Published in final edited form as:

Biochem Biophys Res Commun. 2009 March 20; 380(4): 818–822. doi:10.1016/j.bbrc.2009.01.183.

STEAROYL-CoA DESATURASE-1 DEFICIENCY ATTENUATES OBESITY AND INSULIN RESISTANCE IN LEPTIN-RESISTANT OBESE MICE

Makoto Miyazaki^{1,3,*}, Harini Sampath^{2,4,*}, Xueqing Liu¹, Matthew T. Flowers^{1,2}, Kiki Chu¹, Agnieszka Dobrzyn^{1,5}, and James M. Ntambi^{1,2}

¹ Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, 53706

² Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, WI, 53706

Abstract

Obesity and adiposity greatly increase the risk for secondary conditions such as insulin resistance. Mice deficient in the enzyme stearoyl-CoA desaturase-1 (SCD1) are lean and protected from diet-induced obesity and insulin resistance. In order to determine the effect of SCD1 deficiency on various mouse models of obesity, we introduced a global deletion of the *Scd1* gene into leptin-deficient ob/ob mice, leptin-resistant Agouti (*A^{y/a}*) mice, and high-fat diet-fed obese (DIO) mice. SCD1 deficiency lowered body weight, adiposity, hepatic lipid accumulation and hepatic lipogenic gene expression in all three mouse models. However, glucose tolerance, insulin, and leptin sensitivity were improved by SCD1 deficiency only in *A^{y/a}* and DIO mice, but not ob/ob mice. These data uncouple the effects of SCD1 deficiency on weight loss from those on insulin sensitivity and suggest a beneficial effect of SCD1 inhibition on insulin sensitivity in obese mice that express a functional leptin gene.

Supplemental Key Words

leptin resistance; hepatic lipids; high-fat diet

INTRODUCTION

Stearoyl-CoA desaturase (SCD) is a $\Delta 9$ desaturase that catalyzes the conversion of saturated fatty acids into monounsaturated fatty acids, which serve as the preferred substrates for synthesis of storage lipids [1,2]. There are four known isoforms of *Scd* in the mouse and two known human isoforms. Mouse *Scd1* is highly expressed in lipogenic tissues such as adipose

Address correspondence to: James M. Ntambi, Department of Biochemistry, University of Wisconsin-Madison, 433, Babcock Drive, Madison, WI, 53706, Tel.: 608-265-3700, Fax.: 608-265-3272, E-mail: ntambi@biochem.wisc.edu.

*These authors contributed equally to this work.

³Present address: Division of Endocrinology, Metabolism and Diabetes, University of Colorado at Denver and Health Sciences Center, BRB452A 4200 E. 9th Ave C281 Denver, CO 80262.

⁴Present address: Center for the Study of Weight Regulation and Associated Disorders, Oregon Health and Science University, Portland, OR 97239.

⁵Present address: Laboratory of Cell Signaling and Metabolic Disorders, Nencki Institute of Experimental Biology, 3 Pasteur St., 02-093 Warsaw, Poland.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

tissue and liver [1,3–5], and mice lacking SCD1 are lean and protected from diet-induced obesity, despite being hyperphagic [2,6–8]. *Scd1*^{−/−} mice have increased whole body glucose tolerance and increased insulin sensitivity in skeletal muscle, brown adipose tissue, heart and liver [9–13], however, the mechanisms by which SCD1 deficiency leads to increased insulin sensitivity remain unclear. Furthermore, *Scd1* is a known target of the anorexigenic hormone, leptin, and a significant portion of the metabolic effects of leptin are thought to be mediated by its inhibition of *Scd1* [14,15] [9,10]. While SCD1 deficiency improves insulin sensitivity in lean mice, it has been reported that glucose tolerance in ob/ob mice may not improve due to SCD1 inhibition, despite reductions in body weight [11]. Given that human obesity is rarely characterized by leptin deficiency but rather by leptin resistance, we became interested in determining the effects of SCD1 inhibition on adiposity and insulin sensitivity in various mouse models of obesity. In order to address this goal, we introduced the global *Scd1* deletion into three different mouse models of obesity: leptin-deficient ob/ob mice (ob/ob), agouti-induced obese mice (A^y/a) and high-fat diet-induced obese mice (DIO). While the ob/ob mice serve as a model of leptin deficiency, the A^y/a and DIO mice serve as genetic and dietary models, respectively, of obesity and leptin-resistance [16–18]. We report here that SCD1 deficiency decreases body weight, white adipose tissue mass and hepatic TG in all three models of obesity. Leptin and insulin sensitivity are also significantly improved by SCD1 deficiency in leptin-resistant A^y/a and DIO mice. In contrast, despite a 30% reduction in body weight and 80% reduction in hepatic TG accumulation, *Scd1*^{−/−}; ob/ob mice remain hyperglycemic and insulin-resistant. These results thus uncouple the effects of SCD1 on body mass and adiposity from its effects on insulin sensitivity and glucose tolerance.

