Biochemical and Biophysical Research Communications 424 (2012) 675–680

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Anti-diabetic and hypolipidemic effects of *Sargassum yezoense* in *db*/*db* mice

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ARTICLE INFO

Article history:
Received 25 June 2012
Available online 10 July 2012

Keywords:
Sargassum yezoense
PPARα/γ
Type 2 diabetes mellitus
Dyslipidemia

ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) have been considered to be desirable targets for metabolic syndrome, even though their specific agonists have several side effects including body weight gain, edema and tissue failure. Previously, we have reported *in vitro* effects of *Sargassum yezoense* (SY) and its ingredients, sargaquinoic acid (SQA) and sargahydroquinoic acid (SHQA), on PPARα/γ dual transcriptional activation. In this study, we describe *in vivo* pharmacological property of SY on metabolic disorders. SY treatment significantly improved glucose and lipid impairment in *db*/*db* mice model. More importantly, there are no significant side effects such as body weight gain and hepatomegaly in SY-treated animals, indicating little side effects of SY in liver and lipid metabolism. In addition, SY led to a decrease in the expression of G6Pase for gluconeogenesis in liver responsible for lowering blood glucose level and an increase in the expression of UCP3 in adipose tissue for the reduction of total and LDL-cholesterol level. Altogether, our data suggest that SY would be a potential therapeutic agent against type 2 diabetes and related metabolic disorders by ameliorating the glucose and lipid metabolism.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disease characterized by the resistance of target tissues to insulin stimulation [1]. And it is usually associated with hyperglycemia, dyslipidemia, obesity, hypertension, fatty liver, atherosclerosis, certain cancers and cardiovascular disease [2]. Relieving insulin resistance has been considered as a current approach to treating T2DM [3].

Thiazolidinediones and fibrate drugs are the most commonly used medications in the T2DM, hyperlipidemia and insulin resistance. They bind to and activate peroxisome proliferator-activated receptors (PPARs), which result in upregulation of several genes involving in glucose and lipid metabolism [4]. The PPARs are members of the nuclear hormone receptors superfamily of ligand-activated transcription factors, and currently appreciated as potential therapeutic targets for the treatment of diabetes and dyslipidemia. PPARs consist of three isoforms, PPARα, PPARβ/δ, and PPARγ [5]. PPARγ, predominantly expressed in adipose tissues and macrophages [6], affects genes involved in lipid synthesis and storage, and glucose homeostasis. PPARγ agonists, such as thiazolidinedione including rosiglitazone and pioglitazone, control lipid metabolism and insulin sensitivity. However, several concerns such as body weight gain associated with excess increase of fat mass arise in T2DM patients [7]. Accumulating evidences indicate that activation of PPARα predominantly expressed in the liver [8], would stimulate lipid consumption by enhancing the expression of fatty acid oxidation genes, resulting in amelioration of hyperlipidemia. PPARα agonists, such as fenofibrate used for treatment hyperlipidemia and reducing cardiovascular disease, have a potent effect to reduce plasma triglycerides [9]. Because of these distinct metabolic effects of PPARα and PPARγ agonists on insulin sensitivity and lipid metabolism, new drug development has focused on dual PPARs which possess PPARγ, as well as PPARα activity. It has been proposed that more desirable effects with few side effects (e.g., extra body weight gain and hepatotoxicity) would be guaranteed by simultaneous activation of PPARα and PPARγ [10–12]. Many PPARα/γ dual agonists have been identified and tested in obese and insulin-resistant individuals, however, most of them have shown unexpected side effects such as body weight gain, heart failure, renal failure, urinary cancer and anemia [13,14]. Therefore there is in urgent need of the development of novel PPARα/γ dual agonists with little adverse effects.

Marine natural products provide a rich source of chemical diversity that can be used to design and develop new potentially useful therapeutic agents [15–17]. Previously, we screened active marine natural products able to increase PPARα/γ transcriptional activity, then found that *Sargassum yezoense* (SY) extract and its

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http://dx.doi.org/10.1016/j.bbrc.2012.07.005

