The Cancer Drug Dasatinib Increases PGC-1α in Adipose Tissue but Has Adverse Effects on Glucose Tolerance in Obese Mice

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Dasatinib (Sprycel) is a tyrosine kinase inhibitor approved for treatment of chronic myeloid leukemia. In this study, we identify dasatinib as a potent inducer of Peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α mRNA. Dasatinib increased PGC-1α mRNA expression up to 6-fold in 3T3-F442A adipocytes, primary adipocytes, and epididymal white adipose tissue from lean and diet-induced obese mice. Importantly, gene expression translated into increased PGC-1α protein content analyzed in melanoma cells and isolated mitochondria from adipocytes. However, dasatinib treatment had adverse effect on glucose tolerance in diet-induced obese and *Ob/Ob* mice. This correlated with increased hepatic PGC-1α expression and the gluconeogenesis genes phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. In conclusion, we show that dasatinib is a potent inducer of PGC-1α mRNA and protein in adipose tissue. However, despite beneficial effects of increased PGC-1α content in adipose tissue, dasatinib significantly impaired glucose tolerance in obese but not lean mice. As far as we are aware, this is the first study to show that dasatinib regulates PGC-1α and causes glucose intolerance in obese mice. This should be considered in the treatment of chronic myeloid leukemia. **(*Endocrinology* 157: 4184–4191, 2016)**

Drug therapy for chronic myeloid leukemia (CML) was, until 1999, limited to nonspecific agents such as busulfan and interferon-α (1–3). The development of small-molecule tyrosine kinase inhibitors (TKIs), such as dasatinib and imatinib, has dramatically improved the prognosis for CML patients within the last 10 years. CML, which accounts for 10% of all leukemias, is almost always (95%) associated with hyperactivation of a BCR-ABL1 fusion protein resulting in uncontrolled proliferation (4, 5). Dasatinib and imatinib act by interfering with the interaction between the fused BCR-ABL1 protein to block proliferation (6). This "targeted" approach has improved 10-year CML overall survival from less than 20% up to 90% (1). However, TKIs approved for first- and second-line treatment of CML-chronic phase have a distinct toxicity profile that includes the metabolic syndrome and impaired fasting plasma glucose concentration (7). In agreement, a recent study reported that in a group of patients treated with TKIs, 30%–50% showed hyperglycemia (8). Due to increased CML survival rates (9) and an ageing population, it can be predicted that prevalence of CML will increase. However, very limited data are available on the effects of TKIs on glucose metabolism. Moreover, obesity is a predictor of impaired glucose homeostasis, and for the first time, more people are overweight compared with underweight globally (10). Interestingly, a case control study has reported that obesity is associated with 2- to 3-fold increased risk of CML (11). However, no

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Abbreviations: ABL1, abelson murine leukemia viral oncogene homolog 1; BCR, breakpoint cluster region protein; CML, chronic myeloid leukemia; DIO, diet-induced obese; eWAT, epididymal WAT; G6Pase, glucose-6-phosphatase; GTT, glucose tolerance test; PEPCK, phosphoenolpyruvate carboxykinase; PGC, PPARγ coactivator; qPCR, quantitative polymerase chain reaction; TBP, TATA-binding protein; TKI, tyrosine kinase inhibitor; UCP, uncoupling protein; WAT, white adipose tissue.

study to date has investigated the effect of dasatinib on glucose metabolism in the context of obesity.

A major player in maintaining glucose metabolism is the transcriptional coactivator Peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α. PGC-1α regulates a program of mitochondrial biogenesis and adaptive thermogenesis. In adipose tissue PGC-1α seems to play a beneficial role on glucose homeostasis maintenance, and it is down-regulated in insulin resistant murine (12) and human (13–15) adipose tissue. Importantly, adipose tissue-specific PGC-1α knockout mice develop glucose intolerance on a fat diet (16), indicating that adipose PGC-1α is protective against glucose intolerance. Although PGC-1α is beneficial in adipose tissue, augmented liver PGC-1α can be detrimental to glucose homeostasis. In the liver, PGC-1α is induced by fasting and regulates the transcription of genes that stimulate gluconeogenesis (17–19), thereby increasing liver glucose output. In the current study, we identified dasatinib as a potent inducer of PGC-1α. Because normal regulation of PGC-1α in adipose tissue and the liver is essential in regulating glucose metabolism, dasatinib might influence glucose homeostasis. Therefore, the purpose of the current study was to investigate the effect of dasatinib on PGC-1α mRNA and protein expression in adipose tissue and the liver and to examine whether dasatinib treatment altered glucose metabolism in the context of obesity.