MATERIALS AND METHODS

Animals

The generation of *Scd1*^{−/−} mice was previously described [6]. *Scd1*^{+/-} mice were crossed 11 times with C57BL/6J mice to generate *Scd1*^{−/−} and wild-type (WT) mice on a C57BL/6J background. Eight week-old males were individually caged and fed either a standard chow diet (Purina 5008) or a HF diet (RD12492, Research Diets Inc.). To generate the SCD1 mutation in A^y/a mice, female B6 A^y/a mice were bred with male *Scd1*^{−/−} mice. The F1 generation of female *Scd1*^{+/-};A^y/a; and male *Scd1*^{−/−} mice were bred to obtain *Scd1*^{−/−}; A^y/a mice. To generate the SCD1 mutation in ob/ob mice, female B6 ob/+ mice were bred with male *Scd1*^{−/−} mice. F1 male and female *Scd1*^{+/-}; ob/+ mice were bred to obtain *Scd1*^{−/−}; ob/ob mice. The breeding and care of the animals was in accordance with the protocols approved by the Animal Care Research Committee of the University of Wisconsin-Madison.

Glucose, insulin, and leptin tolerance

Glucose tolerance and basal plasma insulin levels were measured in mice fasted for 4 hours. Animals were administered 2g/kg body weight of glucose by oral gavage. Plasma samples were collected at 0 and 90 minutes post-gavage of glucose. For leptin tolerance tests, mice were infused with recombinant leptin (Amgen) through a microosmotic pump (Alza model 1002, DURECT Corp.) inserted sub-cutaneously into the interscapular region. Plasma glucose was measured using the glucose oxidase method. Plasma insulin and leptin were measured using the insulin radioimmunoassay and leptin ELISA kits, respectively (Linco Research).

Lipid and protein analyses

Plasma cholesterol and TG were analyzed by colorimetric enzyme assay using Infinity TG and cholesterol reagents (Thermo Electron). Tissue lipids were extracted from liver according to the methods of Bligh and Dyer [19] and analyzed by thin-layer chromatography followed by gas chromatography, as previously described [20]. Protein samples were prepared from frozen liver and skeletal muscle, and insulin signaling parameters were measured as previously

described [9]. Briefly, 400 µg of total cellular protein from liver or red gastrocnemius muscle were immunoprecipitated with 1.2 µg of anti-IR-β antibody and immunoblotted with anti-phosphotyrosine or IR-β antibodies. 30 µg of total protein were also immunoblotted with a phospho-serine-473 Akt/PKB antibody or total Akt/PKB antibody. All antibodies were from Santa Cruz Biotechnology.

Real-time PCR

Total RNA was extracted with TRI reagent (Molecular Research). DNAase-treated total RNA (0.9 µg) was reverse-transcribed with Superscript III reverse transcriptase (Invitrogen). Real-time quantitative PCR was performed on an ABI Prism 7500 Fast instrument using gene-specific primers. SYBR green was used for detection and quantification of given genes expressed as mRNA level normalized to a gene encoding a ribosomal protein (L32) using the $\Delta\Delta C_t$ method. Primer sequences are available upon request.

Statistical analysis

Results were analyzed using one-way ANOVA with student-Newman post-hoc test. A difference of $p < 0.05$ was considered significant. Values are presented as means $\pm$ SE.

