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Voglibose administration regulates body weight and energy intake in high fat-induced obese mice

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ABSTRACT

We tested whether long-term administration of voglibose (VO) prevents diet induced obesity in addition to hypoglycemic effects in high fat fed mice and further investigated the underlying mechanisms by which voglibose exerts its weight lowering effect. Male C57BL/6 mice were fed ad libitum for 12 weeks with the control diet (CTL), high-fat diet (HFD) or the HFD with VO supplementations. Blood lipid profile, plasma leptin levels and hepatic triglyceride content, as well as expressions of genes involved in appetite and mitochondrial function were examined. The results showed that VO significantly reduced body weight, fat mass and energy intakes in high fat fed mice. VO showed improved metabolic profiles including blood glucose, triglyceride and free fatty acid. Elevated levels of plasma leptin in HFD were significantly reduced with the VO, furthermore, VO modulated the hypothalamic expressions of leptin receptors and appetite related genes. VO showed the upregulated expressions of PGC-1 in the liver and epididymal adipose tissue. In conclusion, VO may exert antiobesity properties through reductions in energy intake and improvement in mitochondrial function, indicating that VO has potential therapeutic use in patients with obesity, type 2 diabetes, and related complications.

1. Introduction

It is well known that obesity is an established risk factor for type 2 diabetes mellitus (T2DM), and weight loss is recommended for obese patients with T2DM because of the numerous benefits of weight loss [1,2]. An intestinal enzyme, α-glucosidase, acts on carbohydrate digestion and glucose absorption [3]. The action of α-glucosidase inhibitors is to delay intestinal absorption of carbohydrates by inhibiting degradation, which results in altered postprandial glucose and insulin levels [4]. Acarbose, miglitol and voglibose (VO) are 3 major oral hypoglycemic drugs used to treat patients with T2DM by delaying the absorption of glucose, thereby managing the disease and related complications [5]. Recently, it was reported that the α-glucosidase inhibitors provide significant beneficial health outcomes in post hoc analyses of randomized placebo-controlled trials [6]. For example, both acarbose in STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) [7] and VO in a Japanese trial [8] were shown to slow the progression to T2DM. In addition, α-glucosidase inhibitors were reported to favorably affect several cardiovascular endpoints; in particular, VO was shown to inhibit cardiac remodeling by decreasing myocardial oxidative stress through improvement of glycemic control in mice with cardiac pressure overload [9]. While there is evidence for the beneficial effects of α-glucosidase inhibitors on cardiovascular risk, there is limited information on weight beneficial effects of them.

VO is known to demonstrate anti-hyperglycemic effects in Japanese patients [8,10]; more importantly, being superior to both acarbose and miglitol in terms of potency and side effect profile [3]. In the present study, we tested whether long-term administration of VO prevents diet-induced obesity and hypoglycemic effects in mice fed a high-fat diet (HFD). The study provides novel information that VO may exert antiobesity properties through reductions in energy intake and improvement of mitochondrial function, indicating that VO has potential therapeutic use in patients with obesity, T2DM and related complications.

Abbreviations: T2DM, type 2 diabetes mellitus; HOMA, homeostatic model assessment; GLP-1, glucagon like peptide-1; DDP-4, dipeptidyl peptidase-4; OB-R, leptin receptor; POMC, proopiomelanocortin; Cart, cocaine and amphetamine-regulated transcript; AgRP, agouti-related protein; NPY, neuropeptide Y; PGC-1α, peroxisome proliferator-activated receptor γ coactivator- 1α; GLUT4, insulin-responsive glucose transporter type 4; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

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2. Materials and methods

2.1. Animals and study design

Male C57BL/6 mice (5 weeks old) were randomly assigned to 3 groups after a 1 week adaptation period. Group 1 received a normal control diet (CTL, $n = 10$), Group 2 received a HFD ($n = 10$), and Group 3 received a HFD supplemented with VO ($n = 10$). VO (Santa Cruz Biotechnology, Dallas, TX, USA) was prepared in distilled water and administered orally on the basis of body weight (1 mg/kg once daily). The mice in the CTL and HFD groups received an equivalent volume of vehicle (distilled water). The CTL was based on the composition of the American Institute of Nutrition (AIN)-76 rodent diet. The HFD was identical to the CTL but included 200 g fat/kg (170 g lard plus 30 g corn oil) and 1% cholesterol. The mice were housed under standard (18–24 °C, 50–60% humidity) laboratory conditions and maintained on a 12/12-h light/dark schedule (lights on at 8:00 am) with free access to food and water for 12 weeks. Daily feed intake and weekly gains in body weight were routinely recorded throughout the experimental period using a computing scale (Acominc Co., Pocheon, Korea). All experimental procedures were approved by the Committee on Animal Experimentation and Ethics of Korea University.

