HHS Public Access

Author manuscript

Heart Fail Clin. Author manuscript; available in PMC 2015 August 25.

Published in final edited form as:

Heart Fail Clin. 2012 October ; 8(4): 633–641. doi:10.1016/j.hfc.2012.06.003.

Sphingolipids, Lipotoxic Cardiomyopathy, and Cardiac Failure

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Keywords

Ceramide; Cardiomyopathy; Diabetes; Ischemia; Sphingosine 1-phosphate

INTRODUCTION

Obesity is associated with an elevated risk of chronic diseases, including diabetes and cardiovascular disease. Accumulation of lipotoxic metabolites in nonadipocyte tissues may be a major cause of dilated cardiomyopathy in patients with obesity or diabetes. Recent studies in humans have related cardiac lipid content with disturbance of cardiac function. Moreover, ectopic disposition of lipids alters substrate metabolism in these tissues and contributes to the development of obesity-mediated diseases.

The heart uses lipids for energy and for cellular structures. Fatty acids supply energy for cardiac muscle contraction and are required substrates for the synthesis of several esters, including phospholipids and sphingolipids. Patients with diabetes and obesity have elevated circulating plasma free fatty acids (FFA) levels. This state might drive greater heart FFA uptake; when uptake exceeds the requirements for energy production, these FFA accumulate as lipid metabolites and neutral lipids. Lipotoxicity is the term used when lipid overload leads to cellular dysfunction and cell death–mediated organ dysfunction.[1] Because neutral lipids and other lipid metabolites accumulate in the cardiomyocytes of nonischemic failing hearts,[1,2] a hypothesis that lipotoxicity contributes to the development of cardiac dysfunction is gaining credibility.[3] In addition, ischemia has been reported to increase heart levels of some lipids.[4,5]

Of the complex bioactive lipids, ceramide and its metabolites draw particular attention. Studies in animal models of diabetes, obesity, and dilated cardiomyopathy demonstrated that the inhibition of sphingolipid production prevents or delays the onset of the diseases.[6,7] In addition, the activation of ceramidase by adiponectin was associated with reduced cardiac injury after apoptosis.[5] Thus, there is experimental evidence that ceramide is one of the lipotoxic lipids.

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The authors have nothing to disclose.

Ceramide is a major molecule in sphingolipid metabolism and has been studied extensively. In addition to its structural role in plasma membranes and lipoproteins, ceramide and its metabolites have profound effects on cellular signaling, such as apoptosis and insulin response.[8] Ceramide is also a precursor for other bioactive sphingolipid metabolites, such as ceramide 1-phosphate, sphingosine, and sphingosine 1-phosphate (S1P) (Fig. 1). These sphingolipids regulate cellular processes, including cell proliferation, differentiation, and apoptosis.[9] In this review, the authors intend to describe the role of sphingolipids in cardiovascular pathophysiology as a regulator of cardiac energy metabolism and signaling. Understanding the role of sphingolipids in cardiovascular events may lead to strategies to correct the abnormal signaling pathways in failing hearts.

FAILING HEARTS HAVE ABNORMAL LIPID METABOLISM

The heart requires several forms of lipids, including cholesterol and fatty acids. Most circulating plasma fatty acids are esterified and are incorporated into lipoprotein, phospholipids, and triglycerides. Fatty acids supply energy for heart contraction and are used for structural lipids in cells. Tissue uptake of whole lipoproteins by specific receptors leads to intracellular degradation of phospholipids and triglycerides to varying degrees. FFA uptake caused by either albumin-associated FFA or FFA liberated from lipoproteins supplies cardiac energy substrates. Loss of either lipoprotein lipase (LpL)[10] or the putative FFA transporter CD36[11] in the heart increases cardiac uptake of glucose, suggesting that the heart is fatty acid deprived and needs an alternative source of energy.