RESULTS

SCD1 deficiency attenuates obesity and adiposity in three mouse models of obesity

Scd1^{-/-} mice were hyperphagic relative to wild-type (*Scd1*^{+/+}) mice on a regular chow diet (Fig. 1A). While SCD1 deficient mice continued as much or more than *Scd1*^{+/+} counterparts (Fig. 1A), weight gain (Fig. 1B–D) and adiposity (Fig. 1E) were significantly attenuated by SCD1 deficiency in all three models of obesity. Histological examination of livers revealed that all three mouse models of obesity developed liver steatosis, while SCD1 deficiency protected against hepatic lipid accumulation in all three models (Fig. 1F). Hepatic triglycerides (TG) were reduced by SCD1 deficiency in ob/ob, A^y/a and DIO mice by 83%, 92% and 92%, respectively (Fig. 1G). SCD1 deficiency also reduced plasma TG in DIO and A^y/a mice by 31% and 20%, respectively, but not in ob/ob mice (Fig. 1H), despite the significant reduction in hepatic TG (Fig. 1G). All obese mouse models showed an induction of lipogenic genes including *Acc*, *Fas*, *Scd1*, fatty acid elongase (*Elovl6*) and *Srebp-1c*, relative to chow-fed *Scd1*^{+/+} mice (Fig. 1I). SCD1 deficiency prevented this increase in lipogenic gene expression in all mouse models. *Srebp-1c* expression was attenuated by SCD1 deficiency in A^y/a and DIO mice but not in ob/ob mice (Fig. 1I).

SCD1 deficiency increases whole body insulin sensitivity and glucose tolerance in DIO and A^y/a mice

Relative to chow-fed *Scd1*^{+/+} controls, basal plasma glucose levels were 76%, 41%, and 65% higher in ob/ob, A^y/a, and DIO mice, respectively (Fig. 2A). 90 minutes after oral gavage of glucose, plasma glucose levels remained elevated in the obese mice (Fig. 2A), indicating impaired glucose tolerance in these animals. SCD1 deficiency completely normalized 90-minute plasma glucose levels in A^y/a and DIO mice; however, ob/ob mice did not show a similar increase in glucose clearance due to SCD1 deficiency. In fact, relative to their *Scd1*^{+/+} counterparts, *Scd1*^{-/-} ob/ob mice had 2-fold higher basal (460 mg/dL vs. 220 mg/dL) and 90-minute (668 mg/dL vs. 413 mg/dL) plasma glucose levels, suggesting further impairment of insulin sensitivity in these mice (Fig. 2A). While all three models of obesity were hyperinsulinemic, SCD1 deficiency corrected plasma insulin levels in A^y/a and DIO mice, but not in ob/ob mice (Fig. 2B). Coupled with the data on glucose clearance (Fig. 2A), these results suggested that SCD1 deficiency improved insulin signaling in A^y/a and DIO mice, but not in ob/ob mice. We therefore measured components of the insulin signaling pathway (Fig.

2C) in liver and skeletal muscle (red gastrocnemius) of all mice. Tyrosine phosphorylation of insulin receptor- β (IR- β) was increased by SCD1 deficiency in both liver and muscle of chow-fed mice as well as A^y/a and DIO mice, without any changes in total IR- β protein levels (Fig. 2C). Consequently, serine phosphorylation of Akt at Ser-473 was increased in liver and muscle of these mice without any significant changes in total Akt protein levels (Fig. 2C). In contrast, SCD1 deficiency did not increase IR- β tyrosine phosphorylation or Akt serine phosphorylation in liver or muscle of ob/ob mice (Fig. 2C). These data correspond well with the lack of improvement in glucose sensitivity in *Scd1*^{-/-}; ob/ob animals (Fig 2A). While we have previously found that SCD1 deficiency decreases protein tyrosine phosphatase-1B (PTP-1B) levels in lean mice on a 129SvEv background [9,10], we did not find any changes in PTP-1B gene or protein levels due to SCD1 deficiency in our current study (not shown) performed in C57BL/6 mice.