2.2. Quantification of plasma metabolic parameters and hepatic triglyceride

Plasma triglyceride (TG) and free fatty acid (FFA) levels were measured using an Olympus AU400 Chemistry Analyzer (Tokyo, Japan). Hepatic lipids were extracted using the method developed by Folch et al. [11] and dried lipid residues were dissolved in 0.5 mL isopropanol. The concentrations of TG in the hepatic-lipid extracts were measured using commercial kits (Asan Pharm, Seoul, Korea).

2.3. Plasma glucose, insulin, homeostatic model assessment of insulin resistance, and homeostatic model assessment of beta cell function

Fasting plasma levels of glucose were measured by hexokinase method using an Olympus AU400 Chemistry Analyzer. Insulin was measured by radioimmunoassay with kits from Biosource (Carlsbad, CA, USA). Insulin sensitivity was estimated using the homeostatic model assessment (HOMA) index which is an arithmetic way of deriving indices of peripheral tissue insulin resistance and pancreatic endocrine function (beta cell function, HOMA-β). HOMA-IR and HOMA-β are derived using the following formulae: HOMA-IR = (Fasting plasma insulin [μIU/mL] × fasting plasma glucose [mmol/L])/22.5 and HOMA-β = (20 × fasting plasma insulin [μIU/mL])/(fasting plasma glucose [mmol/L] − 3.5) [12].

2.4. Plasma leptin measurements

Plasma leptin levels were measured using enzyme linked immunosorbent assay kits (Komabiotech, Seoul, Korea), as per the manufacturer's instructions.

2.5. RNA extraction and quantitative real time polymerase chain reaction

Total RNA was extracted from the hypothalamus, liver, and epididymal adipose tissue using an RNeasy Lipid Tissue Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Complementary DNA was synthesized from 1 μg of RNA using oligo-dT and Superscript II reverse transcriptase (Invitrogen, Carlsbad, CA, USA). Primer sequences for polymerase chain reaction were as follows: leptin receptor α (OB-Rα), 5′-AAGTTGTTTTGGGACGATG-3′ (forward) and 5′-ATTGGGTTCATCTGTAGTGG-3′ (reverse); OB-Rβ, 5′-ACTCTGGTCAGCAACGATAAACTA-3′ (forward) and 5′-GAAAAATGTCTGGGCCTCTGTCTC-3′ (reverse); proopiomelanocortin (POMC), 5′-ATGCCGAGATTCTGCTACAG-3′ (forward) and 5′-TGCTGCTGTTCCTGGGGC-3′ (reverse); agouti-related protein (AgRP), 5′-ATGCTGACTGCAATGTTGCTG-3′ (forward) and 5′-CAGACTTAGACCTGGGAACTCT-3′ (reverse); neuropeptide Y (NPY), 5′-ATATGGCAAGAGATCCAGCCC-3′ (forward) and 5′-ACATGGAAGGGTCTTCAAGCC-3′ (reverse); cocaine and amphetamine-regulated transcript (Cart), 5′-CTGGACTACCACAGGGTCCTT-3′ (forward) and 5′-AGACCTGACCTCACCTTCCAG-3′ (reverse); peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), 5′-CGGAAATCATATCCAACCAG-3′ (forward) and 5′-TGAGGACCGCTAGCAAGTTTG-3′ (reverse); PGC-1β, 5′-AACCCAACCAGTCTCACAGG-3′ (forward) and 5′-ATGCTGTCCTTGTGGGTAGG-3′ (reverse); insulin-responsive glucose transporter type 4 (GLUT4), 5′-CAACAGCTCTCAGGCATCAA-3′ (forward) and 5′-CTCAAAGAAGGCCACAAAGC-3′ (reverse); glyceraldehyde 3-phosphate dehydrogenase (GAPDH), 5′-AACTTTGGCATTGTGGAAGG-3′ (forward) and 5′-ACACATTGGGGGTAGGAACA-3′ (reverse). The real-time PCR (Step One Plus, Applied Biosystems, Foster City, CA, USA) conditions were: 15 min at 95 °C, followed by 40 cycles of 94 °C for 30 s, 52–60 °C for 20 s and 72 °C for 30 s. GAPDH was used as the control in the comparative cycle threshold method.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 12.0.1 (Chicago, IL, USA). The results were presented as means ± standard error (SE). The differences among the experimental groups were analyzed using a one-way ANOVA, followed by Bonferroni's post hoc test. P-values < 0.05 indicate a significant difference.

