Hepatic stearoyl CoA desaturase 1 deficiency increases glucose uptake in adipose tissue partially through the PGC-1α–FGF21 axis in mice

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Running title: SCD1 deficiency promotes FGF21 expression

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Abstract

Increased carbohydrate consumption increases hepatic de novo lipogenesis, which has been linked to the development of chronic metabolic diseases, including obesity, hepatic steatosis, and insulin resistance. Stearoyl CoA desaturase 1 (SCD1) is a critical lipogenic enzyme that catalyzes the synthesis of two monounsaturated fatty acids (MUFA), oleate and palmitoleate, from the saturated fatty acids, stearate and palmitate, respectively. SCD1-deficient mouse models are protected against diet-induced adiposity, hepatic steatosis, and hyperglycemia. However, the mechanism of this protection by SCD1 deficiency is unclear. Using a liver-specific SCD1 knockout (LKO) mouse model fed a high-carbohydrate, low-fat diet (HCD), we show that hepatic SCD1 deficiency increases systemic glucose uptake. Hepatic SCD1 deficiency enhanced glucose transporter type 1 (GLUT1) expression in the liver and also up-regulated GLUT4 and adiponectin expression in the adipose tissue. The enhanced glucose uptake correlated with
increased liver expression and elevated plasma levels of fibroblast growth factor 21 (FGF21), a hepatokine known to increase systemic insulin sensitivity and to regulate whole-body lipid metabolism. Feeding LKO mice with triolein-supplemented, but not tristearin-supplemented, HCD reduced FGF21 expression and plasma levels. Consistently, SCD1 inhibition in primary hepatocytes induced FGF21 expression, which was repressed by treatment with oleate but not palmitoleate. Moreover, deletion of the transcriptional coactivator PPARγ coactivator 1α (PGC-1α) reduced hepatic and plasma FGF21 and white adipocyte tissue–specific GLUT4 expression and raised plasma glucose levels in the LKO mice. These results suggest that hepatic oleate regulates glucose uptake in adipose tissue either directly or partially by modulating the hepatic PGC-1α–FGF21 axis.

Introduction

Obesity is a worldwide health problem. There is abundant evidence that obese individuals are more susceptible to developing chronic metabolic diseases including insulin resistance, type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease (NAFLD) (1). There are several factors that influence weight gain including dietary, genetic, lifestyle and environmental variables which in turn affect food intake and energy expenditure. Attempts to reduce fat consumption usually accompanies increased carbohydrate intake which significantly enhances endogenous hepatic de novo lipogenesis (DNL). Accordingly, high carbohydrate diet (HCD)-induced adiposity and hepatic steatosis are partially attributed to increased hepatic DNL followed by very low-density lipoprotein (VLDL) mediated transport of triglyceride to white adipose tissue (WAT). Moreover, DNL is a source of liver fat accumulation leading NAFLD associated with hepatic insulin resistance and enhanced glucose intolerance (2,3). NAFLD patients exhibit increased liver expression of lipogenic genes, including sterol regulatory element binding protein (SREBP)1, stearoyl CoA desaturase (SCD)1, and fatty acid synthase (FAS) (4). Monounsaturated fatty acids (MUFAs) are the major substrates for complex lipid synthesis including triglycerides (TG), phospholipids, cholesterol esters and wax esters. SCD1, the central enzyme in lipogenesis, catalyzes the rate limiting step in MUFA synthesis. It desaturates saturated fatty acids (SFA), mainly stearate (18:0) and palmitate (16:0) into MUFAs, oleate (18:1n9) and palmi toleate (16:1n7), respectively. SCD1 expression is highly responsive to different stimuli that trigger or suppress liver lipogenesis. SCD1 desaturation index, the ratio of MUFAs to SFAs, shows positive correlation with changes in human body adiposity and insulin resistance (5-7). Similarly, a number of studies have reported positive correlation of SCD1 desaturation index with human plasma TGs or dyslipidemia in patients with familiar combined hyperlipidemia, suggesting that excess MUFAs may contribute to the development of metabolic diseases (8-10). Despite this controversy the accumulating evidence indicating its involvement in the regulation of body weight validates the need to study SCD1 as a potential molecular target in lipid-associated metabolic disorders.