SCD1 deficiency increases peripheral leptin sensitivity

In addition to insulin resistance, obesity and adiposity are also inversely related to leptin signaling and sensitivity [17,21]. In order to determine if SCD1 deficiency alters leptin sensitivity in the two mouse models of leptin resistance, we measured peripheral leptin sensitivity after subcutaneous infusion of leptin or PBS via a micro-osmotic pump. At baseline, *Scd1*^{-/-}; A^y/a and *Scd1*^{-/-}; DIO mice had 79% and 80% lower plasma leptin levels than their respective *Scd1*^{+/+} counterparts (Fig. 3A), corresponding with their decreased adipose mass (Fig. 1E). Leptin infusion achieved comparable levels of increase in plasma leptin levels in all mice (data not shown). In response to 4 days of subcutaneous leptin infusion, *Scd1*^{-/-}; A^y/a (Fig. 3B) and *Scd1*^{-/-}; DIO (Fig. 3C) mice lost 7% and 6% more body weight than their respective *Scd1*^{+/+} counterparts. Leptin infusion reduced food intake in both A^y/a (Fig. 3D) and DIO mice (Fig. 3E); however, the anorexigenic effect of leptin infusion was significantly lower in the *Scd1*^{-/-} mice, which continued to consume more food than their *Scd1*^{+/+} counterparts. Leptin infusion did not affect glucose and insulin levels in any mouse model, compared to PBS infusion alone (data not shown). These results indicate that SCD1 deficiency increases peripheral leptin sensitivity in leptin-resistant obese mice. Central leptin sensitivity, as assessed by changes in food intake in response to leptin, was not significantly increased due to SCD1 deficiency by peripheral leptin administration at this particular dose.

DISCUSSION

We and others have previously shown that SCD1 deficiency improves whole body, hepatic and skeletal muscle insulin sensitivity [9–11]. Furthermore, *Scd1*^{-/-} mice are protected from induction of lipogenesis under a variety of conditions including high carbohydrate feeding [6] as well as high saturated fat feeding [22]. It has also been shown that SCD1 deficiency improves adiposity in leptin-deficient ob/ob mice [14]. In order to determine if SCD1 deficiency improves insulin sensitivity in various mouse models of obesity, we introduced the global *Scd1* deletion into leptin-deficient ob/ob mice, leptin-resistant A^y/a , and high-fat fed DIO mice. We show here that while SCD1 deficiency improves insulin sensitivity in A^y/a and DIO mice, ob/ob mice do not benefit from SCD1 deficiency despite significant reductions in body weight and adiposity.

This outcome was quite surprising, since even moderate reductions in body mass as low as 7–10% have been linked to increased insulin sensitivity [23–25]. In contrast, *Scd1*^{-/-}; ob/ob mice tended to become even more hyperglycemic (Fig. 2A) and insulin resistant (Fig. 2C) relative to ob/ob counterparts. A similar worsening of the diabetic state due to SCD1 inhibition has been reported in lipodystrophic aP2-SREBP-1c transgenic mice, another mouse model of leptin-deficiency [15]. It has been previously reported that deletion of SCD1 in ob/ob mice reduces pancreatic insulin content which leads to worsening of hyperglycemia [11]. This

worsening of glucose clearance in ob/ob mice due to SCD1 deficiency was more consistently observed in the diabetes-prone BTBR strain, than in the C57BL/6J strain [11]. While we did not measure pancreatic insulin content in the current study, the persistent hyperinsulinemia (Fig. 2B) we observed in *Scd1*^{-/-}; ob/ob C57BL/6J mice suggests that impaired insulin sensitivity rather than decreased insulin secretion contributes to the defects in glucose clearance observed in our study. Nonetheless, in spite of high plasma insulin levels, SCD1 deficiency does not ameliorate insulin signaling despite significant reductions in body weight and hepatic lipids in ob/ob mice.

Increased levels of both hepatic and plasma lipids are thought to contribute to the development of insulin resistance. It is interesting to note that while SCD1 deficiency decreased hepatic lipids in all three mouse models of obesity (Fig. 1F and 1G), plasma TG were not lowered by SCD1 deficiency in ob/ob mice, alone (Fig. 1H).

Since SCD1 deficiency ameliorates insulin signaling in A^y/a and DIO mice, but not leptin-deficient ob/ob mice, it is tempting to speculate that leptin signaling plays a part in increased insulin sensitivity due to SCD1 deficiency. Indeed, peripheral leptin sensitivity is also increased by SCD1 deficiency in both models of leptin resistance (Fig. 3B, 3C). Several lines of evidence in both cell culture and animal models suggest a complex interplay between insulin and leptin signaling in the periphery [21, 26, 27]. For instance, the AMP-activated protein kinase (AMPK) has been suggested to mediate the effects of leptin on insulin sensitivity [28]. We have previously shown that AMPK activation is increased by SCD1 deficiency in skeletal muscle and livers of lean mice, and in livers of ob/ob mice [29, 30]. In our current study, we found that AMPK phosphorylation was not significantly increased in liver or muscle of *Scd1*^{-/-};A^y/a or *Scd1*^{-/-};DIO mice, relative to *Scd1*^{+/+} counterparts (data not shown), suggesting an AMPK-independent mechanism for increased insulin signaling in these mice.