In normal adult hearts, ATP is produced via the oxidation of fatty acids, glucose, lactate, and ketone bodies, with glucose and fatty acids being the principal substrates.[12] Of these substrates, fatty acids are the major fuel supplying 70% of the ATP for normal cardiac function.[13–15] During diabetes, the heart seems to oxidize more fatty acid and less glucose.[16] Heart LpL activity is increased, presumably to allow greater lipoprotein-derived fatty acid uptake.[16,17] One well-studied model is the isolated working heart of obese db/db mice. These hearts have decreased glucose oxidation rates and increased fatty acid oxidation.[18] Although fatty acid oxidation has not been studied in detail, diet-induced obesity rapidly leads to cardiac insulin resistance.[19]

Diabetic cardiomyopathy is a syndrome in which heart failure is not caused by ischemic heart disease or hypertension.[20] The activity of peroxisome proliferator-activated receptor (PPAR) α, a major regulator of fatty acid oxidation in the heart, is increased in diabetic hearts. PPARα overexpression in mice leads to cardiac dysfunction.[21] This cardiomyopathy could result from excess fatty acid oxidation, which is postulated to increase reactive oxygen production, or from accumulation of intracellular lipids, which also occurs in this model. Mice with cardiomyocyte PPARα transgenic expression have enhanced activity of enzymes that catalyze the synthesis of triglycerides and, like diabetic hearts, have greater intracellular triglyceride stores.[22,23] Hydrolysis of this triglyceride supplies fatty acids to the diabetic hearts.[17] In moderately obese individuals, triglyceride accumulation is detected in the myocardium.[24]

Whether greater reliance on fatty acids is harmful or is an adaptive change is debated. In the setting of ischemia, more specifically hypoxia, the creation of more ATP using less oxygen can occur by the use of glucose and has been proposed as a beneficial therapeutic strategy.[25] Whether this strategy is applicable to nonischemic disease is unclear, and some in vivo studies in animal models fail to support a role for reducing fatty acid oxidation in heart failure. Diets with greater amounts of fat and less carbohydrate lead to better function in some failure models.[26–29]

Another option for the cause of heart failure in diabetic or obese conditions is that toxicity is caused by an alteration of lipid metabolism leading to lipotoxic events. Sphingolipids might be one such lipid.

ELEVATED CERAMIDE CORRELATES WITH LIPOTOXIC CARDIOMYOPATHY

The accumulation of neutral lipids in or around the myocardium is observed in humans or animal models with nonischemic heart failure,[1,2,22,23] and it is hypothesized that excess lipid contributes to the development of cardiac dysfunction.[3,30,31] Several transgenic animal models of lipotoxic cardiomyopathy have been created to support this notion. When hearts internalize excess lipids or have a defect in lipid oxidation, lipid storage is increased. Cardiomyocyte transgenic expression of long-chain acyl coenzyme A synthetase 1 (myosin heavy chain [MHC]-ACS1),[32] fatty acid transport protein 1 (MHC-FATP1),[33] and the cell membrane anchored form of LpL (LpL^{GPI})[34] are characterized by elevated myocardial fatty acid uptake and lipid deposition and cardiomyopathy.

How does myocardial lipid accumulation lead to cardiomyopathy? Neutral droplets or fatty acids could produce direct toxic effects on myofibrillar function.[35] Fatty acids can induce apoptosis[36] in response to increased levels of reactive oxygen species generated as a toxic by-product of lipid oxidation[35] and activation of protein kinase C signaling pathway.[37] Fatty acids also induce the synthesis of ceramides, which mediate several toxic processes.[6] Although it is still unclear which lipid metabolites directly cause cardiomyopathy, in several models, ceramide accumulation in the heart correlates with these pathophysiological events and heart dysfunction (Table 1).[6,32,38] When the balance between fatty acid uptake and oxidation is altered, excess fatty acids are directed toward the synthesis of complex lipids, including triglycerides and phospholipids. An alternative route to use fatty acid surplus is via the ceramide biosynthetic pathway. Increased myocardial ceramide levels are associated with diastolic dysfunction in Akita Ins2 (WT/C96Y) mice and Zucker diabetic fatty (ZDF) rats.[39] To support this notion of ceramide toxicity, improvement in cardiac dysfunction by pharmacologic and genetic intervention in ZDF rats, Akita Ins2 (WT/C96Y), and MHC-ACS1 mice was accompanied by the reduction of cardiac ceramide.[28,36,39] The previously mentioned results suggest that myocardial ceramide levels correlate with the development of cardiac dysfunction found in obese and diabetic hearts.

