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Biochemical and Biophysical Research Communications 344 (2006) 446–452
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α-Lipoic acid prevents lipotoxic cardiomyopathy in acyl CoA-synthase transgenic mice

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Received 13 February 2006
Available online 20 March 2006

Abstract

α-Lipoic acid (α-LA) mimics the hypothalamic actions of leptin on food intake, energy expenditure, and activation of AMP-activated protein kinase (AMPK). To determine if, like leptin, α-LA protects against cardiac lipotoxicity, α-LA was fed to transgenic mice with cardiomyocyte-specific overexpression of the acyl CoA synthase (ACS) gene. Untreated ACS-transgenic mice died prematurely with increased triacylglycerol content and dilated cardiomyopathy, impaired systolic function and myofiber disorganization, apoptosis, and interstitial fibrosis on microscopy. In α-LA-treated ACS-transgenic mice heart size, echocardiogram and TG content were normal. Plasma TG fell 50%, hepatic-activated phospho-AMPK rose 6-fold, sterol regulatory element-binding protein-1c declined 50%, and peroxisome proliferator-activated receptor-γ cofactor-1α mRNA rose 4-fold. Since food restriction did not prevent lipotoxicity, we conclude that α-LA treatment, like hyperleptinemia, protects the heart of ACS-transgenic mice from lipotoxicity.
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Keywords: Leptinomimetic; Lipotoxic cardiomyopathy; α-Lipoic acid; Metabolic syndrome; Fatty heart

Lack of leptin action in rodents, whether due to a deficiency of the hormone [1] or to a loss-of-function mutation of its receptors [2], is accompanied by ectopic deposition of lipids in various organs, leading to cellular dysfunction (lipotoxicity) and apoptosis [3,4]. The cluster of associated clinical disorders includes hyperlipidemia, insulin resistance, type 2 diabetes, fatty liver, and fatty heart, abnormalities that are also present in the metabolic syndrome of humans. Despite considerable evidence suggesting that this disease cluster is secondary to ectopic lipid overload resulting from lack of anti-lipotoxic action of hyperleptinemia in the various affected organs, this has been difficult to prove because of the complex relationships between the various organ malfunctions.

Chiu et al. [5] have created a model of single organ lipotoxicity by transgenic cardiomyocyte-specific overexpression of the ACS gene in otherwise normal mice. Unlike leptin-deficient or leptin-unresponsive rodents, these ACS-transgenic mice are nonobese and metabolically normal; their severe lipotoxic cardiomyopathy is not caused by lack of leptin or by resistance to leptin or insulin. Rather it is the result of a single abnormality, excessive import of fatty acids into cardiomyocytes. Nevertheless, the mice develop precisely the same echocardiographic evidence of left ventricular dysfunction, biochemical and electron microscopic evidence of excessive lipid deposition in cardiomyocytes, and histologic evidence of myofiber disorganization, interstitial fibrosis, and apoptosis of cardiomyocytes as in

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0006-291X/$ - see front matter Published by Elsevier Inc.
doi:10.1016/j.bbrc.2006.03.062

congenitally unleptinized rodents [6]. Like them, they die prematurely with dilated cardiomyopathy. Consequently the ACS-transgenic mice provide a simple in vivo model in which to test the role of leptin in preventing lipotoxicity in a single organ.

Previously we observed that the cardiac lipotoxicity of ACS-transgenic mice could be completely prevented by early induction of hyperleptinemia [7]. The mechanism of the protection involved a reduction in the elevated cardiac lipid content, the result of a profound lowering of plasma triglycerides (TG) and free fatty acids (FFA), together with activation of AMPK in the heart. The hypolipidemic action of leptin would reduce lipid delivery to the heart, while AMPK-activation would presumably enhance myocardial oxidation of fatty acids [8].

Thus far, the concept that metabolic syndrome in human is the same as lipotoxicity in rodents has been controversial. Nevertheless, there is now evidence in humans of a relationship between body mass index and cardiomyocyte lipid content, and an adverse effect on cardiac function [9–11]. The high prevalence of overweight in the US population raises the possibility that millions of Americans now suffer from fatty heart, a relatively unrecognized cardiac complication of obesity. It would therefore seem prudent to devise pharmacologic strategies for prevention of lipotoxic cardiomyopathy. Since leptin therapy might not be the strategy of choice in obese patients, who tend to be hyperleptinemic and leptin-resistant, a lipopenic agent, preferably orally administered, that is independent of leptin receptor-mediated signaling, would be desirable.