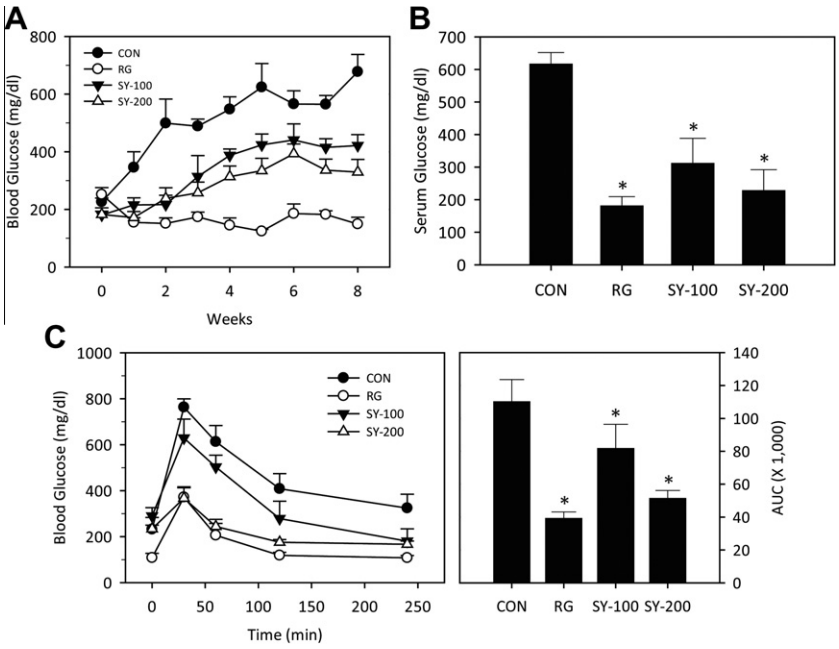

Fig. 1. Antidiabetic activity of the extract of SY in *db*/*db* mice. (A) Non-fasting blood glucose changes of rosiglitazone (RG; 4 mg/kg), SY (100 or 200 mg/kg)-administered obese and diabetic *db*/*db* mice ($n = 7$ for each group) at baseline (week 0) and indicated time points. (B) Fasting blood glucose changes of rosiglitazone (RG; 4 mg/kg), SY (100 or 200 mg/kg)-administered obese and diabetic *db*/*db* mice ($n = 7$ for each group) at week 0 and 8 after treatment. $^{*}P < 0.05$ vs. control. (C) SY improves glucose tolerance in *db*/*db* mice. Mice were fasted and injected with glucose (2 g/kg). Blood glucose levels were measured from the blood samples that were drawn at baseline ($t = 0$ min) and indicated time points ($n = 7$). The area under the curve (AUC) of the glucose tolerance test was calculated. $^{*}P < 0.05$ vs. control.

active ingredients, sargaquinoic acid (SQA) and sargahydroquinoic acid (SHQA) have strong therapeutic potential for metabolic disorders [18]. In current study, we explored the pharmacological properties of SY on glucose and lipid metabolism *in vivo*. In obese and diabetic *db*/*db* mice model, SY ameliorated the abnormalities of lipid metabolism and insulin resistance without severe side effects of PPARγ agonists such as body weight gain, hepatomegaly, and hepatotoxicity. Altogether, these data suggest that SY would be potential therapeutic agents for T2DM and lipid dysregulation through PPARα/γ dual activation.

2. Materials and methods

2.1. Preparation of S. yezoense extracts

The *S. yezoense* (SY; Sargasaceae) were collected from the seashore of Gangwon province, Republic of Korea, and identified via a voucher specimen deposited at the KIST Gangneung Institute Herbarium, Gangneung, Korea. The wet SY (1000 g) was homogenized and crude components were extracted three times with methanol using ultrasonic apparatus. The filtered supernatant was evaporated under a vacuum at 40 °C (6.63 g) and stored at −70 °C until use.

2.2. Animal experiments

All experiments were performed according to the procedures approved by Korea Institute of Science and Technology's Institutional Animal Care and Use Committee. Seven week-old male C57BLKS/J lar-*Lep*$^{db/db}$ mice were purchased from Shizuoka Laboratory Animal Center (Japan). The mice were housed under temperature (23 ± 2 °C) and humidity (55 ± 5%) condition with a standard light (12 h light/dark) cycle and fed a regular diet (10% kcal fat, 38057, Purina Inc.) for 8 weeks. The mice were orally administered once a day with rosiglitazone (4 mg/kg), or SY (100 mg/kg or 200 mg/kg) for 8 weeks before gene expression or blood biomarker analysis. For glucose tolerance tests, same set of experiments were performed for 8 weeks and fasted overnight before oral administration of 2 g/kg D-glucose. Glucose was measured by tail vein bleeds at the indicated intervals using an Accu-Chek glucometer (Roche, Mannheim, Germany). At the end of the experimental period, liver/body weight and epididymal white tissue/body weight were measured and blood samples were taken from abdominal aorta to determine the plasma biomarkers.