Materials and Methods

Cell culture

3T3-F442A adipocyte differentiation was induced by treating confluent cells with 850nM insulin and 1μM rosiglitazone for 2 days. Cells were then maintained in 850nM insulin for another 4 days. Primary adipocytes were acquired from fractions obtained from 4-week-old male or female mice as described (20). Green fluorescent protein control and Flag-human influenza hemagglutinin-PGC-1α adenovirus have been previously described (21, 22).

Quantitative polymerase chain reaction (qPCR) and primers

RNA was extracted from cultured cells or frozen tissue samples using TRIzol and purified with QIAGEN RNeasy minicolumns. Normalized RNA was reverse transcribed using a high-capacity cDNA reverse-transcription lot (Applied Biosystems), and cDNA was analyzed by quantitative RT-PCR as described (23). Relative mRNA levels were calculated using the comparative threshold cycle method and normalized to TATA-binding protein (TBP) mRNA. All primers used are listed with their sequence in Supplemental Table 1.

Nuclear fractionation

In primary adipocytes, nuclear fractionations were performed using an extraction kit (NXTRACT; Sigma) according to manufacturer's instructions. Mouse epididymal adipose tissue was rapidly excised and homogenized in mitochondrial isolation buffer (250mM sucrose, 2mM EDTA, 10mM sodium citrate, 0.6mM $MnCl_2$, and 100mM Tris-HCl; pH 7.4) followed by mitochondrial isolation by differential centrifugation as described (24).

Immunoblotting

For Western blotting, homogenized tissues or whole-cell lysates were lysed in radioimmunoprecipitation assay buffer containing protease-inhibitor cocktail and phosphatase-inhibitor cocktail (all from Thermo Scientific), separated by SDS-PAGE, and transferred to ImmobilonP membranes (Millipore). Lysate protein concentrations were measured using the bicinchoninic acid method with BSA as standard (Pierce). Membranes were incubated with primary antibodies overnight at 4°C, followed by incubation with horseradish peroxidase-conjugated secondary antibody for ½ hour at room temperature. The primary antibodies used were anti-PGC-1α (4C1.3, ST1202; Millipore) and TBP (8515; Cell Signaling Technology).

Animal experiments

All animal experiments were approved by the Institutional Animal Care and Use Committee of the Beth Israel Deaconess Medical Center. Male mice (*Mus musculus*, C57/b6) and 16-week-old *Ob/Ob* mice were purchased from The Jackson Laboratory. *Ob/Ob* and lean mice were fed a standard irradiated rodent chow diet, whereas 26-week-old diet-induced obese (DIO) mice received a 60% high-fat diet (D12331; Research Diets) for 16 weeks. All mice were maintained in 12-hour light, 12-hour dark cycles (6 AM to 6 PM) at 22°C and received water and food ad libitum.

Glucose tolerance test (GTT)

For GTT, mice were fasted overnight. Glucose (2 g/kg) was administered ip, and blood glucose levels were measured at 0, 20, 40, 60, and 120 minutes using a glucometer.

Statistical analyses

Results are shown as mean ± SEM. Statistical testing was performed using *t* tests or one-way ANOVA as appropriate. Two-way ANOVA with repeated measures was used for the GTT studies. Tukey's post hoc test was performed when ANOVA revealed significant main effects. Statistical analysis was performed using GraphPad Prism. The significance level was set at $P < .05$.