Kim et al. [12] have recently reported that α-LA, a cofactor in the pyruvate dehydrogenase complex, exerts certain actions that mimic those of leptin, including reduced food intake and increased energy expenditure. α-LA, which is widely available as an over-the-counter anti-oxidant, has been shown to protect against liver reperfusion injury [13] and to lower TG accumulation in skeletal muscle and pancreatic islets of Otsuka Long–Evans Tokushima Fatty (OLETF) rats [14]. Taken together, these reports suggest the possibility that α-LA has leptinomimetic actions independent of the leptin receptor. Therefore, we compared its anti-lipotoxic efficacy with that of leptin in the same ACS-transgenic mouse model of severe cardiac-specific lipotoxicity. We found similar antilipotoxic efficacy, despite certain differences in mechanism.

Materials and methods

Animals. Breeding pairs of MHCα-ACS-transgenic mice were provided by one of us (JES). Mice were bred, genotyped, and housed in individual cages with a constant temperature and 12 h of light alternating with 12 h of darkness. All mice were fed standard chow ad libitum. At 4 weeks of age, 6 of the ACS-transgenic mice were fed an ad lib diet of powdered standard chow (Teklad 4% mouse/rat diet, Teklad, Madison, WI) with 1% α-LA (w/w, Sigma, St. Louis, MO), while 6 other mice were fed ad lib a standard powered diet alone for 6 weeks. A third group was fed the standard diet alone but in restricted quantities that were less than those consumed by the α-LA-fed mice.

Plasma measurements. Plasma TG were measured by the glycerol phosphate oxidase-Trinder triglyceride kit (Sigma, St. Louis, MO). Plasma FFA were measured using the Wako NEFA kit (Wako Chemical USA, Richmond, VA). Plasma leptin was assayed using the Linco leptin assay kit (Linco Research, St. Charles, MO).

Triglyceride content of heart. Mice were anesthetized with a mixture of xylazine and ketamine–HCl. After sacrifice, hearts were rinsed with phosphate-buffered saline (pH 7.4), dissected, and placed in liquid nitrogen immediately. Total lipids from hearts were extracted and dried under N_2 gas. Cardiac TG content was assayed as previously described [15].

Echocardiography. Longitudinal noninvasive transthoracic echocardiograms were performed in unsedated mice 6 weeks after receiving either standard powder diet containing 1% α-LA acid or the chow alone. Transthoracic echocardiographic examination was performed using a General Electric Vivid7 Pro equipped with a 12 mHz transducer. M-mode and two-dimensional echo images were obtained in the parasternal long- and short-axis views. Fractional shortening was calculated from M-mode images as the left ventricular end-diastolic dimension (LVEDD) minus the left ventricular end-systolic dimension (LVESD) divided by LVEDD [7].

Electron microscopy of myocardium. Cardiac muscle fragments were fixed with 2% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4). After rinsing in phosphate buffer, postfixation in 1% osmic acid for 1 h at the room temperature, and en bloc staining with uranyl acetate, specimens were processed for epoxy embedding (Polybed R812;Fluka). Thin sections were stained with uranyl acetate and lead citrate, and photographed in a JEOL 1200 EX electron microscope (JEOL USA, Peabody, MA).

Histology. Hearts were perfused with paraformaldehyde, fixed overnight, and embedded in paraffin. Paraffin embedded sections were stained with hematoxylin and eosin (H and E) or Masson's trichrome for collagen.

Quantitative real-time RT-PCR. Total RNA was extracted from hearts and livers by the Trizol isolation method according to the manufacturer's protocol (Life Technologies, Gaithersburg, MD). All reactions were done in triplicate. The real-time amount of all mRNA was calculated using standard curve method. 18S mRNA was used as the invariant control for all studies. Primer sequences of genes used for quantification of mRNA by real-time PCR are shown in Table 1.

Immunoblotting. Hearts were lysed in a RIPA buffer with 10 μg/ml leupeptin and 10 μg/ml aprotinin, and processed for immunoblotting with anti-phospho-AMPK (Thr-172) (Cell Signaling Technology, Beverly, MA).