2.3. Analysis of plasma biomarkers

After the experiment, the blood was collected in 0.18 M EDTA containing tubes and centrifuged at 5000 rpm for 5 min at 4 °C. After centrifugation, plasma was separated for estimation of total cholesterol, LDL-cholesterol, triglyceride, and free fatty acid. Total cholesterol levels were measured by enzymatic methods using SICDIA L T-CHO reagents (Eiken Chemical, Tokyo, Japan) and LDL-cholesterol levels were determined by enzymatic methods using L-Type LDL-C (Wako Pure Chemical, Osaka, Japan) reagents. Triglyceride levels were measured by GPO-HMMPS using SICDIA L TG reagent (Eiken Chemical) and free fatty acid were measured by enzymatic methods using NEFAZYME-S (Eiken Chemical).

2.4. Total RNA isolation and gene expression analysis

The mice were sacrificed after 8 weeks, and tissues (liver and epididymal white adipose tissue) were collected in liquid nitrogen and stored at −80 °C until use. Total RNA was isolated from the tissues using the QIAgen RNeasy kit and QIAgen Lipid Tissue kit (Qiagen, Valencia, CA), and the integrity of the RNA was checked by the Agilent 2100 BioAnalyzer (Agilent Technologies, Santa Clara, CA). cDNA synthesis was performed with 1 μg of total RNA in 20 μl using random primers (Invitrogen, Carlsbad, CA) and Superscript II reverse transcriptase (Invitrogen, Carlsbad, CA). The primer sets were the following: C/EBPα, forward 5′-AGGTGCTGGAGTTGACCAGT-3′ and reverse 5′-CAGCCTAGAGATCCAGCGAC-3′; G6Pase, forward 5′-ATGACTTTGGGATCCAGTCG-3′ and reverse 5′-TGGAACCAGATGGGAAAGAG-3′; PPARγ, forward 5′-CAAGAATACCAAAGTGCGATCAA-3′ and reverse 5′-GAGCTGGGTCTTTTCAGAA