We have previously shown that global deletion of SCD1 is protective against diet-induced adiposity and hepatic steatosis despite hyperphagia observed in SCD1 deficient mice. This protection is associated with decreased hepatic DNL, enhanced fatty acid oxidation and
increased energy expenditure (11). Furthermore, SCD1 global deletion elevated insulin signaling and increased glucose uptake in muscle and brown adipose tissue (BAT) (12). Increased glucose uptake phenotype was also observed in heart in response to SCD1 global deletion (13).

To further understand the role of hepatic MUFAs in the regulation of systemic glucose metabolism in response to HCD, we created a mouse model of SCD1 liver tissue specific knockout (LKO) mice. Employing this model, we showed that hepatic SCD1 deficiency protects against HCD induced hepatic steatosis and improves insulin sensitivity (14,15). Reduced hepatic MUFAs levels prevented the normal insulin-SREBP-1c-mediated lipogenic response, resulting instead in a dramatic decrease in the rate of fatty acid synthesis. Despite continuous ingestion of HCD, the block in hepatic DNL was paradoxically associated with hypoglycemia and reduced levels of hepatic glycogen (15,16). Here we show that hepatic SCD1 deficiency increases glucose uptake in the liver and adipose tissue through GLUT 1 and GLUT4, respectively. The increased systemic glucose uptake correlates with elevated hepatic expression and plasma levels of FGF21 which was reduced upon feeding triolein, but not tristearin supplemented HCD. Furthermore, oleate suppressed the expression of FGF21 caused by SCD1 inhibition in primary hepatocytes, whereas FGF21 expression remained elevated in the cells co-treated with SCD1 inhibitor and palmitate or palmitoleate. Hepatic PGC-1α deletion reduced FGF21 gene expression and partially increased basal glucose levels in LKO mice. Our data shed light on the regulatory effect(s) of hepatic oleate on glucose uptake and identify liver PGC-1α, FGF21 and adiponectin as its downstream targets.

Results

Hepatic SCD1 deficiency enhances systemic glucose uptake

We have previously shown that global SCD1 deficiency protects against diet-induced adiposity and improves glucose metabolism. SCD1 global knockout (GKO) mice demonstrated increased glucose uptake in BAT, heart and skeletal muscle (12,13,17). Given that SCD1 is deleted from all tissue, using GKO mice alone was not sufficient to determine the individual contribution of SCD1 from different tissues to these phenotypes. To do so, we used LKO mice to investigate the role of hepatic SCD1 in regulating glucose metabolism. LOX control and LKO mice were fed HCD for 10 days and in vivo 2-[^3]H]deoxyglucose uptake assay was performed at the end of the feeding period. All mice were fasted for four hours before receiving oral gavage (15 µCi/ mouse) of 2-[^3]H]deoxyglucose in 20% dextrose solution. Mice were euthanized after 1.5 hours and radioactivity was quantified in collected tissues using the liquid scintillation counter. Liver, spleen, WAT and BAT of LKO mice showed increased glucose uptake relative to corresponding tissues of LOX control mice (Figure 1). Brain tissue of LKO mice showed a trend towards increased glucose uptake (P value =0.068). No significant change was observed in glucose uptake in the muscle and heart of LKO mice. Our data indicate that hepatic SCD1 deficiency results in increased glucose uptake in liver and extra-hepatic tissues like WAT and BAT.

Hepatic SCD1 differentially regulates genes encoding glucose transporters in metabolic tissues

To determine how hepatic SCD1 deficiency enhances glucose uptake in
metabolic tissues, we measured the expression of glucose transporter genes in liver, WAT and BAT. The liver of LKO mice fed HCD demonstrated increased GLUT1 expression and decreased GLUT2 expression (Figure 2A). On the other hand, in the WAT, hepatic SCD1 deficiency caused significant upregulation of GLUT4 gene and protein expression and showed no effect on GLUT1 expression (Figure 2B, C). The BAT of LKO mice showed a similar trend displaying increased GLUT4 protein expression (P value = 0.054) (Figure 2D). Next, to determine if increased glucose uptake is associated with enhanced lipogenesis, we measured the expression of lipogenic genes in adipose tissues. The gene expression analysis performed using WAT and BAT of LKO mice showed no significant alteration in the levels of carbohydrate response element binding protein (ChREBP) α and ChREBP β, elongation of very long chain fatty acids protein (ELOV) 5 and ELOV 6, compared to control mice (Figure 2E, 2F). The relative expression of other lipogenic genes such as SCD1 and Fatty acid synthase 1 (FASN) were unchanged (14). Taken together, our studies suggest that during the 10-14 day feeding of a high carbohydrate low fat diet, hepatic SCD1 deficiency has little effect on the expression of lipogenic genes in WAT and BAT of LKO mice.