Results

Effects of α-LA treatment on clinical parameters

Four-week-old transgenic mice with high-level cardiac expression of ACS received either chow containing 1% α-LA, or chow alone, for a period of 6 weeks. Food intake of treated mice during the 6-week period averaged significantly less than in untreated control transgenics, as did body weight at the end of 6 weeks (Fig. 1) ($p < 0.001$; $p < 0.001$) (Table 2). Plasma triglyceride levels were significantly lower ($p < 0.002$) in the treated group after 6 weeks of treatment (Table 2), but FFA were the same in all groups. Plasma glucose and insulin levels were unchanged, but leptin levels were significantly lower in α-LA-treated mice, presumably because of the weight loss (Table 2).

Because of the reduced food intake in the α-LA-treated mice, we restricted the chow diet of a group of ACS-transgenic mice to match that of the α-LA-treated mice and compared the foregoing parameters. Body weight declined by 19%, but neither plasma glucose, TG, insulin nor leptin was significantly different (Table 2).

Table 1
Primers used for real-time PCR

Name	GenBank #	Forward primer	Reverse primer
ACC1	AF374169	CCCAGCAGAATAAAGCTACTTTGG	TCCTTTTGTGCAACTAGGAACGT
ACC2	AF290178	AACTCCCTGCCAAGCTCATG	GGAGGGCCAGGTGTCATTG
ACO	NM_017340	GGCCAACTATGGTGGACATCA	ACCAATCTGGCTGCACGAA
AMPKα-2	U11494	CAGCCGTGCCATCCAAA	GACCGACCCAATCCCAATG
AMPK-B	AF108215	AGGACACGGGCATCTCTTGT	GCATAGAGGTGGTTCAGCATGA
AP2	NM_024406	GCGTGGAATTCGATGAAATCA	CCCGCCATCTAGGGTTATGA
CPT-1	NM_013495	CCTGGGCATGATTGCAAAG	ACGCCACTCACGATGTTCTTC
FAS	XM_126624	CCTGGATAGCATTCCGAACCT	AGCACATCTCGAAGGCTACACA
GPAT	M77003	ATCTTCAGAACAGCAAAATCGAAA	CAGCGGAAAACTCCAAATCC
PPARα	X57638	CTGCAGAGCAACCATCCAGAT	GCCGAAGGTCCACCATTTT
PPARγ	AF156666	TCAGAGGGACAAGGATTCATGA	CACCAAAGGGCTTCCGCAGGCT
PPARγ-1	NM_005037	CACGGAACACGTGCAGCTA	GGAGCGGGTGAAGACTCATG
SPT	NM_009269	CCTCCAAGCATCAGGGTTGT	GGATGCAGCCCTCTGTAGCT
PGC-1α	AB025784	GCGCCAGCCAACACTCA	TGGGTGTGGTTTGCATGGT
SREBP-1c	L16995	GCAACACTGGCAGAGATCTACGT	TGGCGGGCACTACTTAGGAA
SCD-1	NM_009127	CCAGAATGACGTGTACGAATGG	GCGTGTGTTTCTGAGAACTTGTG
SCD-4	NM_183216	GGCTTTCCAGAATGACGTGTATG	GCGTGTGTTTCTGAGAACTTGTG
Bax	NM_007528	CCAAGAAGCTGAGCGAGTGTC	CCTCTGCAGCTCCATATTGCT
Bcl2	NM_009741	TGGGATGCCTTTGTGGAACT	GAGACAGCCAGGAGAAATCAAAC
UCP-2	NM_011672	TGTTGATGTGGTCAAGACGAGAT	CATGGTAAGGGCACAGTGA

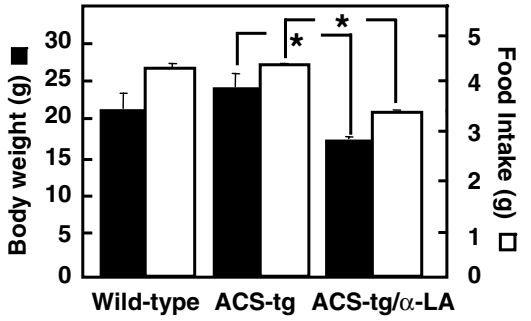

Fig. 1. Comparison of mean (±SEM) food intake □ and body weight ■ in untreated wild-type, untreated ACS-transgenic or α-LA-treated ACS-transgenic mice (ACS-tg/α-LA). *$p < 0.001$ represents changes in body weight and food intake.