Methods to reduce ceramide synthesis include the reduction of fatty acid uptake by the heart and conversion of fatty acids to nontoxic triglyceride. Several intervention studies to reduce circulating fatty acids improved cardiac function of lipotoxic animals and reduced cardiac

ceramide. These interventions include the administration of the PPARγ agonist troglitazone in ZDF rats, insulin treatment of Akita Ins2 (WT/C96Y) mice, and the overexpression of diacylglycerol acyltransferase 1 in MHC-ACS1 mice.[28,36,39]

To find a direct connection between ceramide and lipotoxic cardiomyopathy, the authors studied the involvement of ceramide in the development of lipotoxic cardiomyopathy. LpL^{GPI} mice also have increased cardiac ceramide and apoptosis markers, including cytosolic cytochrome c and caspase 3 expression and activity.[40] The authors demonstrated that the inhibition of ceramide biosynthesis by myriocin or heterozygous deletion of Sptlc1, a serine palmitoyltransferase (SPT) subunit, decreased the expression of some apoptotic genes and improved cardiac contraction in LpL^{GPI} (Fig. 2).[6] In this study, blockage of ceramide biosynthesis seems to modulate mitochondrial substrate oxidation. LpL^{GPI} hearts have increased uptake of FFA and rely on fatty acid oxidation for cardiac energy production. A potential mechanism for the improvement with myriocin is that pharmacologic and genetic inhibition of SPT upregulated pyruvate dehydrogenase kinase-4 and decreased the rate of glucose oxidation but led to greater fatty acid (FA) oxidation. However, glucose uptake was increased in LpL^{GPI} hearts. This paradoxic fate of glucose is explained by the accumulation of glucose as glycogen with increased phosphorylated glycogen synthase kinase 3β.[6] In isolated perfused LpL^{GPI} hearts, myriocin restored cardiac efficiency, enhancing myocardial energetics by maintaining cardiac performance at a lower oxygen cost. Even with improved cardiac function and balanced substrate use by myriocin treatment, a long-term treatment of LpL^{GPI} mice with myriocin only partially rescued the survival rate. A potential reason is the involvement of other lipid metabolites in cardiac dysfunction. Other probable candidates for cardiac failure are diacylglycerol, which alters protein kinase C (PKC) signaling, and FFA. More studies are needed to distinguish the role of ceramide from other lipid metabolites.

CERAMIDE-MEDIATED APOPTOSIS OF CARDIOMYOCYTES

Lipotoxic cardiomyopathy is also associated with the loss of cardiomyocytes via apoptosis.[41,42] Ceramide is a proapoptotic second messenger that activates several signaling pathways, including PKC, protein phosphatase 1 or 2A, and cathepsin D.[43] These signaling pathways are involved in proapoptotic events, including the suppression of Bcl2, the dephosphorylation of protein kinase B (AKT), and the activation of caspases.[43] The accumulation of ceramide was reported to be accompanied by cardiomyocyte apoptosis, and pharmacologic inhibition of ceramide biosynthesis reduced cardiomyocyte apoptosis in ZDF rats and MHC-ACS1 mice.[28,36] However, a recent report demonstrated that the myocardium of ob/ob mice and rats fed a high saturated-fat diet did not show increased cardiomyocyte apoptosis even with elevation of ceramide.[44] These conflicting data suggest that the elevation of cardiac ceramide does not always lead to the activation of apoptosis.