Hepatic SCD1 deficiency enhances systemic glucose uptake through GLUT1 dependent and independent mechanisms

To further investigate the role of GLUT1 in hepatic SCD1 deficiency-induced glucose uptake in liver and adipose tissues, we performed positron emission tomography-computed tomography (PET/CT) scanning using 2-Deoxy-2-[18F] Fluoro-D-glucose (FDG). Animals maintained on HCD for 10 days, were fasted overnight prior to an intravenous injection of either vehicle or the GLUT1 inhibitor, Phloretin, 10 mg/Kg body weight (18). After an hour, mice were injected with approximately 9 MBq of FDG before performing imaging studies. Consistent with the 2-[3H]deoxyglucose uptake study, the liver of LKO mice showed increased glucose uptake in comparison with the liver of control LOX mice. This induction of glucose uptake was reduced to control levels upon phloretin treatment which suggests that SCD1 deficiency induces glucose uptake in the liver through recruitment of GLUT1 (Figure 3, S1). Furthermore, we observed similar increase in glucose uptake in small intestine and WAT of LKO animals, reduced to control levels in the former but not the latter upon phosphatetin treatment (Figure 3). This indicates that increased glucose uptake in WAT is independent of GLUT1. Similarly, comparative studies in the brain demonstrated more glucose uptake in the LKO compared with the LOX mice. However, no appreciable difference in glucose uptake levels between phloretin-treated animals suggesting a redundant role of GLUT1 in the brain of LKO mice (Figure 3).

Hepatic SCD1 deficiency induces FGF21 and plasma adiponectin expression

Next, we assessed the effect of hepatic SCD1 deficiency on the expression of genes encoding hepatokines previously shown to enhance systemic glucose metabolism. LKO mice fed HCD showed higher expression of hepatic FGF21 compared with LOX control mice (Figure 4A). The increase in hepatic FGF21 expression correlated with a similar elevation of plasma FGF21 levels in LKO mice (Figure 4A). Consistent with elevated
plasma FGF21 and possibly increased FGF21 signaling, LKO mice showed higher hepatic expression of fibroblast growth factor co-receptor β Klotho (KLB) (Figure 4B). To determine the source of elevated FGF21 plasma levels and probable contribution of other tissues, we measured the expression of FGF21 in adipose tissues. Interestingly, there was no change in FGF21 expression in WAT and BAT of LKO mice when compared with tissues from LOX mice (Figure 4C). This suggested that increased circulating plasma FGF21 levels in LKO mice are mainly derived from the liver. Next, we investigated the effect of elevated plasma FGF21 on WAT metabolism. We measured the expression of adiponectin in WAT which has been shown to be increased upon FGF21 treatment (19). Adiponectin expression was significantly increased in the adipose tissue of LKO relative to the WAT of LOX mice. Accordingly, plasma adiponectin levels were increased in LKO when compared to LOX animals (Figure 4D).