Effects of α-LA on the cardiac phenotype of ACS-transgenic mice

Severe dilated cardiomyopathy was grossly apparent in untreated ACS-transgenic control mice (Fig. 2A). There was marked hypertrophy and dilitation of all chambers, and transthoracic echocardiograms in untreated ACS-transgenic mice revealed markedly impaired systolic cardiac function. Fractional shortening on M-mode images was depressed (Fig. 2B) and the anterior and posterior walls of the left ventricle were thickened. The heart weight was twice normal and the cardiac TG content was 1.7-fold above the wild-type group (Fig. 2D). In striking contrast, the hearts of α-LA-treated ACS-transgenic mice were normal in size, appearance, and weight (Fig. 2C). Fractional shortening was normal, as was their cardiac TG. The diet-restricted ACS-transgenic mice showed a 23% reduction in heart TG ($p < 0.01$) but it remained above that of the α-LA-treated group (Fig. 2A). There was no improvement on echocardiography in fractional shortening.

Table 2
Plasma TG (mg/100 ml) and FFA (mM), glucose (mg/dl), insulin (ng/ml), and leptin (ng/ml) in ACS-transgenic mice before and 4 days and 42 days after treatment with α-lipoic acid and in age-matched, untreated wild-type controls

Diet	Measurement	Baseline	4 days	42 days
Wild-type				
Ad lib	TG	98 ± 7.3	95 ± 9.0	99 ± 8.51
	FFA	0.65 ± 0.12	0.62 ± 0.01	0.53 ± 0.03
	Glucose	100 ± 7.5	107 ± 5.9	119 ± 6.6
	Leptin	0.90 ± 0.09	1.00 ± 0.07	0.90 ± 0.03
	Insulin	0.62 ± 0.02	0.70 ± 0.04	0.75 ± 0.05
ACS-transgenic				
Ad lib	TG	105 ± 10.5	100 ± 11.2	125 ± 16.5
	FFA	0.60 ± 0.15	0.60 ± 0.03	0.58 ± 0.03
	Glucose	120 ± 5.75	110 ± 9.90	127 ± 9.85
	Leptin	1.00 ± 0.07	1.00 ± 0.07	1.08 ± 0.04
	Insulin	0.72 ± 0.02	0.75 ± 0.07	0.70 ± 0.05
Ad lib + α-LA	TG	102 ± 6.5	98 ± 9.5	64 ± 8.9*
	FFA	0.62 ± 0.05	0.59 ± 0.03	0.46 ± 0.05
	Glucose	100 ± 8.5	95 ± 10.2	115 ± 7.22
	Leptin	0.98 ± 0.09	0.88 ± 0.13	0.68 ± 0.05**
	Insulin	0.70 ± 0.02	0.66 ± 0.11	0.58 ± 0.05
Diet-matched to α-LA	TG	100 ± 9.6	97 ± 9.5	95 ± 2.6
	FFA	0.60 ± 0.05	0.62 ± 0.04	0.61 ± 0.05
	Glucose	110 ± 11.0	101 ± 9.5	110 ± 8.6
	Leptin	0.95 ± 0.05	0.90 ± 0.15	0.80 ± 0.03
	Insulin	0.70 ± 0.03	0.68 ± 0.05	0.60 ± 0.04

* $p < 0.002$ vs. baseline.
** $p < 0.02$ vs. baseline.

Effects of α-LA treatment on cardiac histology

Hematoxylin and eosin staining of hearts of control ACS-transgenic mice revealed myofiber disorganization, enlarged cardiomyocytes, and interstititial fibrosis