The notion that cardiac dysfunction of LpL^{GPI} hearts results from its dysregulation of substrate use and not from apoptotic loss of cardiomyocytes suggests that ceramide accumulation does not necessarily accompany apoptosis. The incubation of human cardiomyocyte AC16 cells with C6-ceramide downregulated glucose transporter 4 and upregulated pyruvate dehydrogenase kinase 4 gene expression.[6] These changes in metabolic

genes were consistent with what was found in LpL^{GPI} mice that has elevated ceramide levels in hearts. These findings also suggest that ceramide modulates cardiac energy metabolism via transcriptional regulation of metabolic genes rather than apoptosis.

PPARs REGULATE CARDIAC SPHINGOLIPID METABOLISM

PPAR transcription factors regulate the oxidation of FA and play an important role in the regulation of substrate metabolism in hearts. There are 3 distinct PPAR isoforms: α, β, and γ. Of these isoforms, PPARα and γ are highly expressed in hearts and thought to regulate FA metabolism in cardiomyocytes.[45] High fat feeding of cardiac PPARα transgenic mice accelerated the development of cardiomyopathy and was associated with excess FA oxidation and accumulation of ceramide in hearts.[46,47] These effects were not observed in wild-type mice and suggest that PPARα is involved in the regulation of ceramide metabolism in hearts. Baranowski and colleagues[48,49] demonstrated that activation of PPARα by WY-14643, a PPARα agonist, causes ceramide and sphingomyelin accumulation in the myocardium of high fat–fed rats. This result was caused by the activation of de novo sphingolipid synthesis via elevated SPT activity and increased availability of intracellular palmitate, a substrate of SPT. However, it is unclear whether PPARα regulates SPT expression directly or indirectly by elevating FFA pools. Because PPARα agonist activity did not increase myocardial ceramide levels or SPT activity in regular chow-fed rats, both changes in enzymes and substrates (ie, the high-fat diet) are needed to alter de novo ceramide biosynthesis.[48] Alternative pathways for ceramide generation, such as sphingomyelinase and ceramidase, were not affected by PPARα activation.

The treatment of patients with diabetes with thiazolidinediones, selective PPARγ activators, increases heart failure risk.[50] These clinical observations could have resulted from either greater salt or water retention, despite reduced blood pressure and vasodilation, or direct effects of PPARγ agonists on heart metabolism. In support of this latter hypothesis, Son and colleagues[38] reported that cardiac transgenic expression of PPARγ led to cardiac dysfunction associated with the induction of FA oxidation genes, the accumulation of glycogen and lipids in mouse myocardium, and the disruption of mitochondrial structure. Cardiac ceramide levels were also elevated modestly. The effects of pharmacologic PPARγ agonists on heart metabolism and function in animal models are mixed. These drugs induce glucose transporters 1 and 4 and increase glucose uptake in cultured rat cardiomyocytes and in the heart of diabetic animal models.[51–54] In ZDF rats, the administration of thiazolidinedione reduced cardiac accumulation of ceramide.[36] Similarly, PPARγ agonist treatment of LpL^{GPI} mice reduced heart dysfunction and, in this model, was shown to divert circulating lipids to greater adipose and reduced heart uptake.[55] So the use of agonists in vivo is likely to reflect the level of cardiac PPARγ expression and the importance of the induction of PPARγ in adipose.

Another possible action of PPARγ agonists is the induction of ceramide synthesis. In one study, the administration of PPARγ agonists elevated SPT activity and intracellular levels of palmitate, whereas the activation of PPARγ did not change the activities of sphingomyelinase and ceramidase.[56] Thus, the accumulation of cardiac ceramide is via the activation of de novo ceramide biosynthesis. A modest increase in the expression of SPT

protein or mRNA did not match the elevated activity, suggesting SPT activity is regulated by posttranscriptional modification. It has been widely accepted that the increased availability of palmitate, a substrate of SPT reaction, increases SPT activity and expression.[57,58] Holland and colleagues[59] found that palmitate activates a toll-like receptor pathway and increases intracellular levels of ceramide by activating de novo ceramide synthesis. These findings indicate that palmitate is not only acting as a substrate for SPT-mediated de novo ceramide synthesis but acting as an activator of the rate-limiting enzyme in this biosynthetic pathway. Collectively, PPARs regulate myocardial sphingolipid metabolism mainly via de novo synthesis (see Fig. 2).

