Lipotoxicity in cardiac and skeletal muscle

Jennifer L. Peura and Jean E. Schaffer
Center for Cardiovascular Research, Division of Cardiology, Department of Internal Medicine, Washington University School of Medicine, St Louis, Missouri, USA

Correspondence: Jean Schaffer, Box 8086, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, Missouri, 63110, USA.
E-mail: jschaff@wustl.edu

Abstract

Lipotoxicity is defined as the untoward consequences of the accumulation of excess lipid in non-adipose tissue. Fatty acids are an important substrate for myocyte metabolism, yet mismatch of cellular uptake and utilization results in lipid accumulation that is clearly detrimental. Within the myocyte, lipotoxicity can lead to cellular dysfunction, resulting in defective contraction or relaxation or both, alterations in key signaling pathways, and apoptotic cell death. In this review we discuss the significance of myocyte lipotoxicity in human disease and present insights into the pathophysiology gained from transgenic animal models of toxic lipid overload in skeletal and cardiac muscle.
Heart Metab. 2006;30:4–6.

Keywords: Lipotoxicity, cardiomyopathy, myopathy, fatty acids, triglycerides

Skeletal and cardiac muscle have limited capacity for de novo fatty acid synthesis and thus rely on uptake of fatty acids from the circulation, given their high metabolic utilization of this substrate. Free fatty acids (FFAs) can be released from adipose stores and are transported to the heart through the circulation, bound to albumin. Fatty acids are also supplied to the heart and skeletal muscle as chylomicron and very-low-density lipoprotein particles. Local hydrolysis of triglyceride from these particles by lipoprotein lipase* tethered to the endothelium provides FFAs in close proximity to the target tissues that use this metabolic substrate. The findings of recent studies suggest that the latter mechanism accounts for the majority of fatty acids transported to the heart for metabolism [1]. Several proteins have been shown to facilitate the subsequent import of FFA substrates across the plasma membrane of myocytes, and these proteins may serve as molecular targets for regulation of the use of substrate in response to hormonal and metabolic cues [2].

Lipotoxicity in the myocyte occurs in the setting of increased substrate availability or decreased substrate utilization, or both. In humans, disease states associated with pathologic concentrations of serum lipids provide increased substrate to muscle tissues. Increased fasting and postprandial concentrations of FFAs and triglyceride are observed in obesity and metabolic syndrome – highly prevalent disorders characterized by excess adiposity. Dyslipidemia is also a central feature of lipodystrophies in which affected individuals have congenital absence or acquired loss of adipose tissue. High serum concentrations of FFA and triglyceride result from dysregulated adipose tissue function in the case of obesity and the metabolic syndrome, and from lack of appropriate storage depot for these lipids in the case of lipodystrophies. In these disorders, excess FFA is taken up into non-adipose tissues such as the heart and skeletal muscle, resulting in the accumulation of triglyceride. In contrast, congenital defects in fatty acid oxidation are characterized by the inability of target tissues to utilize FFAs. This sets the stage for massive accumulation of unmetabolized substrate in the heart and skeletal muscle – tissues that normally take up this substrate for the generation of ATP.

The accumulation of lipid in skeletal and cardiac muscle may lead to clinical manifestations of muscle dysfunction. First, epidemiological studies have shown that the incidence of heart failure is increased

in obese individuals and in patients with diabetes mellitus [3]. Impaired diastolic function and structural abnormalities are early evidence for cardiomyopathy that can be detected noninvasively in obese and diabetic individuals, using transthoracic echocardiography [4,5]. These may progress over time to result in both diastolic and systolic dysfunction [6]. There have been no systematic studies to examine the contributions of specific metabolic abnormalities in cardiac dysfunction in these disorders, but observations of cardiac accumulation of triglyceride [7] and cardiomyocyte apoptosis in pathological specimens [8] suggest a causal link. Secondly, individuals with inborn errors in fatty acid oxidation have intracellular accumulation of lipids in cardiac and skeletal muscle, and are known to develop skeletal myopathy, heart failure, and arrhythmic sudden cardiac death [9,10]. Thirdly, obese diabetic and prediabetic individuals, in addition to those with lipodystrophy, have intramyocellular triglyceride accumulation that is associated with insulin resistance [11].