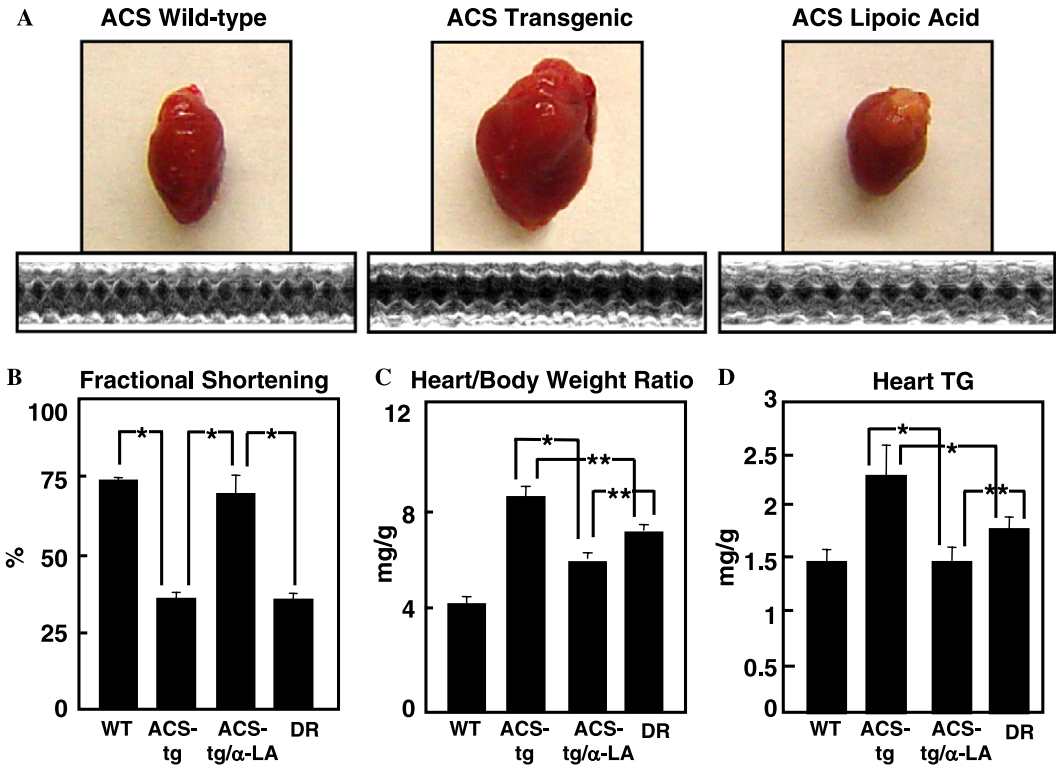

Fig. 2. Comparison of cardiac parameters in untreated wild-type, untreated ACS-transgenic and α-LA-treated ACS-transgenic mice (ACS-tg/α-LA). (A) Gross appearance of a representative heart from each group together with the corresponding transthoracic echocardiogram. There is marked enlargement of the untreated ACS-transgenic heart and marked impairment of systolic function on the echocardiogram. The heart of the α-LA-treated mouse appeared grossly normal and the echocardiogram was within normal limits. (B) Comparison of mean percent fractional shortening in the four groups of mice (WT, wild-type; DR, diet-restricted). (C) Mean (±SEM) heart/body weight ratio in the four groups. (D) Mean (±SEM) heart TG content in the four groups (*$p < 0.001$; **$p < 0.01$); ($n = 6$ in all groups).

(Fig. 3A). Trichrome stains highlighted collagen deposits in the subendocardium and interstitium (Fig. 3B). On electron microscopy intracytoplasmic lipid vacuoles could be identified in untreated transgenic mice (Fig. 3C), but not in those of α-LA-treated mice, which were free of lipid droplets. As noted in ACS-transgenic mice made hyperleptinemic [7], there was an apparent increase in mitochondria in the cardiomyocytes.

Extracardiac mechanisms of prevention of cardiac lipotoxicity

The lipotoxicity caused by ACS overexpression in cardiomyocytes is largely the result of increased import of long-chain fatty acids synthesized elsewhere, rather than of increased lipogenesis and/or decreased oxidation in the cardiomyocytes themselves, as in the cardiac lipotoxicity of congenitally unleptinized rodents. To detect significant early changes in plasma lipids and in the expression of genes involved in hepatic and cardiomyocyte lipogenesis, we sacrificed some treated and untreated mice 4 and 42 days after the start of α-LA treatment. The mean plasma TG and FFA levels of the α-LA-treated mice at 4 days were unchanged from untreated controls and wild-type mice, but at 42 days TG levels were half of the untreated ACS-transgenic and wild-type groups (Table 2). After 4 days of α-LA treatment, the expression profile of genes involved in fatty acid metabolism revealed a 50% decline in SREBP-1c mRNA, a similar reduction in FAS, one of its target enzymes, and a 4-fold increase in PGC-1α, an inducer of mitochondrial biogenesis [16]. There was a 6-fold increase in hepatic P-AMPK (Fig. 4), which promotes fatty acid oxidation and inhibits lipogenesis by inactivating acetyl CoA carboxylase [8].