**Oleate is a critical regulator of FGF21 expression**

We have previously reported that hepatic SCD1 deficiency protects against HCD-induced obesity and hepatic steatosis (15). The body weights of the LKO mice fed a high CHO diet for 10 days were reduced (Figure S2). Reduced body weight of LKO mice correlates with decreased DNL and reduced hepatic lipogenic gene expression (15). The precise mechanism(s) by which hepatic SCD1 deficiency reduces the expression of lipogenic genes and subsequently suppresses hepatic lipogenesis is not known. We showed previously that when LKO mice were fed triolein supplemented HCD, the expression of lipogenic genes and adiposity were restored to the control levels (15). Since an exogenous source of oleate restored lipogenesis in LKO mice, we asked whether hepatic SCD1 deficiency decreases DNL through upregulation of FGF21 expression. We hypothesized that triolein feeding decreases FGF21 expression in the liver of LKO mice. To test this hypothesis, we fed LOX and LKO mice either HCD, triolein supplemented HCD, or tristearin supplemented HCD, and measured plasma FGF21 levels. Moreover, we examined the effect of SCD1 substrate (C18:0) on plasma FGF21 levels. Feeding triolein supplemented HCD was sufficient to reduce plasma FGF21 levels in LKO mice to those observed in LOX animals (Figure 5A). Furthermore, triolein restored blood glucose levels in LKO mice to the control levels, suggesting that hepatic SCD1 deficiency may modulate glucose uptake through FGF21 (Figure 5B). In contrast, tristearin supplemented HCD failed to reduce plasma FGF21 levels to the control levels (Figure 5B). Since SCD1 synthesizes oleate and palmitoleate, we sought to examine the differential effects of these fatty acids on hepatic FGF21 expression. For this, we reverted to cell culture studies. Primary hepatocytes treated with SCD1 inhibitor were evaluated for FGF21 expression with or without supplementation with SCD1 substrates or products. Our studies demonstrated that SCD1 inhibition resulted in induction of FGF21 expression. Remarkably, this induction was suppressed by oleate, but not palmitoleate or palmitate treatment. Treatment with palmitate resulted in higher FGF21 expression in SCD deficient hepatocytes (Figure 5C). These data indicate that reduced oleate levels in response to SCD1 deficiency increase FGF21 expression and decrease blood glucose levels.
Oleate regulates FGF21 partially through PGC-1α

Hepatic SCD1 deficiency increases PGC-1α expression (Figure 6A) consistent with previous reports (14). Restoring oleate levels either through endogenous or exogenous resources reduced PGC-1α in the liver of SCD1 KO mice. Since increased PGC-1α in the liver was previously reported to increase FGF21 expression (20), we examined the expression of FGF21 in the liver and plasma of mice deficient in both SCD1 and PGC-1α (DLKO) mice fed the HCD for 14 days. Our results revealed that PGC-1α deletion decreased FGF21 expression in the liver and plasma of SCD1 KO mice (Figure 4B) as well as reduced GLUT4 expression in WAT (Figure 6C). DLKO mice also showed partial restoration (~25%) of basal glucose levels (Figure 6D). The data indicate that hepatic SCD1 deficiency decreases oleate synthesis and increases FGF21 expression in the liver at least in part through PGC-1α. These changes are expected to increase glucose uptake in adipose tissue either directly or indirectly (Figure 6E).

Discussion

SCD1 deletion protects against diet induced adiposity, increases insulin sensitivity and improves glucose metabolism, implicating SCD1 in the development of metabolic diseases (11,12). SCD1 GKO mice demonstrate enhanced glucose uptake in the heart and peripheral tissues including BAT and skeletal muscle (12,17). Increased glucose uptake in skeletal muscle and BAT correlated with increased insulin signaling and increased glycogen accumulation (12,17). The mechanism by which SCD1 deficiency mediates these phenotypes is unclear. Also, the individual contribution of SCD1 from different tissues to these phenotypes is not yet determined. Here we show that hepatic SCD1 deficiency enhances glucose uptake in the liver and adipose tissue through two distinct mechanisms. The first involves the up-regulation of GLUT1 expression in the liver, while in the second GLUT4 expression is elevated in adipose tissues. Our findings indicate that enhanced systemic glucose uptake in hepatic SCD1 deficient model is associated with elevated plasma FGF21 and adiponectin levels.

The data presented here support a role of fatty acids in the regulation of glucose metabolism at least in part through modulation of genes encoding glucose transporters. We showed previously that reduced MUFA levels increased GLUT1 expression in adipose tissue of adipose-specific SCD1 knockout mice and in vitro in SCD1 inhibitor treated differentiated 3T3L1 cells (21). This indicates that reduced MUFA levels induce tissue specific, or localized, glucose uptake through increasing GLUT1 expression. Consistent with these results, GLUT1 inhibition resulted in significant suppression of glucose uptake in the liver of LKO mice. Even though SCD1 deficiency increased glucose uptake in the liver, our previous work showed no change in hepatic glucokinase gene expression (15). This may suggest that it is the enhanced GK activity that leads to higher glucose metabolism and subsequently the hypoglycemia observed in LKO mice. However, this inference requires further investigation to prove so.