Results

Dasatinib is a potent inducer of PGC-1α mRNA and protein

We previously conducted a qPCR-based screen in 3T3-F442A adipocytes for inducers of PGC-1α gene expression using a collection of approximately 3000 annotated

small molecules, which includes natural products and clinically approved drugs (20). Here, we found that the cancer drug, dasatinib (Sprycel), but not a similar TKI imatiNib, potently induced of PGC-1α mRNA in F442A adipocytes (Figure 1A). A total of 10μM dasatinib sufficed to increase PGC-1α expression by approximately 2-fold in 3T3-F442A adipocytes (Figure 1B). However, at the same dose, imatinib failed to induce PGC-1α mRNA expression (Figure 1C), confirming the findings of the qPCR-based screen. To investigate whether PGC-1α mRNA translated into an increase in PGC-1α protein content, we turned to a melanoma cancer cell line chosen, because it has very high PGC-1α mRNA levels (21, 22). In this cell line, 5μM–10μM dasatinib increased PGC-1α protein expression in a dose-dependent manner (Figure 1D) as detected by the antibody at 97-kDa (PGC-1α-1) and 39-kDa (PGC-1α-4). Short hairpin RNA-mediated knockdown of PGC-1α was included to confirm the antibody's specificity towards PGC-1α (Figure 1D). We then evaluated the time course by which PGC-1α protein expression increased using the high 10μM dasatinib concentration. PGC-1α protein expression increased already after 2 hours of dasatinib treatment and reached maximum expression after 6 hours (Figure 1E). These findings show that dasatinib potently increases both PGC-1α mRNA and protein.

PGC-1α mRNA and protein is induced in primary adipocytes and adipose tissue in vivo by dasatinib

In primary adipocytes from mice, dasatinib increased gene expression of PGC-1α by 60% (Figure 2A). Imatinib had no impact on PGC-1α mRNA in these primary adipocytes from mice. In addition, uncoupling protein (UCP)-1 expression increased 4-fold, suggesting that dasatinib treatment stimulated browning of primary adipocytes (Figure 2B). To investigate whether dasatinib also increased PGC-1α protein, we isolated nuclear fractionations from primary adipocytes and immunoblotted for PGC-1α protein. We found that 5μM–20μM dasatinib