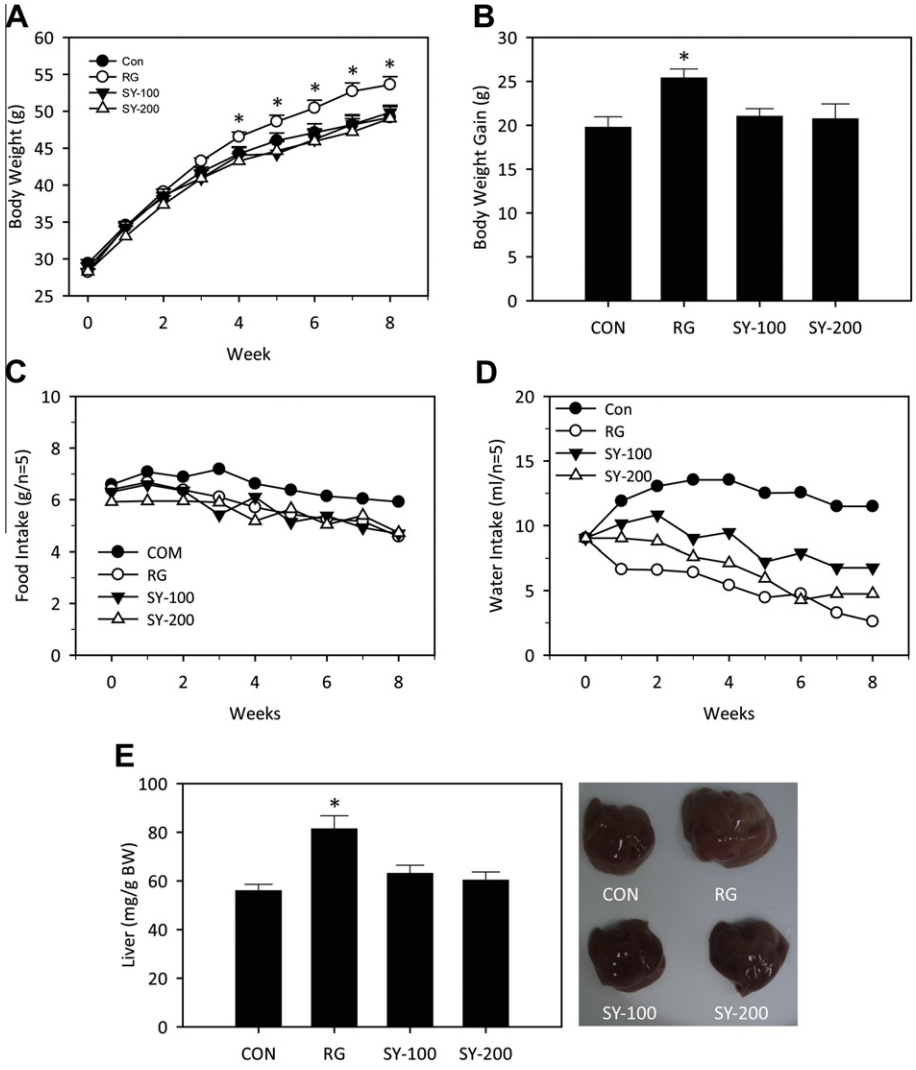

Fig. 2. The effect of SY on the body weight, liver weight, and food and water intake in *db/db* mice. (A) Whole body weight changes with drug administration for 8 weeks. $^{*}P < 0.05$ vs. control. (B) Body weight gains between 0 and 8 weeks. Each bar represents mean ± SD. $^{*}P < 0.05$ vs. control. (C) The food intake by *db/db* mice was measured every day for 8 weeks, and the average food intake of each week is shown graphically. (D) The water intake of *db/db* mice was measured every day, and the average water intake in each week is shown graphically. (E) Average liver weights of RG or SY-administered *db/db* mice. Each bar represents mean ± SD. $^{*}P < 0.05$ vs. control.

TAATAAG-3′; UCP3, forward 5′-ACAAAGGATTTGTGCCCTCC-3′ and reverse 5′-CTTGCCTTGTTCAAAACGGA-3′; adiponectin, forward 5′-AGCCTGGAGAAGCCGCTTAT-3′ and reverse 5′-TTGCAGTAGAACTT GCCAGTGC-3′; and glyceraldehydes-3-phosphate dehydrogenase (GAPDH), forward 5′-TTGTTGCCATCAACGACCCC-3′ and reverse 5′-GCCGTTGAATTTGCCGTGAG-3′.

Real time quantitative PCR analyses for the above metabolic-related genes were performed using the 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA). Reactions were performed in a 25 μl volume containing 12.5 μl of 2X SYBR Green reaction buffer, 1 μl of cDNA (corresponding to 25 ng of reverse transcribed total RNA) and 5 pmol of each primer. After an initial incubation for 2 min at 50 °C, the cDNA was denatured at 95 °C for 10 min followed by 40 cycles of PCR (95 °C, 15 s, 60 °C, 60 s). Data analyses were performed on 7500 System SDS software version 1.3.1 (Applied Biosystems). All the samples were normalized by the corresponding expression of GAPDH.

2.5. Statistics

Data are expressed as mean ± S.D. Statistical differences between the mean values in each groups were analyzed by one-way analysis of variance (ANOVA). $P < 0.05$ was interpreted as being statistically significant.

3. Results

3.1. SY ameliorates glucose impairment and glucose tolerance in db/db mice

In our previous study, we have demonstrated a therapeutic potential of SY on metabolic disorders through dual activation of PPARα/γ activity in 3T3-L1 cell systems [18]. To evaluate the effects of SY *in vivo*, we first confirmed transcriptional activation of PPARα/γ by SY extract. SY treatment led to an increase in transcriptional activities of PPARα/γ in a dose-dependent manner (Supplementary Fig. 1A and B). Then, we evaluated *in vivo* therapeutic potential of SY on metabolic disorders using an obese and diabetic *db/db* mouse model. SY was administered to *db/db* mice for 8 weeks and monitored individual plasma glucose levels at indicated time points. As shown in Fig. 1A and B, SY treatment led to a significant decrease in non-fasting and fasting blood glucose levels in a dose-dependent manner, which is comparable to the effect of rosiglitazone. Furthermore, glucose tolerance was sig-