We previously reported that SCD1 GKO mice showed enhanced GLUT4 expression in adipose tissue (17,21). The induction of GLUT4 expression in the adipose tissue of LKO mice indicates that reducing hepatic MUFA synthesis is sufficient to recapitulate increased glucose uptake phenotype observed in adipose
tissue of SCD1 GKO mice. Analysis of plasma fatty acid composition revealed that hepatic SCD1 deficiency was associated with reduced oleate levels (14). Increased GLUT4 expression may allow for a shift in adipose tissue fuel metabolism to compensate for reduced plasma oleate levels. Accordingly, oleate treatment decreases GLUT4 expression in differentiated 3T3L1 cells (22). Thus, reduced hepatic oleate synthesis and transport may increase glucose uptake and metabolism in WAT of LKO mice. These data build upon the previously described notion of a reciprocal relationship between glucose and fatty acid metabolism in adipose tissue (23). In addition, LKO mice fed HCD demonstrate improved glucose tolerance, suggesting that enhanced insulin sensitivity might contribute to increased glucose metabolism in adipose tissue (14). Active insulin signaling stimulates GLUT4 translocation to the plasma membrane and subsequently increase glucose uptake in adipose tissue (24-27).

Our data provides evidence of the involvement of fatty acid in the regulation of FGF21 expression. SCD1 deficiency causes a significant reduction of MUFA to SFA ratio, which suggests that increased FGF21 is either a result of reduced MUFA levels or accumulated SFA. However, the failure of tristearin supplemented HCD to cause further elevation of FGF21 in LKO mice suggests that SCD1-mediated increase in plasma FGF21 is mediated by reduced MUFA levels but not accumulated SFA. Consistently, feeding triolein supplemented HCD normalized plasma FGF21 in LKO mice to control levels, suggesting that SCD1 deficiency-induced reduction of hepatic oleate levels increases FGF21 expression. This may partially explain why SCD1 GKO mice on a restricted methionine (MR) diet showed reduced hepatic FGF21 expression (28). In support of this, oleate, but not palmitoleate, treatment suppressed SCD1 inhibitor-induced FGF21 expression in isolated primary hepatocytes. Cells co-treated with SCD1 inhibitor and palmitate resulted in higher FGF21 expression compared with SCD1 inhibitor treated cells. In the diet-induced obesity mouse model, palmitoleate treatment increased FGF21 expression compared with oleate (29). These results contradict previously reported in vitro work showing that treating HepG2 cells with oleate, but not palmitate, increased FGF21 expression (30). Even though, more studies are required to further characterize the effect of oleate on FGF21 expression, feeding triolein supplemented diet did not cause a significant elevation in FGF21 relative to HCD fed control mice.

PGC-1α regulates the expression of multiple genes involved in lipid and glucose metabolism. In patients with nonalcoholic fatty liver diseases, low PGC-1α expression was associated with insulin resistance (31). Increased FGF21 correlated with increased ER stress in the liver of LKO mice and both of them are restored to normal levels upon restoring oleate levels (14). Hepatic oleate regulates ER stress through PGC-1α, which is known also to regulate liver FGF21 (14,31). PGC-1α deletion was sufficient to relieve ER stress in the liver of LKO mice as well as reduce FGF21 expression. Taken together, these data reveal that PGC-1α mediated ER stress (14,32, 33) increases FGF21 expression in SCD1 deficient liver. Furthermore, reduced GLUT4 expression in adipose tissue in response to hepatic PGC-1α deletion may explain partial restoration of plasma glucose levels in DLKO mice. This result may further support FGF21 regulation of GLUT4 expression in WAT. Previously, we
showed that hepatic SCD1 decreased protein expression of ChREBP and feeding triolein supplemented diet restored its expression (15). Therefore, in LKO mice fed HCD, the transcription factor ChREBP is less likely involved in SCD1 deficiency induced FGF21 expression. In human and mice, consumption of HCD increases the expression of ChREBP and induces FGF21 (34).

FGF21 regulates systemic glucose metabolism (35,36). Treatment with FGF21 resulted in decreased body weight, reduced blood glucose and increased insulin sensitivity in the obese mouse model (37-40). Therefore, elevated plasma FGF21 in the SCD1 deficient state may contribute to improved insulin sensitivity and enhanced glucose uptake observed in LKO mice. Taken together, our findings indicate that hepatic oleate is a critical regulator of glucose homeostasis.