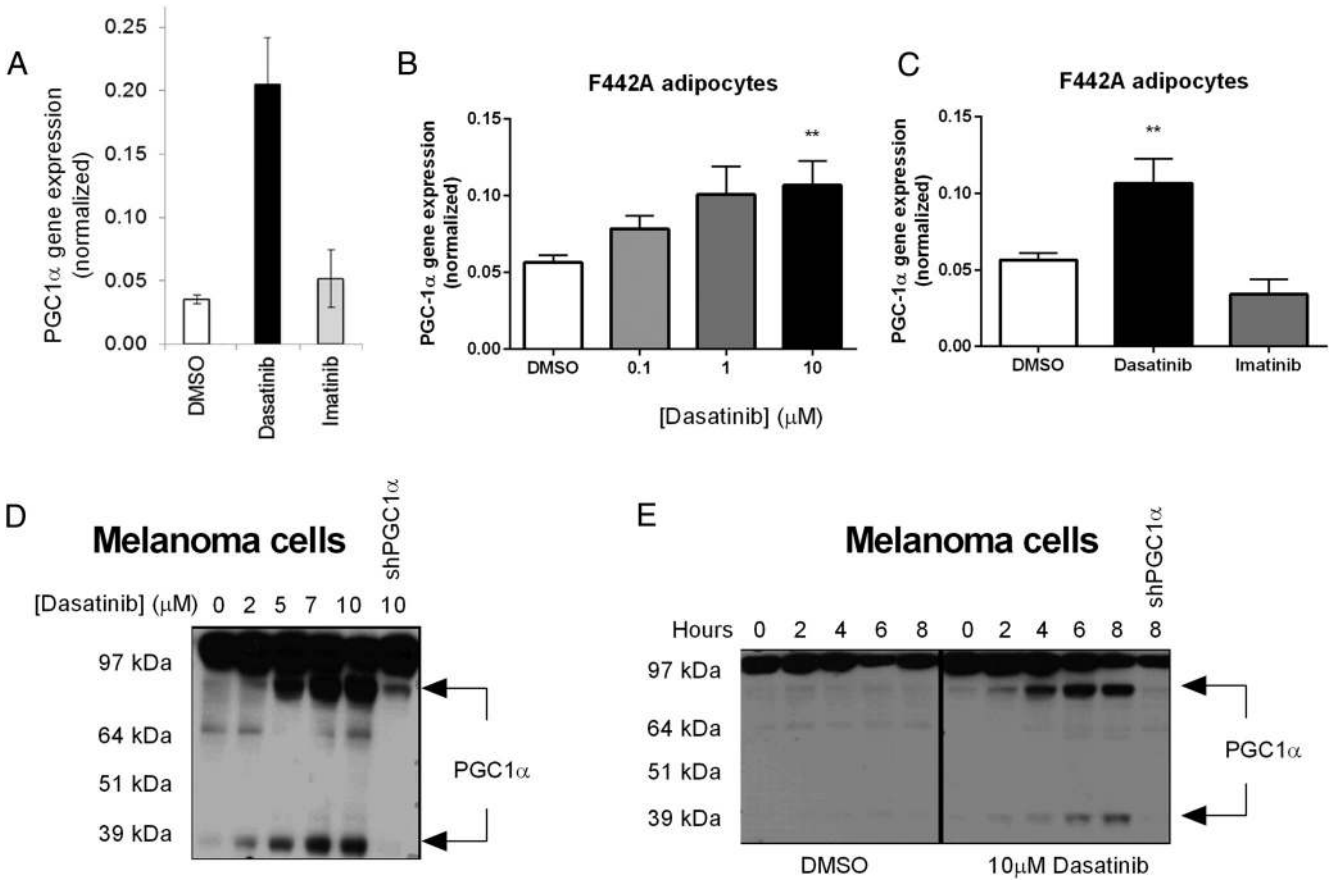

Figure 1. A, qPCR-based screen in 3T3-F442A adipocytes for inducers of PGC-1α gene expression. Bar graph shows mRNA expression of PGC-1α in response to dasatinib, imatinib, or DMSO as vehicle control (10μM, 24-h incubation). B, Dose-response experiment of PGC-1α gene expression in response to dasatinib (24-h incubations) (20). DMSO, n = 9; 0.1μM, n = 2; 1μM, n = 3; 10μM, n = 7. C, Comparison of the effect of imatinib and dasatinib on PGC-1α gene expression in 3T3-F442A adipocytes (10-h incubation). DMSO, n = 9; dasatinib, n = 7; imatinib, n = 3. D, Western blotting showing PGC-1α protein in a dose-response experiment in PGC-1α-overexpressing melanoma cells stimulated with indicated concentration of dasatinib (6 h). E, PGC-1α protein expression during a time course experiment in PGC-1α-overexpressing melanoma cells stimulated with dasatinib for the indicated duration of time; n = 3–9, representing at least 3 independent experiments. Significant effect of treatment compared with DMSO vehicle control is indicated by **, $P < .01$. Values are mean ± SEM.

