is the effects on the heart of lipids and their metabolic intermediates. Studies of the accumulation of specific intermediates such as Acyl-CoA, DAG, and ceramides have all provided suggestive evidence that they can be detrimental to heart function. Recent studies of genetic or diet-induced lipotoxicity in *Drosophila* support the idea that the basic underlying mechanisms relating lipid accumulation and/or metabolism to heart function are evolutionarily conserved. Moving forward, the *Drosophila* model will contribute to our understanding of such relationships by allowing multiple genes involved in lipid metabolism to be manipulated in a tissue-specific manner. This model will also allow genes to be identified that contribute to signaling between the skeletal and cardiac muscles, which will shed further light on the complex tissue-communication system in obese organisms. Finally, the *Drosophila* model of lipid-associated cardiac dysfunction will help to identify the genetic mechanisms or pathways that are essential to normal heart function, as well as those that exacerbate the detrimental effects of obesity and T2D.

Declaration of interest

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