After 42 days of α-LA treatment, the hepatic expression profile revealed only 2 statistically significant changes in genes involved in fatty acid metabolism consistent with the reduction in plasma TG. SREBP-1c mRNA was 75% lower, and FAS was reduced by 50% (Table 3). P-AMPK was not increased at this time point (data not shown).

Intracardiac mechanisms of prevention of lipotoxicity

Although the sharp decline in plasma TG could well explain the protective effect of α-LA on the ACS-transgenic heart, we searched for evidence for direct effects on cardiac metabolism. However, unlike the finding in leptinized mice, the phosphorylation state of cardiac AMPK was not increased at either 4 days or 6 weeks, of α-LA treatment (data not shown). Nevertheless, cardiac PGC-1α mRNA and acyl CoA oxidase mRNA were increased ~2-fold after 4 days of treatment. After 6 weeks PGC-1α mRNA was

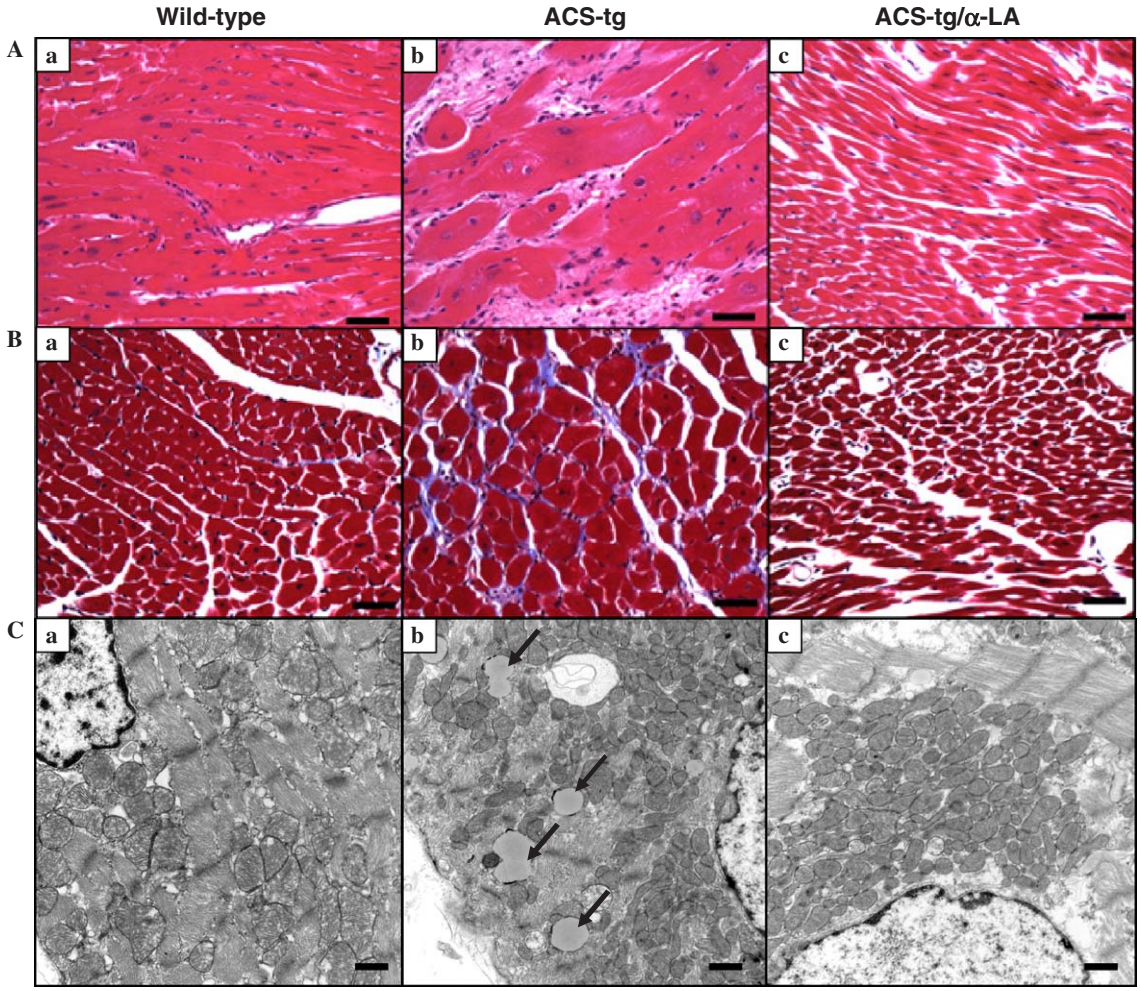

Fig. 3. Comparison of the myocardial histology of 10-week-old wild-type (a), untreated ACS-transgenic (b), and ACS-transgenic mice treated with α-LA (c). (A) Hematoxylin and eosin stain showing myofiber disorganization, cardiomyocyte enlargement, and interstitial fibrosis inflammation in the untreated ACS-transgenic heart, but a normal appearance in the α-LA-treated mouse heart (bar = 40 μm). (B) Trichrome stain of the hearts, showing collagen deposition in the untreated ACS-transgenic heart. The α-LA-treated ACS-transgenic group is entirely normal (bar = 40 μm). (C) Electron microscopic appearance of myocardial cells of the three groups. Lipid vacuoles are present in cardiomyocytes of the untreated ACS-transgenic mice (arrows). None are noted in the other groups (bar = 500 nm).

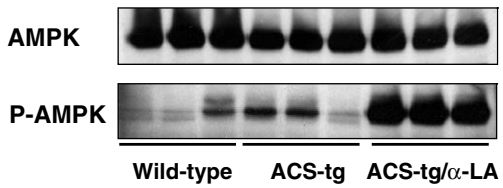

Fig. 4. Total and phosphorylated AMP-activated kinase in the livers of untreated wild-type, untreated ACS-transgenic, and α-LA-treated mice.

still elevated, and stearoyl destaturase-4 (SCD-4) mRNA was markedly increased. No changes in mRNA of enzymes of fatty acid oxidation were observed (Table 3).