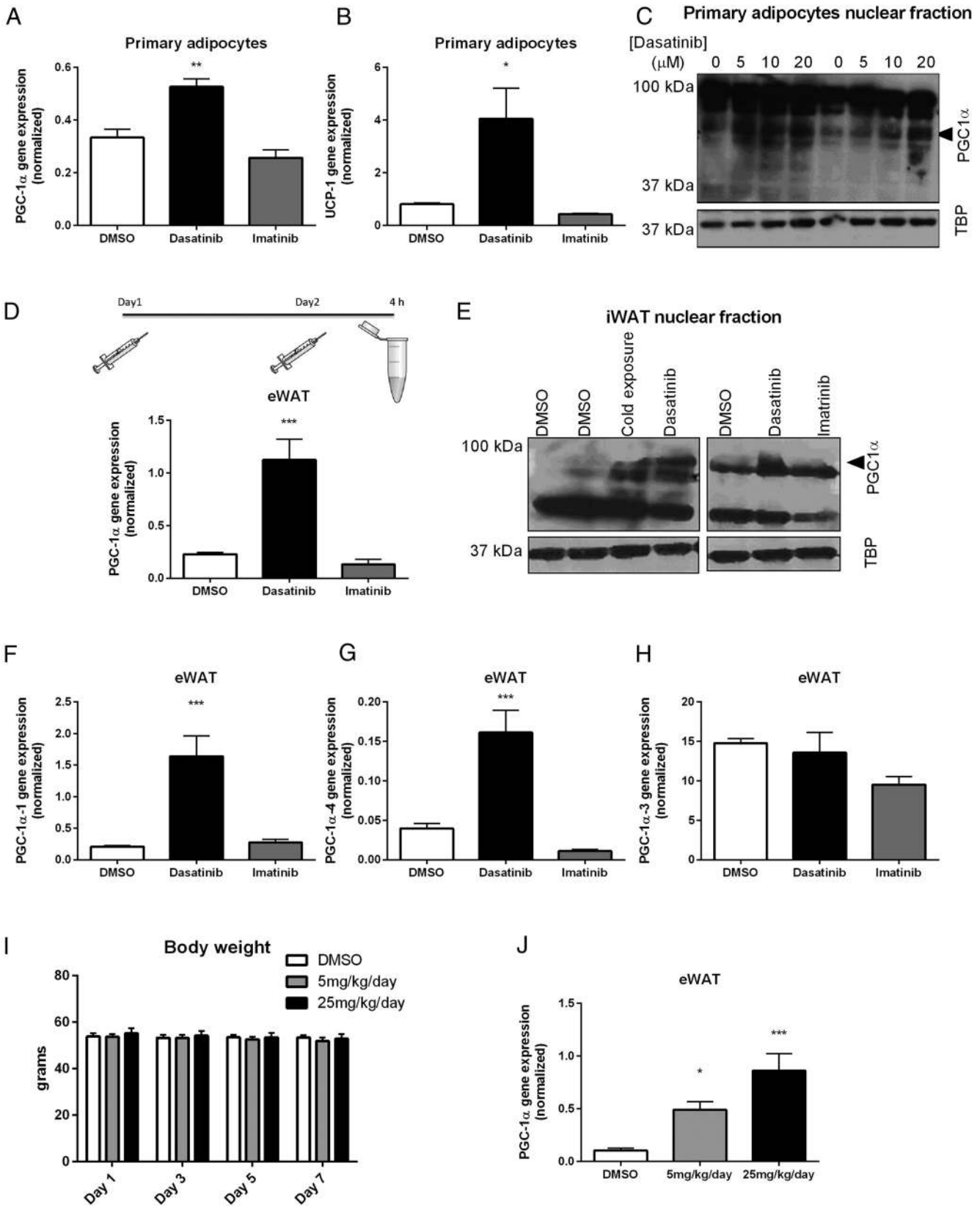

Figure 2. A, Bar graph showing the effect of imatinib and dasatinib on PGC-1α gene expression in primary adipocytes (from inguinal WAT) (10μM, 24-h incubation); n = 3–4. B, Bar graph showing the effect of imatinib and dasatinib on UCP-1 gene expression in primary adipocytes; n = 3–4. C, Nuclear fractionation experiment in primary adipocytes. Western blotting showing nuclear PGC-1α and TBP (control) protein in a dose-response experiment in primary adipocytes stimulated with the indicated concentrations of dasatinib. D, Protocol for ip injections and tissue collection. Bar graph showing the effect of ip injections of imatinib and dasatinib on PGC-1α gene expression in WAT (epididymal) in mice (50-mg/

up-regulated nuclear PGC-1α protein without affecting TBP (control) expression (Figure 2C). We then tested the effect of dasatinib on adipose tissue in vivo to elucidate the relevance of our in vitro findings. We injected dasatinib or imatinib at the dose of 50-mg/kg body weight the day before, and again 4 hours before white adipose tissue (WAT) (epididymal WAT [eWAT]) was collected for analysis. PGC-1α mRNA expression increased 4-fold in response to dasatinib treatment, whereas imatinib did not affect PGC-1α mRNA expression (Figure 2D). Again, nuclear fractionation experiments revealed that PGC-1α protein was also up-regulated to a similar extend as by cold exposure, a known inducer of PGC-1α in mice (Figure 2E). This confirms our findings in vitro, that dasatinib, but not imatinib, exhibits PGC-1α mRNA and protein-inducing properties. The primer used to detect PGC-1α recognizes all PGC-1α isoforms so we next analyzed using isoform gene expression. The induction of PGC-1α could be attributed to a significant increased PGC-1α-1 and PGC-1α-4 mRNA (Figure 2, F and G) but not PGC-1α-3 (Figure 2H) or PGC-1α-2 (data not shown, low copy number). Because 50-mg/kg body weight is a relatively high dose, we performed a dose-response experiment using lower doses (5- and 25-mg/kg body weight) injected every day for 7 days in lean mice. Body weight (Figure 2I) was unaltered by 7-day dasatinib treatment. PGC-1α mRNA expression was increased in a dose-dependent manner by 4- and 7-fold in response to 5- and 25-mg/kg body weight, respectively, in eWAT (Figure 2J). These findings show that dasatinib increases PGC-1α mRNA expression in adipose tissue in vivo in a dose-dependent manner without altering body weight.