3. Results

3.1. Effect of VO supplementation on body weight, food intake, and body fat mass

As shown in Fig. 1A, there were significant differences in body weight gain in mice fed different diets ad libitum over the 12-week period. Mice in the HFD group gained more weight than those in the CTL and VO (1 mg/kg orally once daily) groups, and final body weights were significantly higher in the HFD (37.4 ± 1.27 g) group than in the CTL (30.5 ± 1.23 g) and VO (29.0 ± 1.20 g) groups (Fig. 1B). The average daily food intake was significantly different among the 3 groups; the VO group consumed remarkably less amount of food than the CTL and HFD groups (Fig. 1C). The weights of epididymal and perirenal fat were significantly different among the groups (Fig. 1D and E) and the weights of retroperitoneal and mesenteric fat were significantly lower in the VO group than in HFD group (Fig. 1F and G). As shown in Fig. 1H, the HFD group (2.9 ± 0.26 g) had increased WAT weight compared with that in the CTL (1.6 ± 0.11 g) and VO (1.2 ± 0.16 g) groups.

3.2. Effect of VO supplementation on plasma metabolic parameters and hepatic TG

The VO group had remarkably reduced plasma TG levels (Fig. 2A). Compared with the CTL group, mice in the HFD group had elevated levels of TG in the liver. Hepatic TG levels were significantly lower in VO group than those in HFD group (Fig. 2B). Plasma levels of FFA and glucose were significantly different among the groups (Fig. 2C and D). FFA levels were lower in VO group than in the CTL and HFD groups. Similarly, circulating glucose levels were lower in the VO group than in the HFD group.