Effect of caloric restriction on cardiac function of ACS-transgenic mice

To exclude reduced caloric intake as a significant factor in the prevention of the cardiac phenotype by hyperleptinemia, we restricted the food intake of 6 ACS-transgenic mice to below that of the α-LA-treated mice and studied their cardiac function 8 weeks later. Despite a reduction in cardiac TG content, echocardiograms in the diet-restricted ACS-transgenic mice did not differ from those of untreated ACS-transgenic mice on an ad libitum diet (data not shown).

Discussion

Rodents that lack normal leptin action develop a cluster of disorders that resembles the metabolic syndrome in human. In such rodents, the lipid content of the functionally compromised organs, such as liver, heart and pancreatic islets, is markedly increased, leading to dysfunction, increased apoptosis and, ultimately, organ failure manifested in islets by insulin resistance, type 2 diabetes, and in the heart of lipotoxic cardiomyopathy and premature death. A far simpler model of ectopic lipid overload involving only

Table 3
mRNA of relevant genes that were altered by α-LA treatment in either the heart or liver of ACS-transgenic mice

mRNA	Heart			Liver		
	Wild-type	ACS-tg	ACS-tg/α-LA	Wild-type	ACS-tg	ACS-tg/α-LA
4 days						
ACO	1	1.00 + 0.01	2.00 + 0.29*	1	1.03 + 0.32	0.89 + 0.11
FAS	1	0.47 + 0.07	0.84 + 0.29	1	1.04 + 0.19	0.35 + 0.07*
PGC-1α	1	1.25 + 0.06	2.36 + 0.25**	1	0.80 + 0.12	3.33 + 0.58*
SREBP-1c	1	0.95 + 0.05	1.26 + 0.09	1	2.01 + 0.43	0.94 + 0.20**
6 weeks						
ACO	1	0.60 + 0.04	0.60 + 0.04	1	1.03 + 0.04	0.80 + 0.07
FAS	1	1.95 + 0.37	1.84 + 0.29	1	1.08 + 0.07	0.55 + 0.22**
PGC-1α	1	1.30 + 0.08	2.20 + 0.39*	1	2.03 + 0.39	1.47 + 0.15
SREBP-1c	1	1.26 + 0.06	1.32 + 0.07	1	2.18 + 0.35	0.42 + 0.09**
SCD-4	1	3.00 + 0.20	7.00 + 0.01*			

Genes listed in Table 1 that were not significantly altered are not shown here. $N = 6$ in all groups.
* $p < 0.05$ vs. ACS-tg.
** $p < 0.01$ vs. ACS-tg.