**Experimental Procedures**

**Animal and diets**

All experiments were carried out using C57BL/6 mice background. The process of generating SCD1 lox/lox (LOX) control mice and SCD1 lox/lox; Albumin Cre/+ tissue specific liver knockout (SCD1 LKO) mice as well as SCD1 and PGC-1α double liver knockout mice (DLKO) was previously described (14,15). Mice were maintained at the University of Wisconsin-Madison animal care facility on regular 12 hours light/dark cycles with free access to food and water. Mice were fed a standard rodent chow diet (Purina 5008) unless otherwise stated. All studies were carried out using 8 to 14 weeks old mice. For experiments, mice were fed HCD, which has very low fat, for a period of 10 days and fasted 4 hours before being euthanized with isoflurane overdose. Triolein or Tristearin supplemented HCDs were prepared by supplementing the fat-free basal mix (TD88232; Harlan Teklad) with 15% by weight of Tristearin (T5016; Sigma) or Triolein (99% purity, T7140; Sigma). Collected tissues were snap frozen in liquid nitrogen and stored at -80°C for future analysis. All in vivo experimental animal procedures performed were approved by the Institutional Animal Care and Use Committee at University of Wisconsin-Madison.

**Fatty acid preparation and cell culture**

Primary hepatocytes were derived from C57BL/6J mice. Briefly, mouse liver was initially perfused with perfusion buffer (400 ml HBSS, 25 mL HEPES (7.2 g/30 mL), and 5 mL EGTA (95 mg/5 mL), pH 7.5). The liver was then perfused with collagenase buffer (80 mL HBSS, 10 mL CaCl2 (74 mg/10 mL), 5 mL HEPES, pH 7.5). Isolated hepatocytes were later passed through 70 μM cell strainer (Biosciences, South San Francisco, CA, USA) and maintained in serum free media 199 (Invitrogen-Gibco, Grand Island, NY, USA) for subsequent experiments (41). Fatty acid stock solutions (1mM) of palmitoleate and oleate were complexed to fatty acid-free BSA in 150mM NaCl. The fatty acids and BSA stock mixtures were incubated at 37 °C for 1 hour with constant vortexing. For the preparation of sodium palmitate BSA solution, briefly, sodium palmitate was dissolved in 150mM NaCl solution at 70 °C for 30 min and then added to filtered fatty-acid free BSA solution while stirring at 37 °C for 1 hour. This created a 1mM sodium palmitate/0.17 mM BSA solution with 6:1 molar ratio of palmitate and BSA. Isolated primary hepatocytes were incubated overnight in serum-free DMEM medium and then treated with either 1 μM A939572 (an SCD1 inhibitor) alone or in combination with 100 μM BSA.
conjugated fatty acids for 12 hours before harvest.

Real-time quantitative PCR analysis
Total RNA isolation was performed using Tri reagent (Molecular Research Center) and subsequently treated with Turbo DNase (Ambion). Isolated RNA was reverse transcribed with a high capacity cDNA reverse transcription kit (Applied Biosystems). Real-time quantitative PCR analysis was performed using Syber Green Master Mix (Applied Biosystems) and an ABI 7500 instrument (Applied Biosystems). Relative relative expression levels were determined using the comparative CT normalized to housekeeping gene 18s. Used primer sequences are available upon request.

Plasma FGF21 assay
Mouse blood samples were collected via cardiac puncture into EDTA containing tube. Collected plasma samples were snap frozen in liquid nitrogen and stored at -80 °C for future analysis. Plasma FGF21 levels were measured using the FGF-21 Quantikine ELISA Kit (R&D Systems, #MF2100).