Dasatinib up-regulates hepatic gluconeogenesis genes

Up-regulation of PGC-1α in adipose tissue is likely beneficial for glucose homeostasis maintenance (13, 16). We therefore analyzed glucose tolerance in DIO mice after treatment with dasatinib. DIO C57/b6 mice develop glucose intolerance (25, 26), and we sought to test whether dasatinib could improve glucose tolerance due to increased PGC-1α protein content in adipose tissue. As we found in lean mice, 7-day dasatinib treatment did not affect body weight in DIO mice (Figure 3A). However, contrary to our hypothesis, we found that dasatinib impaired glucose tolerance (Figure 3B) despite a 4-fold up-regulation of PGC-1α mRNA in adipose tissue (Figure 3C) together with a doubling of UCP-1 mRNA expression (Figure 3D). This led us to investigate the effect of dasatinib treatment on other metabolically active tissues. Dasatinib did not affect PGC-1α gene expression in skeletal muscle but hepatic PGC-1α gene expression was doubled (Figure 3, E and F). In the liver PGC-1α regulates genes involved in gluconeogenesis (19, 27, 28). We therefore analyzed gene expression of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK). Both PEPCK (mitochondrial and cytosolic) and G6Pase mRNA were potently up-regulated in DIO mice treated with dasatinib compared with vehicle control (Figure 3G). To understand the implications of dasatinib in the setting of a more severe condition of glucose intolerance, we also tested the effect of dasatinib treatment in *Ob/Ob* mice. The *Ob/Ob* mouse is genetically deficient in leptin and displays severe metabolic abnormalities, more similar to those seen in obese humans with noninsulin-dependent diabetes mellitus. These abnormalities include obesity, hyperglycemia, glucose intolerance, and hyperinsulinemia (29, 30). Body weight was unaffected by dasatinib treatment (Figure 3H), but fasted blood glucose was significantly increased and glucose tolerance markedly impaired (Figure 3I). Interestingly, dasatinib did not worsen glucose homeostasis in lean mice (Figure 3J). Those findings show that dasatinib treatment in the context of obesity has detrimental effects on glucose homeostasis in mice. This should be considered in particular when treating obese and diabetic CML patients with dasatinib.

Discussion

This study shows evidence that dasatinib increases PGC-1α expression in fat and liver. Interestingly, in DIO and *Ob/Ob* mice, dasatinib treatment significantly worsened the already impaired glucose intolerance. This correlated with up-regulated PGC-1α mRNA liver expression and induction of gluconeogenesis enzymes such as PEPCK and G6Pase (27, 28). Impaired glucose tolerance in dasatinib treated mice could thus be due to increased gluconeogenesis and glucose output from the liver, although this was not analyzed in the current study. Correspondingly, overexpression of hepatic PGC-1α caused hepatic insulin resistance, manifested by higher glucose produc-

Figure 2 (Continued). kg body weight); n = 5. E, Western blotting showing PGC-1α protein expression in nuclear fractionation of inguinal adipose tissue after ip injections of imatinib or dasatinib in WAT (epididymal) in mice (50-mg/kg body weight), or 4 hours of cold exposure (4°C). F, Bar graph showing the effect of ip injections of imatinib and dasatinib PGC-1α-1 (F), PGC-1α-4 (G), and PGC-1α-3 (H) gene expression in WAT (epididymal) in mice (50-mg/kg body weight); n = 5. I, Body weight in mice treated daily with 5- or 25-mg dasatinib per kg body weight for 7 days; n = 5. J, PGC-1α gene expression in mouse epididymal adipose tissue after 7 days of treatment of the indicated doses of dasatinib; n = 5. Significant effect of treatment compared with DMSO vehicle control is indicated by *, $P < .05$; **, $P < .01$; ***, $P < .001$. Values are mean ± SEM.