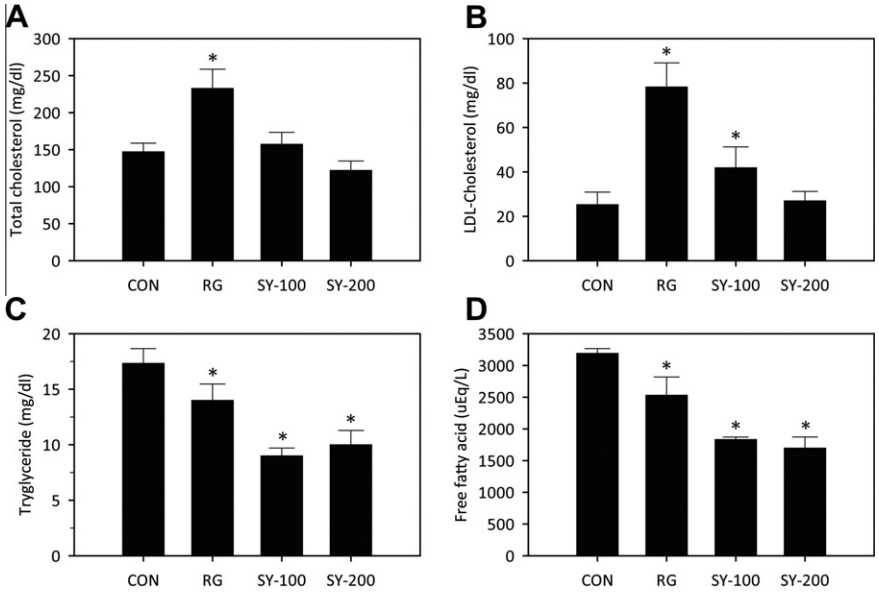

Fig. 3. SY improves metabolic markers in blood of *db/db* mice. Blood total cholesterol (A), LDL-Cholesterol (B), triglyceride (C), and free fatty acids (D) levels were measured as described in Section 2. Each bar represents means ± SD. $^{*}P < 0.05$ vs. control.

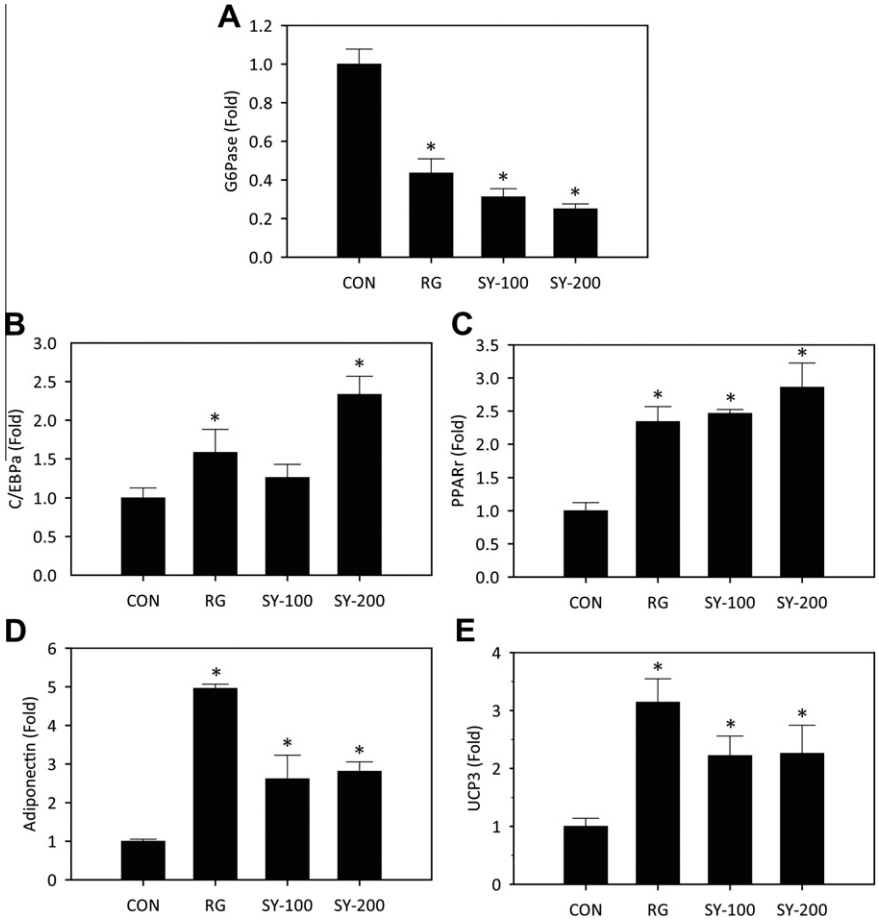

Fig. 4. SY improves metabolic markers in liver and white adipose tissue (WAT) of *db/db* mice. Relative gene expression of Glucose-6-phosphatase (G6Pase) (A) from the liver of indicated drug-treated obese *db/db* mice ($n = 7$) were determined by using q-PCR. Data represent means ± SD. $^{*}P < 0.05$ vs. control. C/EBPa (B) and PPARγ (C), adiponectin (D) and UCP3 (E) from the WAT were determined by using q-PCR. Data represent means ± SD. $^{*}P < 0.05$ vs. control.

nificantly improved by SY treatment, which is accompanied with AUC of the oral glucose tolerance test (Fig. 1C). These results strongly indicate that SY ameliorates glucose impairment and glucose tolerance in *db/db* mice.