Immunoblot analysis
An aliquot of frozen animal tissues was homogenized by using beads homogenizer (Omni International, Inc., Kennesaw, GA, USA) in ice-cold RIBA buffer (cell signaling) with 1 mM PMSF and protease inhibitor (Protease inhibitor Cocktail Set III, Calbiochem, La Jolla, CA). After homogenization, samples were then centrifuged 14000 rpm for 20 min at 4°C. For adipose tissues, samples were spun twice to ensure complete removal of residual lipids and supernatant was collected in each time. The supernatant was immediately stored at -80 °C. For immunoblot analysis, 20 or 30 µg protein was resolved on 12% polyacrylamide gels and transferred to a nitrocellulose membrane. For plasma samples, 10 µg protein was loaded on the gel. Membranes were incubated with primary antibody at 4 °C overnight followed with incubation with anti-rabbit or anti-mouse secondary antibody horseradish peroxidase conjugate. Anti Glut4 (#2213, 1/1000) was purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA), and Anti Vinculin (#18058, 1/2000) was purchased from Abcam (Cambridge, UK). Blots were detected by chemiluminescence and autoradiography using Bio-Rad Gel Doc (Bio-Rad laboratories In, Hercules, CA). For densitometry, values of target proteins were first divided by values for Vinculin (loading control), and presented relative to their expression in control mice.

In vivo 2-[3H]deoxyglucose uptake assay
In vivo 2-[3H]deoxyglucose uptake assay was performed as previously reported with minor changes (12). Briefly, mice were fed HCD for 10 days and fasted 4 hours before the experiment. An oral gavage dose of 15 µCi of 2-[3H]deoxyglucose per mouse in 20% dextrose solution were administered and mice were euthanized after 1.5 hours with Isoflurane overdose. Isolated samples were digested with 1 M KOH and subsequently neutralized with 1 M HCl. Neutralized samples were mixed with scintillation reagent and radioactivity was quantified in liquid scintillation counter.

Positron Emission Tomography (PET)/Computed Tomography (CT)
Imaging and analysis
After overnight fasting, mice received tail vein injections of either vehicle or phloretin 10 mg/Kg body weight. After one hour, all mice received another tail vein injection of
approximately 9 MBq of 2-Deoxy-2-\[^{18}\text{F}\] Fluoro-D-glucose (FDG) one hour before imaging (42,43). Mice were anesthetized with 2% isoflurane gas mixed with oxygen till the time of imaging (42,43). All images were obtained using Siemens Inveon Hybrid micro PET/CT (Siemens Medical Solutions, Knoxville, TN) in the prone position. Forty-million counts per mouse were collected for the PET scan to obtain adequate signal-to-noise. PET data was histogrammed into single frame and later restructured using ordered-subset expectation maximization (OSEM) of three dimensions followed by maximum \textit{posteriori} algorithm (Matrix size = [128,128,159], Pixel size = [0.776, 0.776, 0.796] mm, iterations = 18, subsets = 16, and beta smoothing factor = 0.004) with CT attenuation correction applied but not scatter correction (43,44). Images were analyzed using the General Analysis tools provided by Siemens Inveon Research Workplace (Siemens Medical Solutions, Knoxville, TN). Data were identically windowed and scaled based on each animal’s decay corrected injection activity. To avoid inaccuracies in quantitative measurements due to partial volume affects, three relatively small regions of interest (~1/3 size the tissue of interest) were drawn within the brain, kidneys, liver, heart, intestine, and WAT, and then averaged. Regions of interest (ROIs) were quantified as the percent injected dose (ID) normalized by the mass of the tissue (%ID/g tissue), assuming tissue density of water =1g/mL

\textbf{Statistical Analyses}

Results are presented as mean ± SEM. Comparisons were performed using an unpaired, two-tailed student’s $t$ test. Results with a $P$ value < 0.05 were considered statistically significant compared with control LOX mice.

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\textbf{Conflict of interest}

The authors declare that they have no conflicts of interest with the contents of this article.
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**Figure Legends**

**Figure 1. Hepatic SCD1 deficiency enhances systemic glucose utilization.** 10 weeks old LOX and LKO male mice were fed HCD for 10 days. Mice fasted four hours before an oral gavage dose of 15 µCi mouse of 2-[^3H]deoxyglucose in 20% dextrose solution. Tissues were collected after 90 minutes and radiolabel activity was measured by liquid scintillation counter. (n = 3/group). Values are mean ± SEM, * P<0.05, # P =0.068 vs. LOX counterparts by Student’s two-tailed t test.