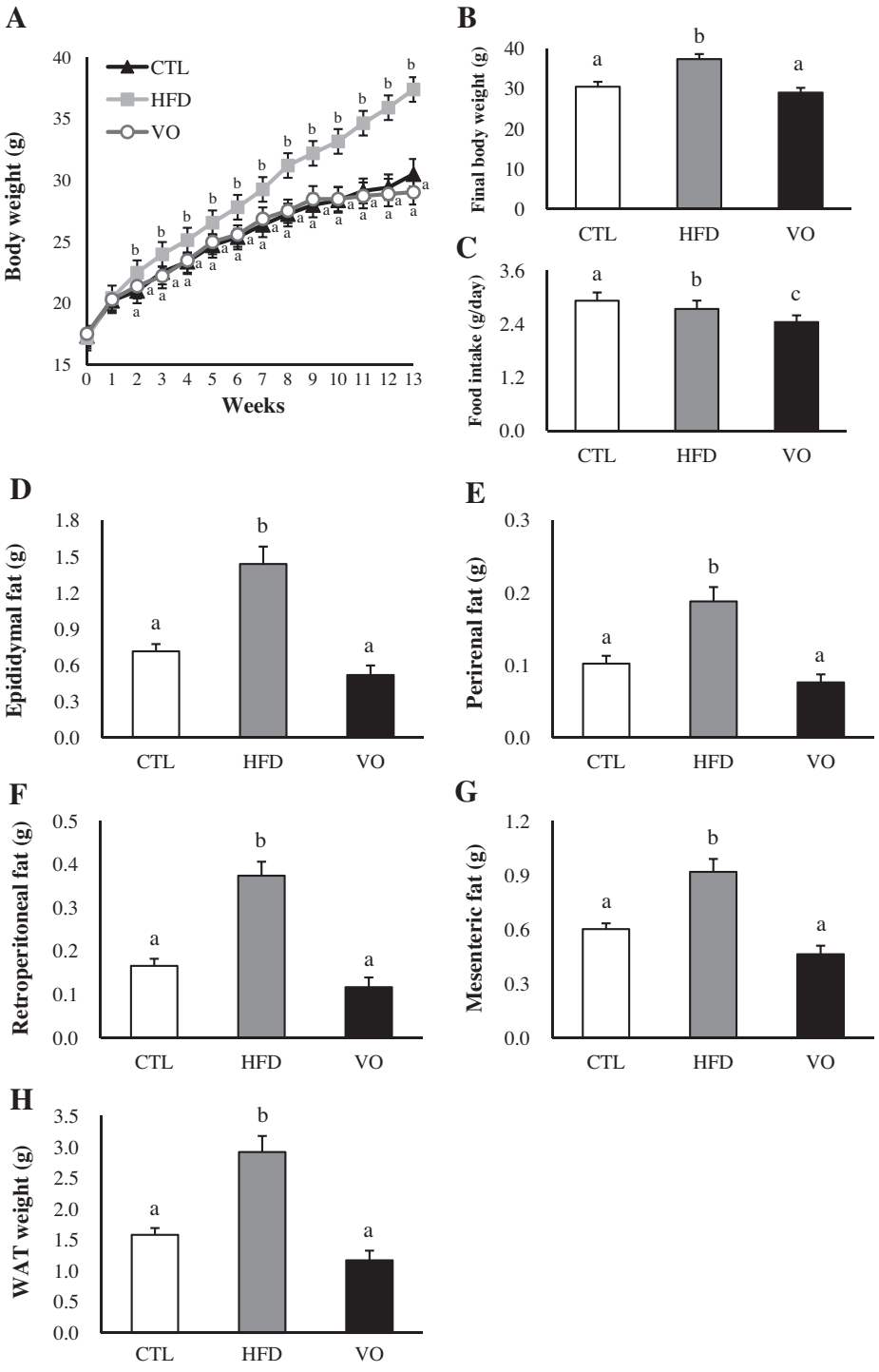

Fig. 1. Effect of administration of voglibose (VO) (1 mg/kg orally once daily) on body weight gain (A) per week in mice. Final body weights (B) and daily food intake (C) were significantly lower in the VO group than in the HFD group. Values for epididymal fat (D), perirenal fat (E), retroperitoneal fat (F), and mesenteric fat (G), and total white adipose tissue (WAT) weights (H) were significantly lower in the VO group than in the HFD group. CTL ($n = 10$): normal control diet, HFD ($n = 10$): high fat diet, VO ($n = 10$): high fat diet supplemented with VO. The results were expressed as means ± SE. Tested by one-way ANOVA with Bonferroni's post hoc test. Values with the same superscript letter are not significantly different (a–c).

3.3. Effect of VO supplementation on plasma insulin levels, insulin resistance, and β-cell function

Plasma insulin levels were significantly increased in the HFD group, and the VO group displayed a tendency of reduced plasma insulin levels, but this did not reach statistical significance (Fig. 2E). The HOMA-IR was significantly decreased in the VO group compared with that in the HFD group (Fig. 2F), whereas HOMA-β showed a strong tendency toward an increases in VO group compared with that in HFD group (Fig. 2G).

3.4. Effect of VO supplementation on plasma leptin levels and hypothalamic OB-R gene expressions

Fasting leptin levels were significantly increased in the HFD group compared with those in the CTL group and reversed to the