3.2. SY treatment does not affect body weight and liver size in db/db mice

Next, we analyzed the effect of SY on body weight gain, liver weight gain, and water and food intake. Rosiglitazone, a PPARγ agonist, yielded significant body weight gain, but SY treatment did not allow to significant body weight gain (Fig. 2A and B) and food intake (Fig. 2C). And water intake was reduced in SY- and rosiglitazone-treated groups in a dose-dependent manner (Fig. 2D), which is accompanied with glucose lowering effects (Fig. 1A and B). In addition, unlike rosiglitazone, we could not observe a significant increase in liver weight in SY-treated groups (Fig. 2E). Altogether, these results strongly suggest that SY would efficiently improve glucose impairment without side effects such as a significant body weight gain and hepatomegaly.

3.3. SY improves plasma lipid profiles in db/db mice

We next examined whether SY is capable of improving lipid abnormalities. Rosiglitazone treatment led to a significant increase in total plasma cholesterol and LDL-cholesterol levels in *db/db* mice, but SY treatment did not affect total plasma cholesterol and LDL-cholesterol levels (Fig. 3A and B). Furthermore, plasma levels of triglycerides and free fatty acids were significantly decreased in SY-treated mice, which are comparable to the result of rosiglitazone (Fig. 3C and D). These results indicate that SY improves lipid abnormalities, leading to prevention of hypertriglyceridemia and hypercholesterolemia.

3.4. SY modulates the levels of gene expression for glucose and lipid metabolism in db/db mice

Because hepatic gluconeogenesis gene expression in diabetic animals is markedly increased and contributes to hyperglycemia, we observed glucose-6-phosphatase (G6Pase) expression, one of key enzyme for gluconeogenesis, in liver of *db/db* mice. G6Pase expression was significantly reduced in SY-treated mice (Fig. 4A), supporting anti-diabetic effects of SY. We next analyzed the effect of SY on adipogenic transcription factors and marker gene expression in adipose tissue. After 8 week treatment of *db/db* mice with SY, we analyzed the mRNA levels of C/EBPα, PPARγ and adiponectin using quantitative real time PCR in white adipose tissue (WAT). Treatment of SY led to increases in mRNA levels of C/EBPα, PPARγ and adiponectin (Fig. 4B–D). In addition, we analyzed the expression levels of UCP3 in WAT, because UCP3 expression is directly up-regulated by PPARγ agonists [19,20]. PPARγ expression was dramatically increased in SY-treated white adipose tissues (Fig. 4C). In parallel, this induction of PPARγ was accompanied by UCP3 expression in white adipose tissues (Fig. 4E), which might be related to the increased rate of lipid metabolism.

4. Discussion

We demonstrate here the anti-diabetic and hypolipidemic potentials of SY in *db/db* mice, which are evidenced by the observations that SY ameliorates glucose impairment and lipid abnormalities in *db/db* mice through dual activation of PPARα/γ transcriptional activities. In addition, unlike other PPARγ agonists, SY seems to exhibit favorable effects on hyperlipidemia, without severe side effects of weight gain and hepatomegaly.

Many anti-hypoglycemic agents are currently available for the treatment of T2DM patients: insulin secretagogues (sulfonylureas and meglitinides), metformin, thiazolidinediones (rosiglitazone and pioglitazone), α-glucosidase inhibitors, and incretin-based therapies (exenatide and sitagliptin). The anti-diabetic effects of insulin secretagogues and incretin-based therapies are basically depending on insulin action. However, metformin and thiazolidinediones, which are classified into insulin sensitizers, decrease hepatic glucose production and reduce insulin resistance without changing insulin secretion from pancreas. AMPK activation is associated with pharmacological actions of metformin [21], and transcriptional activation of PPARs is involved in pharmacological effects of thiazolidinediones [22,23]. Therefore, insulin sensitizers are considered to be more suitable agents for the treatment of T2DM patients with insulin resistance. However, clinical use of thiazolidinediones, especially rosiglitazone, is currently challenged by their severe side effects including hepatotoxicity, weight gain, dyslipidemia, and possible worsening of cardiovascular risk [24,25]. So there are enormous efforts to discover novel insulin sensitizers with less toxicity. In this study, we describe that the extract of SY has anti-diabetic and hypolipidemic effects *via* dual agonistic action on PPARα/γ, which is evidenced by *in vitro* and *in vivo* experiments. In addition, SQA and SHQA were identified as active ingredients of SY for its anti-diabetic and hypolipidemic effects, previously [18].