Animal models of obesity and diabetes provide insights into mechanisms of the toxic consequences of lipid overload. Perhaps the best characterized with respect to lipotoxicity in muscle, are Zucker Diabetic Fatty rats, which have genetic unresponsiveness to leptin*, leading to increased serum lipid concentrations, morbid obesity, and diabetes [12]. On a standard diet, these rodents have increased cardiac uptake and esterification of FFA, decreased fatty acid oxidation, and evidence of cardiomyocyte apoptosis and fibrosis [13]. These biochemical and histological changes are associated with impaired contractility and relaxation, consistent with endstage cardiomyopathy. Another leptin-resistant model that has been extensively characterized is the obese diabetic db/db mouse*, in which an early phase of increased fatty acid oxidation precedes the development of contractile dysfunction [14,15]. In a third leptin-unresponsive model, the ob/ob mouse*, the accumulation of lipid is accompanied by diastolic dysfunction [16]. Together, these models provide experimental systems in which a number of groups have effectively examined changes in cardiac metabolism, structure, and function that accompany extreme obesity, insulin resistance and diabetes.

Transgenic models with tissue-restricted increases in lipid uptake, in the absence of systemic metabolic disturbances, have provided independent evidence for a central role of altered lipid homeostasis in the genesis of myopathy. In mice with skeletal muscle overexpression of lipoprotein lipase, increased tissue uptake of FFAs leads to myofibrillar degeneration, mitochondrial and peroxisome proliferation, and insulin resistance [17,18]. The findings of a number of animal studies suggest that accumulation of fatty acid metabolites (eg, triglycerides, diacylglycerols, acyl coenzyme As [CoA]) activates a serine/threonine kinase* cascade that phosphorylates insulin receptor substrates in such a way that they fail to activate glucose transport in response to insulin [19]. Mice with cardiac overexpression of long-chain acyl CoA synthetase (MHC-ACS)*, peroxisome proliferator activated receptor alpha (MHC-PPARα)* or a glycophosphatidylinositol-linked lipoprotein lipase* (hLpL^{GPI}) also demonstrate increased cardiac uptake of FFA substrates. Each of these models develops dilated cardiomyopathy characterized by systolic dysfunction with accompanying diastolic dysfunction [20–22]. Different lipid species accumulate in the different models (triglyceride in the cases of MHC-ACS and MHC-PPARα, compared with cholesterol in hLpL^{GPI}), but several show evidence of oxidative stress [23,26], suggesting a common lipid stress response pathway. Apoptosis is observed in MHC-ACS and hLpL^{GPI} hearts, consistent with the inexorable progression of heart failure in these models. A fourth transgenic model with cardiac restricted overexpression of the fatty acid transport protein 1 (MHC-FATP1) demonstrates a contrasting phenotype. In this model, increased uptake and metabolism of FFAs lead to diastolic dysfunction and electrophysiological disturbances [24]. These models represent the spectrum of cardiac dysfunction in obesity and diabetes, and they serve as powerful tools with which to study the lipotoxic events that contribute to early (primarily diastolic) and late (both diastolic and systolic) lipotoxic cardiomyopathy.

These transgenic models have also been used to evaluate novel therapeutic approaches to cardiac lipotoxicity. Treatment of the obese Zucker Diabetic Fatty rats with troglitazone was found to reduce cardiac triglyceride, and to prevent apoptosis and loss of function [12]. In the MHC-PPARα model, myocyte lipotoxicity was observed when mice were fed a normal diet, was exacerbated by a diet enriched in long-chain triglycerides, and was improved by a diet enriched in medium-chain triglycerides. Reversibility of the phenotype in these mice is consistent with the lack of evidence for cardiomyocyte cell death [23]. Treatment of MHC-ACS mice with an adenovirus encoding the hormone leptin effected a marked improvement in cardiac triglyceride accumulation and function [25]. These three examples suggest that measures which divert lipid to adipose stores, decrease overall serum lipid concentrations, or increase myocyte β-oxidation will be beneficial in lipotoxic myopathies in humans.