While these data are suggestive of a role for leptin in increasing insulin signaling due to SCD1 deletion, it is also possible that the leptin-deficient phenotype is simply too severe and thus masks any potential beneficial effects of SCD1 deficiency in ob/ob mice. Nonetheless, these data indicate that in the context of leptin deficiency, weight loss and decreased fat mass due to SCD1 deficiency are not sufficient to improve insulin sensitivity. These data provide further insight into the potential mechanisms by which SCD1 deficiency exerts its multiple metabolic effects by uncoupling its effects on weight loss from its effects on insulin signaling. Furthermore, the divergent regulation of lipogenic genes in liver vs. skeletal muscle of SCD1-deficient mice is extremely intriguing and warrants further study. Ongoing studies in our lab are therefore aimed at dissecting the tissue-specific contributions of SCD1 to adiposity and insulin sensitivity in various dietary and genetic models of obesity. In conclusion, our current observation of differential regulation of insulin sensitivity by SCD1 deficiency in different mouse models of obesity is of particular relevance to the understanding of human obesity, which is generally characterized by leptin resistance rather than leptin deficiency.

Acknowledgements

This work was supported by American Heart Association pre-doctoral fellowship 0415001Z to H.S., NIH postdoctoral training grant to M.T.F., and NIH grant NIDDK-R0162388 to J.M.N.

References

1. Ntambi JM, Miyazaki M. Regulation of stearoyl-CoA desaturases and role in metabolism. *Prog Lipid Res* 2004;43:91–104. [PubMed: 14654089]
2. Ntambi JM, Miyazaki M, Stoeckl JP, Lan H, Kendziorski CM, Yandell BS, Song Y, Cohen P, Friedman JM, Attie AD. Loss of stearoyl-CoA desaturase-1 function protects mice against adiposity. *Proc Natl Acad Sci U S A* 2002;99:11482–11486. [PubMed: 12177411]