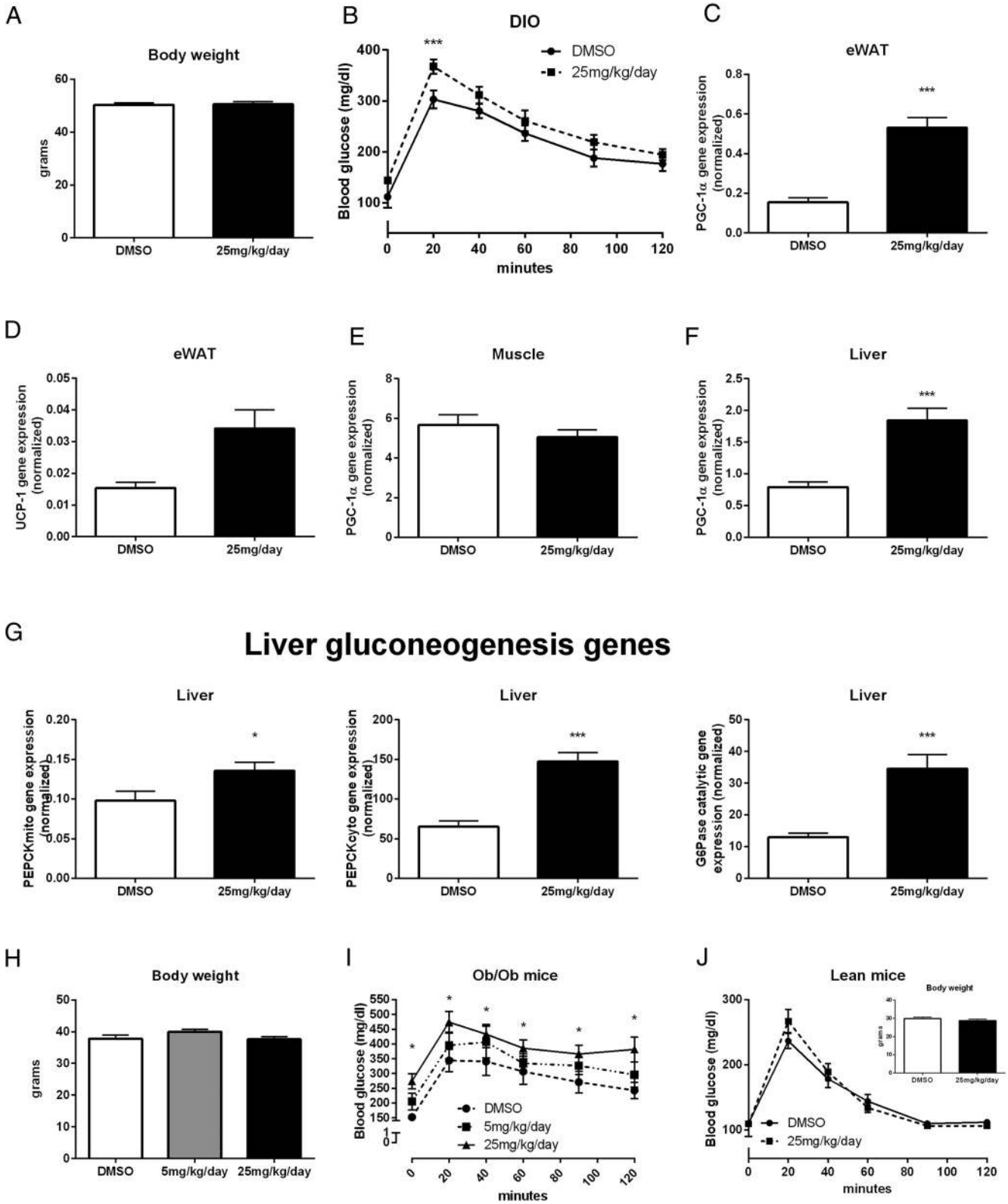

Figure 3. A, Body weight of DIO mice after 7 days of daily ip dasatinib administration; n = 11. B, Blood glucose concentration during a GTT in DIO mice; n = 11. PGC-1α (C) and UCP-1 (D) mRNA expression in eWAT, PGC-1α mRNA expression in muscle (E) and liver (F) tissue of DIO mice. Mitochondrial (G) and cytosolic (G) PEPCK, and G6Pase mRNA expression in liver from DIO mice; n = 11. H, Body weight of *Ob/Ob* mice after 7 days of daily ip dasatinib administration; n = 9–10. I, Blood glucose concentration during a GTT in *Ob/Ob* mice; n = 9–10. J, Blood glucose concentration during a GTT in lean mice and body weight in insert; n = 9–10. Significant effect of treatment compared with DMSO vehicle control is indicated by *, $P < .05$; ***, $P < .001$. Values are mean ± SEM.