Summary

Human patients with disease states associated with pathologic concentrations of serum lipids suffer from

myocyte dysfunction, cardiomyopathy, and early cardiovascular death. The findings from studies in transgenic and genetic animal models suggest that changes in cardiac lipid metabolism underlie the changes in heart structure and function that accompany extreme obesity, insulin resistance, and diabetes. Evidence of oxidative stress and apoptotic cell death suggests a common metabolic stress pathway. Continued investigation may lead to novel therapeutic targets that could significantly reduce the morbidity and mortality associated with obesity and diabetes.

Acknowledgment

This work was supported by a grant from the NIH (DK064989 to J.E.S.). ■

* See glossary for definition of these terms.

REFERENCES

1. Augustus AS, Kako Y, Yagyu H, Goldberg IJ. Routes of FA delivery to cardiac muscle: modulation of lipoprotein lipolysis alters uptake of TG-derived FA. *Am J Physiol Endocrinol Metab*. 2003;284:E331–E339.
2. Schaffer JE. Fatty acid transport: the roads taken. *Am J Physiol Endocrinol Metab*. 2002;282:E239–E246.
3. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313.
4. Perez JE, McGill JB, Santiago JV, et al. Abnormal myocardial acoustic properties in diabetic patients and their correlation with the severity of disease. *J Am Coll Cardiol*. 1992;19:1154–1162.
5. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol*. 2004;93:870–875.
6. Zarich SW, Nesto RW. Diabetic cardiomyopathy. *Am Heart J*. 1989;118:1000–1012.
7. Alavaikko M, Elfving R, Hirvonen J, Jarvi J. Triglycerides, cholesterol, and phospholipids in normal heart papillary muscle and in patients suffering from diabetes, cholelithiasis, hypertension, and coronary atheroma. *J Clin Pathol*. 1973;26:285–293.
8. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. *Circ Res*. 2000;87:1123–1132.
9. Galloway JH, Cartwright IJ, Bennett MJ. Abnormal myocardial lipid composition in an infant with type II glutaric aciduria. *J Lipid Res*. 1987;28:279–284.
10. Kelly DP, Strauss AW. Inherited cardiomyopathies. *N Engl J Med*. 1994;330:913–919.
11. Shulman GI. Unraveling the cellular mechanism of insulin resistance in humans: new insights from magnetic resonance spectroscopy. *Physiology (Bethesda)*. 2004;19:183–190.
12. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A*. 2000;97:1784–1789.
13. Young ME, Guthrie PH, Razeghi P, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes*. 2002;51:2587–2595.
14. Aasum E, Belke DD, Severson DL, et al. Cardiac function and metabolism in Type 2 diabetic mice after treatment with BM 17.0744, a novel PPAR-alpha activator. *Am J Physiol Heart Circ Physiol*. 2002;283:H949–H957.
15. Belke DD, Larsen TS, Gibbs EM, Severson DL. Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. *Am J Physiol Endocrinol Metab*. 2000;279:E1104–E1113.
16. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology*. 2003;144:3483–3490.
17. Levak-Frank S, Radner H, Walsh A, et al. Muscle-specific overexpression of lipoprotein lipase causes a severe myopathy characterized by proliferation of mitochondria and peroxisomes in transgenic mice. *J Clin Invest*. 1995;96:976–986.
18. Kim JK, Fillmore JJ, Chen Y, et al. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proc Natl Acad Sci U S A*. 2001;98:7522–7527.
19. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest*. 2000;106:171–176.
20. Chiu HC, Kovacs A, Ford DA, et al. A novel mouse model of lipotoxic cardiomyopathy. *J Clin Invest*. 2001;107:813–822.
21. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest*. 2002;109:121–130.
22. Yagyu H, Chen G, Yokoyama M, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. *J Clin Invest*. 2003;111:419–426.
23. Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U S A*. 2003;100:1226–1231.
24. Chiu HC, Kovacs A, Blanton RM, et al. Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy. *Circ Res*. 2005;96:225–233.
25. Lee Y, Naseem RH, Duplomb L, et al. Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. *Proc Natl Acad Sci U S A*. 2004;101:13624–13629.
26. Borradaile NM, Buhman KK, Listenberger LL, et al. A critical role for eukaryotic elongation factor 1 A-1 in lipotoxic cell death. Mol Biol Cell 2006. In press.