Several reports demonstrate that rosiglitazone is associated with an increased risk of heart attacks, which potentially limit its popularity and further clinical use, despite of its high potency to improve glucose metabolism [24]. However, pioglitazone, another thiazolidinedione PPARγ agonist, is less related with this cardiovascular risk [26], implying that PPARγ activity itself might not entirely associate with this cardiovascular risk, and their chemical structure might be more critical for the risks. So it might be still attractive to develop novel structurally unrelated PPAR agonists with thiazolidinediones, especially rosiglitazone. In this point of view, it is noteworthy that SQA and SHQA which are derived from SY are novel PPARα/γ dual agonists and their chemical structures are unique and quite different from thiazolidinediones [18].

In summary, we here demonstrate that SY has beneficial effects on glucose and lipid metabolism to improve metabolic disorders by activating both PPARα and PPARγ without severe adverse effects, including body weight gain and hepatomegaly, which have been observed in previously identified PPAR agonists. All these effects of SY may be driven mainly by its active ingredients SQA and SHQA. Thus, our findings strongly suggest that SY, SQA and SHQA would be further developed as anti-metabolic agent to improve glucose and lipid abnormalities, insulin resistance and obesity, and SQA and SHQA would be a potential lead compound against insulin resistance and dyslipidemia.

Acknowledgments

This work was supported by a Grant from the Next-generation BioGreen 21 Program (No. PJ008092), Rural Development Administration, and by the Sookmyung Women's University Research Grants 1-1109-0004.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.07.005.

References

[1] W. Rathmann, G. Giani, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care 27 (2004) 2568–2569. author reply 2569.
[2] P.G. Kopelman, Obesity as a medical problem, Nature 404 (2000) 635–643.
[3] A.H. Mokdad, E.S. Ford, B.A. Bowman, W.H. Dietz, F. Vinicor, V.S. Bales, J.S. Marks, Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001, JAMA 289 (2003) 76–79.
[4] L. Michalik, J. Auwerx, J.P. Berger, V.K. Chatterjee, C.K. Glass, F.J. Gonzalez, P.A. Grimaldi, T. Kadowaki, M.A. Lazar, S. O'Rahilly, C.N. Palmer, J. Plutzky, J.K.