3. Miyazaki M, Bruggink SM, Ntambi JM. Identification of mouse palmitoyl-coenzyme A Delta9-desaturase. *J Lipid Res* 2006;47:700–704. [PubMed: 16443825]
4. Miyazaki M, Jacobson MJ, Man WC, Cohen P, Asilmaz E, Friedman JM, Ntambi JM. Identification and characterization of murine SCD4, a novel heart-specific stearoyl-CoA desaturase isoform regulated by leptin and dietary factors. *J Biol Chem* 2003;278:33904–33911. [PubMed: 12815040]
5. Miyazaki M, Dobrzyn A, Elias PM, Ntambi JM. Stearoyl-CoA desaturase-2 gene expression is required for lipid synthesis during early skin and liver development. *Proc Natl Acad Sci U S A* 2005;102:12501–12506. [PubMed: 16118274]
6. Miyazaki M, Dobrzyn A, Man WC, Chu K, Sampath H, Kim HJ, Ntambi JM. Stearoyl-CoA desaturase 1 gene expression is necessary for fructose-mediated induction of lipogenic gene expression by sterol regulatory element-binding protein-1c-dependent and -independent mechanisms. *J Biol Chem* 2004;279:25164–25171. [PubMed: 15066988]
7. Miyazaki M, Kim YC, Ntambi JM. A lipogenic diet in mice with a disruption of the stearoyl-CoA desaturase 1 gene reveals a stringent requirement of endogenous monounsaturated fatty acids for triglyceride synthesis. *J Lipid Res* 2001;42:1018–1024. [PubMed: 11441127]
8. Jiang G, Li Z, Liu F, Ellsworth K, Dallas-Yang Q, Wu M, Ronan J, Esau C, Murphy C, Szalkowski D, Bergeron R, Doebber T, Zhang BB. Prevention of obesity in mice by antisense oligonucleotide inhibitors of stearoyl-CoA desaturase-1. *J Clin Invest* 2005;115:1030–1038. [PubMed: 15761499]
9. Rahman SM, Dobrzyn A, Dobrzyn P, Lee SH, Miyazaki M, Ntambi JM. Stearoyl-CoA desaturase 1 deficiency elevates insulin-signaling components and down-regulates protein-tyrosine phosphatase 1B in muscle. *Proc Natl Acad Sci U S A* 2003;100:11110–11115. [PubMed: 12960377]
10. Rahman SM, Dobrzyn A, Lee SH, Dobrzyn P, Miyazaki M, Ntambi JM. Stearoyl-CoA desaturase 1 deficiency increases insulin signaling and glycogen accumulation in brown adipose tissue. *Am J Physiol Endocrinol Metab* 2005;288:E381–387. [PubMed: 15494611]
11. Flowers JB, Rabaglia ME, Schueler KL, Flowers MT, Lan H, Keller MP, Ntambi JM, Attie AD. Loss of stearoyl-CoA desaturase-1 improves insulin sensitivity in lean mice but worsens diabetes in leptin-deficient obese mice. *Diabetes* 2007;56:1228–1239. [PubMed: 17369521]
12. Gutierrez-Juarez R, Pocai A, Mulas C, Ono H, Bhanot S, Monia BP, Rossetti L. Critical role of stearoyl-CoA desaturase-1 (SCD1) in the onset of diet-induced hepatic insulin resistance. *J Clin Invest* 2006;116:1686–1695. [PubMed: 16741579]
13. Dobrzyn P, Sampath H, Dobrzyn A, Miyazaki M, Ntambi JM. Loss of stearoyl-CoA desaturase 1 inhibits fatty acid oxidation and increases glucose utilization in the heart. *Am J Physiol Endocrinol Metab* 2008;294:E357–364. [PubMed: 18042664]
14. Cohen P, Miyazaki M, Succi ND, Hagge-Greenberg A, Liedtke W, Soukas AA, Sharma R, Hudgins LC, Ntambi JM, Friedman JM. Role for stearoyl-CoA desaturase-1 in leptin-mediated weight loss. *Science* 2002;297:240–243. [PubMed: 12114623]
15. Asilmaz E, Cohen P, Miyazaki M, Dobrzyn P, Ueki K, Fayzikhodjaeva G, Soukas AA, Kahn CR, Ntambi JM, Succi ND, Friedman JM. Site and mechanism of leptin action in a rodent form of congenital lipodystrophy. *J Clin Invest* 2004;113:414–424. [PubMed: 14755338]
16. Cohen P, Friedman JM. Leptin and the control of metabolism: role for stearoyl-CoA desaturase-1 (SCD-1). *J Nutr* 2004;134:2455S–2463S. [PubMed: 15333742]
17. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998;395:763–770. [PubMed: 9796811]
18. Tschop M, Heiman ML. Rodent obesity models: an overview. *Exp Clin Endocrinol Diabetes* 2001;109:307–319. [PubMed: 11571668]
19. Bligh EG, Dyer WJ. A rapid method of total lipid extraction and purification. *Can J Biochem Physiol* 1959;37:911–917. [PubMed: 13671378]
20. Dobrzyn A, Dobrzyn P, Miyazaki M, Sampath H, Chu K, Ntambi JM. Stearoyl-CoA desaturase 1 deficiency increases CTP:choline cytidyltransferase translocation into the membrane and enhances phosphatidylcholine synthesis in liver. *J Biol Chem* 2005;280:23356–23362. [PubMed: 15829484]
21. Chen HC, Smith SJ, Ladha Z, Jensen DR, Ferreira LD, Pulawa LK, McGuire JG, Pitas RE, Eckel RH, Farese RV Jr. Increased insulin and leptin sensitivity in mice lacking acyl CoA:diacylglycerol acyltransferase 1. *J Clin Invest* 2002;109:1049–1055. [PubMed: 11956242]