**Figure 2. Hepatic SCD1 deficiency differentially regulates genes encoding glucose transporters in metabolic tissues.** 12 weeks old LOX and LKO male mice were fed HCD for 10-14 days and mice were fasted four hours before collecting tissues for analysis.
(A, B) Liver and WAT gene expression analysis for the indicated genes using qPCR. Values are mean ± SEM, (n = 6-9/group). (C-D) Western blot with the indicated antibodies performed on white and brown adipose tissues. Values are mean ± SEM, (n = 3-5/group). (E, F) White and brown adipose tissues gene expression analysis for the indicated lipogenic genes using qPCR. Values are mean ± SEM, (n = 7-9/group), * P<0.05, ** P<0.01, *** P<0.001 vs. LOX counterparts by Student’s two-tailed t test.

Figure 3. Hepatic SCD1 deficiency enhances glucose uptake through GLUT1 dependent and independent mechanisms. 12 weeks old LOX and LKO mice were fed HCD for 10 days and fasted overnight prior to an intravenous injection of either vehicle or phloretin of 10 mg/Kg body weight. One hour after phloretin treatment, mice received an intravenous injection of 2-Deoxy-2-[18F] Fluoro-D-glucose (FDG) one hour before imaging. FDG uptake levels were quantified as the percent injected dose normalized by the mass of the tissue of interest (%ID/g tissue). Values are mean ± SEM, (n = 4-6/group). * P<0.05 vs. LOX counterparts by Student’s two-tailed t test.

Figure 4. Hepatic SCD1 deficiency induces FGF21 expression. 10 weeks old LOX, LKO male mice were fed HCD for 10 days and mice were fasted four hours before collecting tissues for analysis. (A) FGF21 relative expression in liver and plasma protein levels. (B) Hepatic gene expression of KLB. (C) FGF21 relative expression in white and brown adipose tissues. (D) Adiponectin relative expression in white adipose tissue and adiponectin plasma levels, (n = 7-8/group). Values are mean ± SEM, * P<0.05, ** P<0.01, *** P<0.001 vs. LOX counterparts by Student’s two-tailed t test.

Figure 5. Oleate is a critical regulator of FGF21 expression. 12 weeks old LOX and LKO mice were fed either HCD, triolein, or tristearin for 10 days. Mice were euthanized after four hours fasting and plasma samples were collected. (A) FGF21 relative expression and plasma protein levels and (B) blood glucose levels after 4 hours fasting. Values are mean ± SEM, (n = 3-5/group). * P<0.05 vs. LOX counterparts by Student’s two-tailed t test. (C) FGF21 expression in primary hepatocytes treated with SCD1 inhibitor or SCD1 inhibitor in combination with either Palmitate (16:0), Palmitoleate (16:1), or Oleate (18:1).

Figure 6. Oleate regulates FGF21 partially through PGC-1α. (A) PGC-1α relative expression in the liver of 10 weeks old LOX and LKO male mice fed HCD for 14 days. (B) Hepatic and plasma FGF21 relative expression of LKO and DLKO mice. (C) GLUT4 relative expression in WAT of LKO and DLKO mice. (D) Plasma glucose levels in 12 weeks old LOX, LKO and DLKO male mice fed HCD. Values are mean ± SEM, (n = 8-10/group). * P<0.05 vs. LOX counterparts by Student’s two-tailed t test. (E) Summary Figure: Hepatic SCD1 deficiency decreases oleate synthesis and increases FGF21 expression in the liver through PGC-1α. These changes are expected to increase glucose uptake in liver and adipose tissue either directly or indirectly.
Fig. 2

A

Liver

B

WAT

C

White Adipose Tissue (WAT)

D

Brown Adipose Tissue (BAT)

E

WAT Lipogenesis

F

BAT Lipogenesis
Fig. 4
Fig. 6

A

Relative Expression (AU)

PGC-1α

LOX  LKO  DLKO

* * ****

B

Relative Expression (AU)

LOX  LKO  DLKO

**

C

Relative Expression (AU)

GLUT4

LOX  LKO  DLKO

*

D

N/albumin

LOX  LKO  DLKO

** P = 0.054

E

Liver

SCD1-/-

Oleate → PGC-1α → FGF21

Oleate → FGF21

White adipose tissue

Glucose uptake

Brown adipose tissue
Hepatic stearoyl CoA desaturase 1 deficiency increases glucose uptake in adipose tissue partially through the PGC-1 α–FGF21 axis in mice

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