Reddy, B.M. Spiegelman, B. Staels, W. Wahli, International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors, Pharmacol. Rev. 58 (2006) 726–741.
[5] C.H. Lee, P. Olson, R.M. Evans, Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors, Endocrinology 144 (2003) 2201–2207.
[6] A.J. Vidal-Puig, R.V. Considine, M. Jimenez-Linan, A. Werman, W.J. Pories, J.F. Caro, J.S. Flier, Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids, J. Clin. Invest. 99 (1997) 2416–2422.
[7] V. Fonseca, Effect of thiazolidinediones on body weight in patients with diabetes mellitus, Am. J. Med. 115 (Suppl. 8A) (2003) 42S–48S.
[8] M. Bunger, G.J. Hooiveld, S. Kersten, M. Muller, Exploration of PPAR functions by microarray technology – a paradigm for nutrigenomics, Biochim. Biophys. Acta 1771 (2007) 1046–1064.
[9] M. Bajaj, S. Suraamornkul, L.J. Hardies, L. Glass, N. Musi, R.A. DeFronzo, Effects of peroxisome proliferator-activated receptor (PPAR)-alpha and PPAR-gamma agonists on glucose and lipid metabolism in patients with type 2 diabetes mellitus, Diabetologia 50 (2007) 1723–1731.
[10] L.C. Pickavance, C.L. Brand, K. Wassermann, J.P. Wilding, The dual PPARalpha/gamma agonist, ragaglitazar, improves insulin sensitivity and metabolic profile equally with pioglitazone in diabetic and dietary obese ZDF rats, Br. J. Pharmacol. 144 (2005) 308–316.
[11] A. Reifel-Miller, K. Otto, E. Hawkins, R. Barr, W.R. Bensch, C. Bull, S. Dana, K. Klausing, J.A. Martin, R. Rafaeloff-Phail, C. Rafizadeh-Montrose, G. Rhodes, R. Robey, I. Rojo, D. Rungta, D. Snyder, K. Wilbur, T. Zhang, R. Zink, A. Warshawsky, J.T. Brozinick, A peroxisome proliferator-activated receptor alpha/gamma dual agonist with a unique in vitro profile and potent glucose and lipid effects in rodent models of type 2 diabetes and dyslipidemia, Mol. Endocrinol. 19 (2005) 1593–1605.
[12] T. Harrity, D. Farrelly, A. Tieman, C. Chu, L. Kunselman, L. Gu, R. Ponticiello, M. Cap, F. Qu, C. Shao, W. Wang, H. Zhang, W. Fenderson, S. Chen, P. Devasthale, Y. Jeon, R. Seethala, W.P. Yang, J. Ren, M. Zhou, D. Ryono, S. Biller, K.A. Mookhtiar, J. Wetterau, R. Gregg, P.T. Cheng, N. Hariharan, Muraglitazar, a novel dual (alpha/gamma) peroxisome proliferator-activated receptor activator, improves diabetes and other metabolic abnormalities and preserves beta-cell function in db/db mice, Diabetes 55 (2006) 240–248.
[13] S. Mittra, G. Sangle, R. Tandon, S. Sharma, S. Roy, V. Khanna, A. Gupta, J. Sattigeri, L. Sharma, P. Priyadarsiny, S.K. Khattar, R.S. Bora, K.S. Saini, V.S. Bansal, Increase in weight induced by muraglitazar, a dual PPARalpha/gamma agonist, in db/db mice. Adipogenesis/or oedema?, Br J. Pharmacol. 150 (2007) 480–487.
[14] E. Adeghate, A. Adem, M.Y. Hasan, K. Tekes, H. Kalasz, Medicinal chemistry and actions of dual and pan PPAR modulators, Open Med. Chem. J. 5 (2011) 93–98.
[15] A.M. Mayer, A.D. Rodriguez, R.G. Berlinck, N. Fusetani, Marine pharmacology in 2007–8: marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous system, and other miscellaneous mechanisms of action, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 153 (2011) 191–222.
[16] A.M. Mayer, A.D. Rodriguez, R.G. Berlinck, M.T. Hamann, Marine pharmacology in 2005–6: marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action, Biochim. Biophys. Acta 1790 (2009) 283–308.
[17] A.M. Mayer, A.D. Rodriguez, R.G. Berlinck, M.T. Hamann, Marine pharmacology in 2003–4: marine compounds with anthelmintic antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 145 (2007) 553–581.
[18] S.N. Kim, H.Y. Choi, W. Lee, G.M. Park, W.S. Shin, Y.K. Kim, Sargaquinoic acid and sargahydroquinoic acid from *Sargassum yezoense* stimulate adipocyte differentiation through PPARalpha/gamma activation in 3T3-L1 cells, FEBS Lett. 582 (2008) 3465–3472.
[19] J. Matsuda, K. Hosoda, H. Itoh, C. Son, K. Doi, I. Hanaoka, G. Inoue, H. Nishimura, Y. Yoshimasa, Y. Yamori, H. Odaka, K. Nakao, Increased adipose expression of the uncoupling protein-3 gene by thiazolidinediones in Wistar fatty rats and in cultured adipocytes, Diabetes 47 (1998) 1809–1814.
[20] V. Emilsson, J. O'Dowd, S. Wang, Y.L. Liu, M. Sennitt, R. Heyman, M.A. Cawthorne, The effects of rexinoids and rosiglitazone on body weight and uncoupling protein isoform expression in the Zucker fa/fa rat, Metabolism 49 (2000) 1610–1615.
[21] G. Zhou, R. Myers, Y. Li, Y. Chen, X. Shen, J. Fenyk-Melody, M. Wu, J. Ventre, T. Doebber, N. Fujii, N. Musi, M.F. Hirshman, L.J. Goodyear, D.E. Moller, Role of AMP-activated protein kinase in mechanism of metformin action, J. Clin. Invest. 108 (2001) 1167–1174.
[22] R.M. Evans, G.D. Barish, Y.X. Wang, PPARs and the complex journey to obesity, Nat. Med. 10 (2004) 355–361.
[23] M. Lehrke, M.A. Lazar, The many faces of PPARgamma, Cell 123 (2005) 993–999.
[24] S.E. Nissen, K. Wolski, Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes, N. Engl. J. Med. 356 (2007) 2457–2471.
[25] A. Kermani, A. Garg, Thiazolidinedione-associated congestive heart failure and pulmonary edema, Mayo Clin. Proc. 78 (2003) 1088–1091.
[26] A.M. Lincoff, K. Wolski, S.J. Nicholls, S.E. Nissen, Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials, JAMA 298 (2007) 1180–1188.