CARDIOPROTECTIVE EFFECTS OF S1P

S1P might protect the heart from ischemiareperfusion injury. S1P is synthesized intracellularly and exerts its function by binding to specific plasma membrane G-protein coupled receptors ($S1P_{1\sim5}$). Intracellular S1P has a proliferative role in cells and is also secreted to the extracellular space (insideout hypothesis). Secreted S1P binds to the S1P receptors on plasma membrane and elicits its regulatory function. When S1P binds to the S1P receptors, phosphatidylinositol 4-kinase is activated and its downstream targets, AKT and glycogen synthase kinase 3β, are phosphorylated and activate these signaling pathways. Of the 5 subtypes of the S1P receptors, cardiomyocytes express $S1P_1$, $S1P_2$, and $S1P_3$.[60] The incubation of rat neonatal cardiomyocytes with S1P or GM1, a ganglioside that induces sphingosine kinase 1 and elevates endogenous S1P production, prevents hypoxia-induced cell death.[61] Cardioprotection by S1P and GM1 during ischemia/reperfusion injury was confirmed in vivo.[62] The infusion of GM1 reduces cardiac injury through PKCε but S1P exerts cardioprotective effects through the PKCε-independent pathway. Later, it was found that the inactivation of the interaction of G protein and G protein coupled receptor by pertussis toxin or $S1P_{1–3}$ antagonist removed GM-1 mediated cardioprotection.[63] These findings suggest that endogenous S1P is transported from cardiomyocytes and exerts its cardioprotective effects by binding to S1P receptors on the membrane surface. Consistent with these findings, ischemia suppressed sphingosine kinase activity and reduced S1P levels in the heart; these effects were maintained during reperfusion.[64] Sphk1-deficient hearts were susceptible to ischemia/reperfusion injury, and adenoviral Sphk1 gene transfer induced cardioprotection and prevented ischemic heart failure.[65] Although S1P is one of the major lipid components in high-density lipoprotein (HDL), it has been reported that S1P action is independent of HDL.[66]

Of the S1P receptors, $S1P_1$ may be most important for cardioprotection. $S1P_1$-specific agonists protected adult mouse cardiomyocytes from hypoxia.[67] In contrast, VPC23019 and FTY720, the synthetic antagonists of $S1P_1$, prevented cardioprotection elicited by S1P. However, other groups suggested that $S1P_2$ and $S1P_3$ also exert S1P-mediated cardioprotective action. $S1P_{2/3}$ double knockout mice have increased myocardial infarct size during ischemia/reperfusion injury,[68] suggesting the overlapping role of S1P receptor isoforms. In addition, $S1P_3$ deficiency abolished S1P-mediated cardioprotection, and the pharmacologic inhibition of nitric oxide synthase also caused the disappearance of cardioprotective effects, suggesting an important role of this pathway.[69] Recently, it was reported that cardiac-specific $S1P_1$-deficient mice are vulnerable to ischemia/reperfusion

injury to the same degree as the wild-type mice.[70] These conflicting data may result from the experimental model systems: $S1P_1$ in cardiomyocytes and $S1P_{2/3}$ in animal hearts. Therefore, the roles of S1P in cardioprotection of nonischemic heart failure deserve further study.