22. Sampath H, Miyazaki M, Dobrzyn A, Ntambi JM. Stearoyl-CoA desaturase-1 mediates the pro-lipogenic effects of dietary saturated fat. *J Biol Chem* 2007;282:2483–2493. [PubMed: 17127673]
23. Rector RS, Warner SO, Liu Y, Hinton PS, Sun G, Cox RH, Stump CS, Laughlin MH, Dellsperger KC, Thomas TR. Exercise and diet induced weight loss improves measures of oxidative stress and insulin sensitivity in adults with characteristics of the metabolic syndrome. *Am J Physiol Endocrinol Metab* 2007;1:1.
24. Petersen KF, Shulman GI. Etiology of insulin resistance. *Am J Med* 2006;119:S10–16. [PubMed: 16563942]
25. Fernandez ML. The metabolic syndrome. *Nutr Rev* 2007;65:S30–34. [PubMed: 17605311]
26. Chinookoswong N, Wang JL, Shi ZQ. Leptin restores euglycemia and normalizes glucose turnover in insulin-deficient diabetes in the rat. *Diabetes* 1999;48:1487–1492. [PubMed: 10389859]
27. Ceddia RB, Koistinen HA, Zierath JR, Sweeney G. Analysis of paradoxical observations on the association between leptin and insulin resistance. *Faseb J* 2002;16:1163–1176. [PubMed: 12153984]
28. Steinberg GR, Jorgensen SB. The AMP-activated protein kinase: role in regulation of skeletal muscle metabolism and insulin sensitivity. *Mini Rev Med Chem* 2007;7:519–526. [PubMed: 17504187]
29. Dobrzyn P, Dobrzyn A, Miyazaki M, Cohen P, Asilmaz E, Hardie DG, Friedman JM, Ntambi JM. Stearoyl-CoA desaturase 1 deficiency increases fatty acid oxidation by activating AMP-activated protein kinase in liver. *Proc Natl Acad Sci U S A* 2004;101:6409–6414. [PubMed: 15096593]
30. Dobrzyn A, Dobrzyn P, Miyazaki M, Ntambi JM. Polyunsaturated fatty acids do not activate AMP-activated protein kinase in mouse tissues. *Biochem Biophys Res Commun* 2005;332:892–896. [PubMed: 15916750]

Fig. 1. Body weight, food intake, and adiposity

A. Food intake was measured at 16 weeks of age.

B–D. Body weight was measured up to 16 weeks in ob/ob mice (B) and up to 20 weeks in A/y/a (C) and DIO (D) mice. High-fat feeding in DIO mice was started at 8 weeks of age.

E. All animals were sacrificed at 24 weeks of age. Gonadal white adipose mass was measured.

F. Fresh liver sections were fixed with 10% buffered formalin and stained by hematoxylin and eosin to visualize lipid droplets. Sections are representative of several animals in each group.

G, H. Hepatic (G) and plasma (H) triglycerides were measured in 24 week-old mice.

I. Expression of hepatic lipogenic genes was measured by real-time PCR using gene-specific primers. The relative quantification for a given gene was corrected to the ribosomal protein L32 mRNA values.

Data represent the mean + SE for >4 animals in each group. $p < 0.05$ compared to # *Scd1*^{+/+} chow and ** compared to respective *Scd1*^{+/+} counterparts.

Fig 2. Oral glucose tolerance and insulin signaling

A. Oral glucose tolerance was assessed in fasted animals by measuring plasma glucose at 0 and 90 minutes post-gavage of 10% glucose at a dose of 2 g/kg body weight.

B. Fasting plasma insulin levels were measured by RIA.

C. Components of the insulin signaling pathway were measured in liver and red gastrocnemius. IR, insulin receptor. ** compared to respective *Scd1*^{+/+} counterparts.

Fig. 3. Plasma leptin and leptin sensitivity

A. 24 week-old males were fasted for 4 hours and sacrificed with isoflurane overdose. Plasma leptin levels were measured by ELISA.

B-E. 12 week-old males were subcutaneously infused with leptin at a rate of 0.2 $\mu\text{g/day/g}$ body weight. Data is presented as percent change from basal body weight and food intake. Change in body weight was measured in leptin-infused A^{y/a} (B) and DIO (C) mice. Change in food intake was measured in leptin-infused A^{y/a} (D) and DIO mice (E). Data represent the mean + SE for >4 animals in each group. $p < 0.05$ compared to #Scd1^{+/+} chow and ** compared to respective Scd1^{+/+} counterparts.