the heart has been engineered by cardiomyocyte-specific overexpression of ACS [5]. Although the ACS-transgenic mouse is free of systemic abnormalities in lipid or glucose metabolism, and is not resistant to leptin or insulin, it develops dilated lipotoxic cardiomyopathy, abnormal echocardiographic patterns, elevated cardiac TG content, and cardiomyocyte hypertrophy, fat droplets, and interstitial fibrosis that is indistinguishable from that of congenitally unleptinized rodents [6]. This heart disease could be completely prevented by raising plasma leptin levels of these lean mice into the range of rodents with advanced diet induced obesity [7]. Yet, rodents with diet-induced obesity become resistant to the lipopenic action of hyperleptinemia, as do their human counterparts. This may justify the search for agents that have lipopenic activity comparable to that of leptin but that do not utilize the leptin signal transduction pathway. The demonstration that α-LA has leptinomimetic activity on the hypothalamus [12] and prevents lipid accumulation in pancreatic islets of OLETF mice [14] implied that it would, like leptin, prevent the lipotoxic phenotype. This was, in fact, the case.

In the ACS-transgenic model of lipotoxicity, the underlying abnormality is excessive import of long-chain fatty acids into the heart, rather than increased myocardial lipogenesis or decreased oxidation as in unleptinized tissues. Reduction by hyperleptinemia of the source of imported fatty acids via plasma TG and FFA may well have been the major factor in the decrease in cardiac TG, at least in this form of lipotoxicity. Hyperleptinemia profoundly reduced both plasma TG and FFA, whereas α-LA reduced plasma TG by ~50% but lowered FFA only slightly. Nevertheless, as had been observed with hyperleptinemia, the cardiac TG content of the ACS-transgenic mice was reduced by α-LA to the level of the wild-type mice. Surprisingly, α-LA-induced a 6-fold increase in AMPK activation in the liver but not in the heart, whereas hyperleptinemia increased cardiac but not hepatic AMPK activity [6].

Changes in the expression level of relevant genes in α-LA-treated mice also differed from those induced by hyperleptinemia. Liver SREBP-1c was reduced and PGC-1α increased at both 4 days and 6 weeks after beginning α-LA treatment (Table 3), but were unchanged by induction of hyperleptinemia [7]. Cardiac PGC-1α mRNA was also increased by α-LA treatment, as was the case in hyperleptinemia [7]. Based on the work of Wu et al. [16], this could be interpreted as evidence that the mitochondrial machinery for fatty acid oxidation had been upregulated by the treatment, as had been observed with hyperleptinemia. There appeared to be an increase in small mitochondria (Fig. 3C), but no morphometric analysis was made. Table 3 compares the expression of all the genes of Table 1 in which a significant change occurred during α-LA treatment.

Despite some differences between the molecular changes associated with α-LA-induced lipopenia and those induced by hyperleptinemia, their antilipotoxic efficacies were comparable in this model of lipotoxicity. Other agents, such as the thiazolidinediones and 5-aminoimidazole-4-carboxamide-ribofuranoside (AICAR), also protect the heart [7] and islets [17,18] of congenitally leptin-unresponsive rats from lipotoxic damage. However, unlike α-LA, the thiazolidinediones do not reduce food intake and tend to increase body fat, while AICAR is injected and its safety and efficacy in humans is unproven. α-LA could therefore be, at least for the present, the drug of choice in preventing ectopic lipid accumulation in human tissues.

Since elevated cardiomyocyte TG with left ventricular dysfunction may be common in overweight individuals [9], this study raises the possibility that a reduction in plasma TG levels, even when they are normal, may have the unexpected benefit of preventing lipid overaccumulation in the myocardium and reducing the risk of myocardial lipotoxicity. Nonalcoholic fatty liver could also benefit, given the striking effects of treatment on hepatic AMPK activation. Finally, reduction in plasma lipids would reduce

lipid delivery to all tissues, including skeletal muscle and islets. This would be expected to reduce insulin resistance while preserving the ability of β-cells to meet the insulin demands. In other words, α-LA seems qualified to prevent those components of the metabolic syndrome that result from ectopic lipid deposition.

Acknowledgments

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases-002700, the Department of Veterans Affairs Merit Award, the Juvenile Diabetes Research Foundation, Takeda Pharmaceuticals North America, Inc., the Jensen Charitable Lead Trust, (R.H.U.), and the American Diabetes Association (J.E.S.).

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