CLINICAL IMPLICATION OF SPHINGOLIPID METABOLISM IN HEART FAILURE

Animal experiments suggest that ceramide is implicated in pathogenesis of cardiac dysfunction associated with obesity and diabetes. However, whether ceramide is relevant to cardiac failure in humans is unclear. Barranowski and colleagues[71] found that the enzymes in sphingolipid biosynthesis were upregulated in the right atrial appendage of overweight patients; the tissue was obtained during coronary bypass graft surgery. These genes include Sptlc1/2, Sphk1, alkaline/acid/neutral ceramidases, and neutral ceramidases. When diabetes was present in the obese patients, the expression of some genes was reduced but higher than lean subjects. They also found increased DNA fragmentation in the hearts of obese nondiabetic patients and it was increased further in obese diabetic hearts. Surprisingly, the elevation of cardiac ceramide was not found. The reason for these conflicting data is likely to be coordinated regulation of ceramide synthesis and degradation. These findings suggested that obesity and type 2 diabetes do not induce ceramide accumulation in the human heart or at least in the atrium.

SUMMARY

All tissues, including the heart, need essential lipids. With obesity and diabetes, hearts are likely to have metabolic imbalance and lipid accumulation. A flurry of recent investigations using animal models suggests that ceramide plays important roles in the pathogenesis of heart failure. In contrast, S1P is implicated in cardioprotection during ischemia/reperfusion injury. Further studies will need to first define the lipid abnormalities that occur in human hearts at various stages of failure, and the associated gene/enzyme alterations associated with heart failure from a variety of causes must be determined. Only then can a reasonable plan be devised to alter sphingolipid metabolism as a method to prevent or treat patients.

Acknowledgments

There is no applicable funding support.

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KEY POINTS

- Sphingolipids, elevated in obesity and type 2 diabetes, may cause cardiomyopathy.
- Ceramide alters cardiac energy metabolism and can cause cardiomyocyte apoptosis.
- Sphingosine 1-phosphate protects against ischemia/reperfusion injury.
- Modulation of sphingolipid metabolism in the heart may become a therapy for cardiac disease in patients with obesity and diabetes.

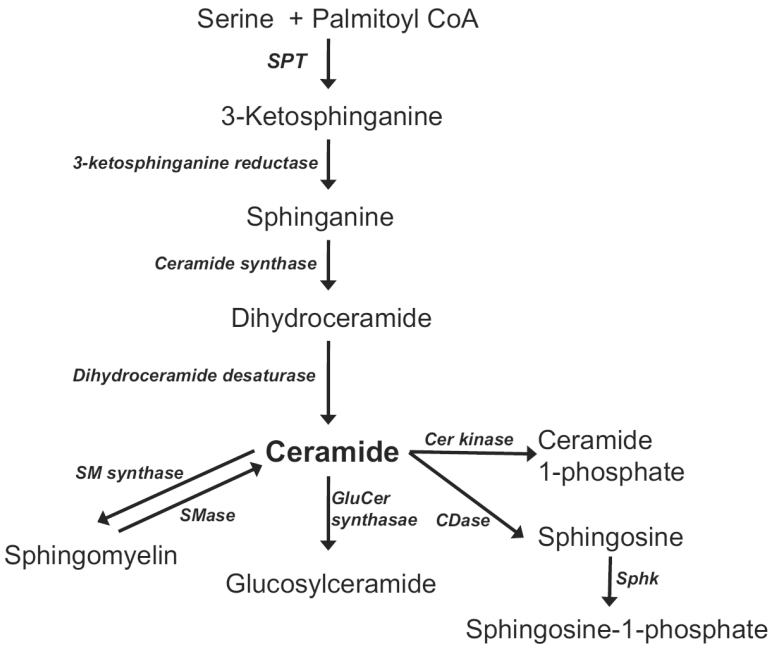

Fig. 1.

Sphingolipid biosynthetic pathway and metabolism. CDase, ceramidase; Cer, ceramide; CoA, coenzyme A; GlucCer, glucosylceramide; SM, sphingomyelin; SMase, sphingomyelinase; Sphk, sphingosine kinase; SPT, serine palmitoyltransferase.