tion and diminished insulin suppression of gluconeogenesis (18), although not all studies support this (31). Similarly, high hepatic expression of PGC-1α is found in animal models of insulin resistance and diabetes (19, 32, 33, 34). Future studies should investigate the effect of dasatinib in liver-specific PGC-1α knockout mice to obtain final proof that dasatinib's detrimental effects on glucose homeostasis occurs via increased PGC-1α and gluconeogenesis gene expression in the liver.

In humans, TKIs approved for treatment of CML have been associated with the metabolic syndrome and impaired fasting glucose (7). However, this is somewhat contradicted by another human study in 7 CML patients showing that dasatinib, but not imatinib, reduced blood glucose (35). This might suggest that in nonobese humans, the induction of PGC-1α in other tissues plays a more dominant role than in the liver, or that some other mechanisms benefit glucose homeostasis. It could also indicate that in nonobese subjects, dasatinib's effect on the liver is less detrimental, which is in agreement with our findings that dasatinib only impairs glucose tolerance in obese mice. Indeed, our findings show that in the context of obesity and prior insulin resistance, dasatinib treatment could be detrimental to maintenance of glucose homeostasis.

The underlying mechanism by which dasatinib induced PGC-1α gene and protein expression was not investigated in the current study. However, we did find that only dasatinib, and not the closely related TKI, imatinib, induced PGC-1α mRNA in adipocytes. Dasatinib is a more potent BCR-ABL1 TKI compared with imatinib due to its stronger inhibition of ABL1 (4, 5). The mechanism for the dasatinib-specific induction of PGC-1α could thus lie in the differences in target and potency of these 2 TKIs, or alternatively other "off target" kinases inhibited by dasatinib but not imatinib. Future studies should investigate the mechanism by which dasatinib increases PGC-1α mRNA and protein expression.

One limitation of our study was that it was performed in cells and models of glucose intolerance in mice. The effect on glucose homeostasis thus remains to be examined in humans. In particular, obese CML patients prescribed high doses of dasatinib should be monitored and evaluated for glucose intolerance. Another limitation is that we did not directly investigate the effect of dasatinib on liver glucose output can therefore not definitely conclude that liver PGC-1α is responsible for the glucose intolerance observed in the current study.

During a 12-month follow-up study, treatment with dasatinib has been found to be favorable compared with imatinib due to higher cytogenetic response (77% vs 66%) and a higher rate of major molecular response (46% vs 28%) (36). Dasatinib is thus excellent news for CML patients. Furthermore, we show that dasatinib significantly increase PGC-1α in adipose tissue, which may be beneficial for these patients. However, longitudinal as well as cross-sectional studies should aim to include investigations of glucose tolerance in CML patients receiving dasatinib treatment in order to understand its potential detrimental effect on glucose metabolism in obese human patients.

Appendix

See Table 1.

Acknowledgments

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Author contributions: L.S., J.L., and B.M.S. designed the study. L.S. conducted the experiments, performed the laboratory analysis, and wrote the manuscript. L.S., J.L, I.A.L., X.Z., E.A.R., and B.M.S. took part in conducting the experiments and/or developing the methods. All authors commented on and approved the final version of the manuscript. B.M.S. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosure Summary: The authors have nothing to disclose.

Table 1. Antibody Table

Peptide/ Protein Target	Antigen Sequence (if Known)	Name of Antibody	Manufacturer, Catalog Number, and/or Name of Individual Providing the Antibody	Species Raised in; Monoclonal or Polyclonal	Dilution Used	RRID
PGC-1α		Anti-PGC-1α	Millipore, 4C1.3, ST1202	Mouse	1:500	AB_2237237
TBP		Anti-TBP	Cell Signaling Technology, 8515	Rabbit	1:1000	AB_10949159

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