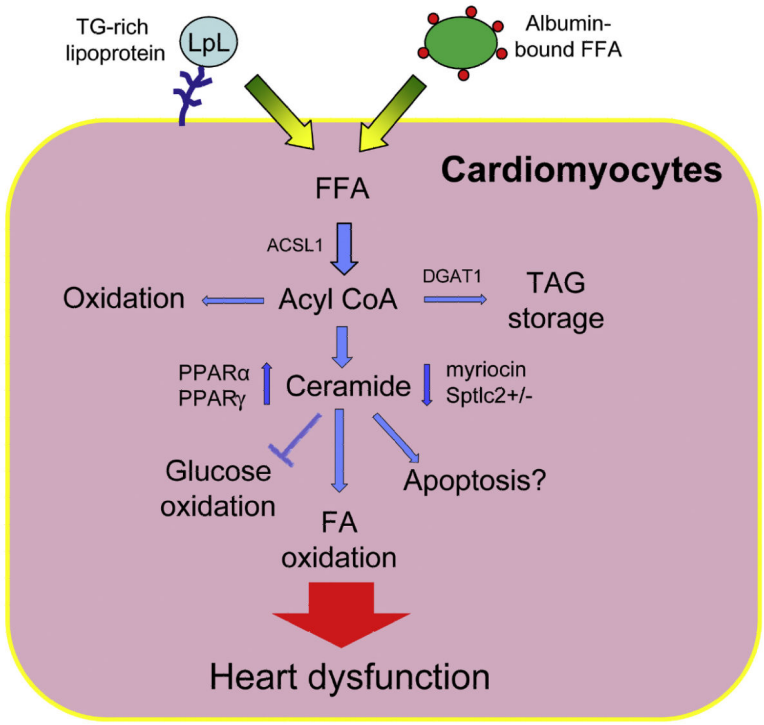

Fig. 2.

Lipotoxicity is created by an imbalanced substrate oxidation in heart. Fatty acids are taken up by heart via hydrolysis of triglyceride within lipoproteins by LpL action or transport of albumin-bound free fatty acids. In cardiomyocytes, the free fatty acids are esterified to coenzyme A (CoA) and used for energy or stored as lipid droplets. When lipid uptake exceeds oxidation, more acyl CoAs are shunted to ceramide biosynthesis. Accumulation of ceramide alters the balance of glucose/fatty acid oxidation and leads to cardiac dysfunction. Agonism of PPARα or γ elevates cardiac ceramide levels and leads to cardiac dysfunction. In contrast, myriocin and heterozygous deletion of Sptlc2 prevent cardiac dysfunction. FA, fatty acid; TAG, triacylglycerol; TG, triglyceride.

Table 1

Cardiac ceramide, cardiomyocytes apoptosis, and cardiac function in animal models of lipotoxic cardiomyopathy, diabetes, and obesity

Animal Models	References	Cardiac Ceramide Changes	Cardiac Function
MHC-ACS1 mice	Chiu et al[32]	Increased	Decreased
LpL^{GPI} mice	Yagyu et al[34]	Increased	Decreased
MHC-PPARγ mice	Son et al[38]	Increased	Decreased
Akita Ins2 (WT/C96Y) mice	Basu et al[39]	Increased	Decreased
Zucker diabetic fatty rats	Zhou et al[36]	Increased	Decreased
ob/ob mice	Torre-Villalvazo et al[44]	Increased	No change
Rats fed a high-fat diet	Torre-Villalvazo et al[44]	Increased	ND

Abbreviations: LpL^{GPI}, cardiomyocyte-specific overexpression of glycosylphosphatidylinositol-anchored lipoprotein lipase; MHC-ACS1, cardiomyocyte-specific overexpression of long chain acyl coenzyme A synthetase 1; MHC-PPARγ, cardiomyocyte-specific overexpression of peroxisome proliferator-activated receptor γ; ND, not determined.