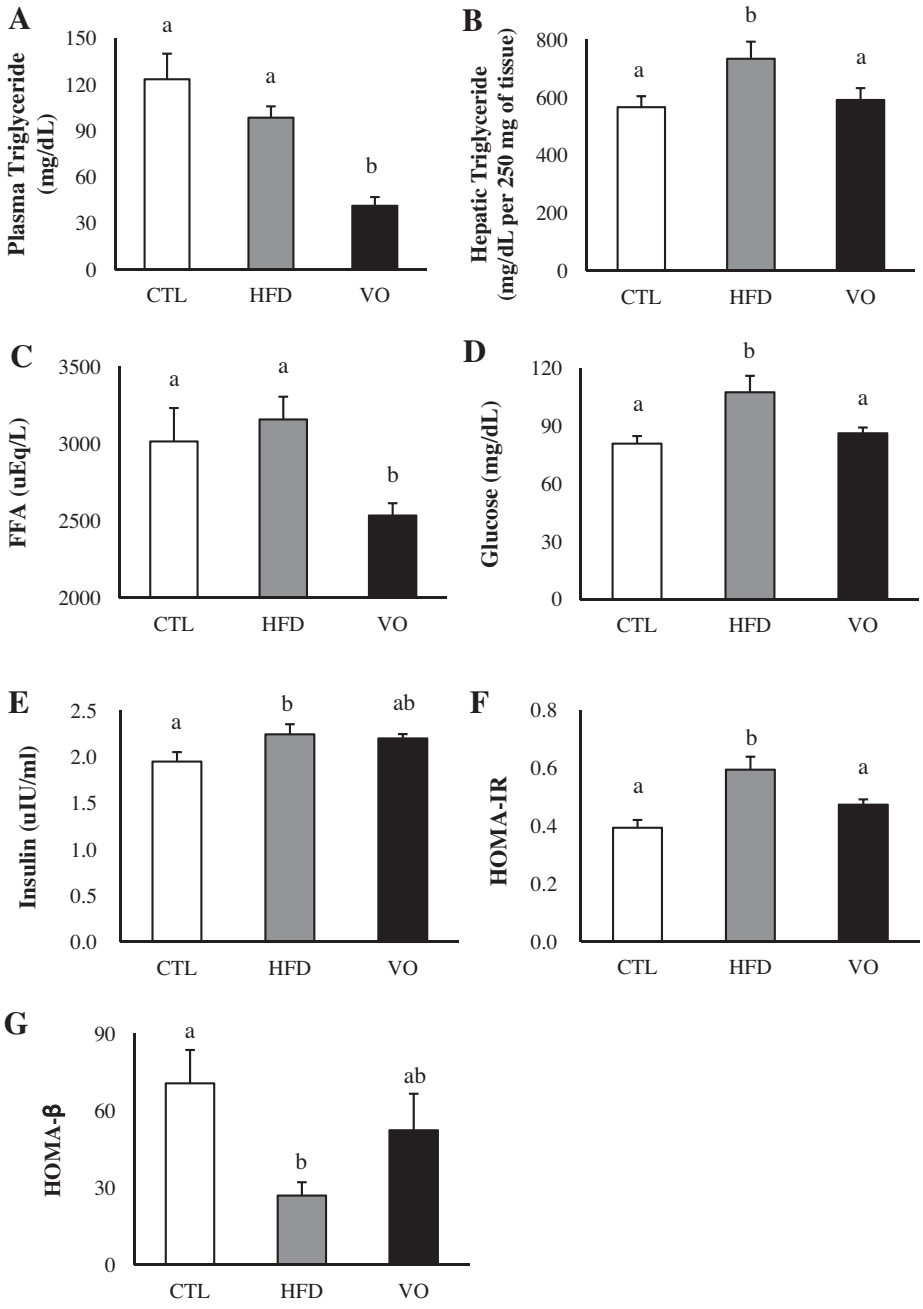

Fig. 2. Effect of administration of voglibose (VO) (1 mg/kg orally once daily) on plasma metabolic parameters (A and C–G) and hepatic TG (B) in mice. CTL ($n = 10$): normal control diet, HFD ($n = 10$): high fat diet, VO ($n = 10$): high fat diet supplemented with VO. The results were expressed as means ± SE. Tested by one-way ANOVA with Bonferroni's post hoc test. Values with the same superscript letter are not significantly different (a, b).

value of the CTL group with VO supplementation (Fig. 3A). Expression of OB-Rα messenger RNA (mRNA) in the hypothalamus was significantly increased in the VO group compared with that in the HFD group (Fig. 3B); similarly, expression of OB-Rβ mRNA was increased in the VO group compared with that in the CTL and HFD groups (Fig. 3C).

3.5. Effects of VO supplementation on expressions of appetite-related POMC, AgRP, NPY, and CART in hypothalamus

Expressions of POMC and Cart mRNA in the hypothalamus were significantly decreased in the VO group compared with those in the HFD group (Fig. 3D and G). Expression of AgRP mRNA was decreased in the VO group compared with that in the HFD group (Fig. 3E, not significant). NPY mRNA levels were significantly increased in the VO group compared with those in the HFD group (Fig. 3F).

3.6. Effects of VO supplementation on expressions of PGC-1α, PGC-1β and GLUT4 in epididymal adipose tissue and liver

Expressions of PGC-1α and PGC-1β mRNA in the liver were increased in the VO group compared with those in the CTL and HFD groups (Fig. 4C and D). Expression of PGC-1α mRNA in epididymal adipose tissue was significantly increased in the VO group compared with that in the HFD group (Fig. 4A); similarly, expression of PGC-1β mRNA was increased in the VO group compared with that in the HFD group (Fig. 4B, not significant). The results

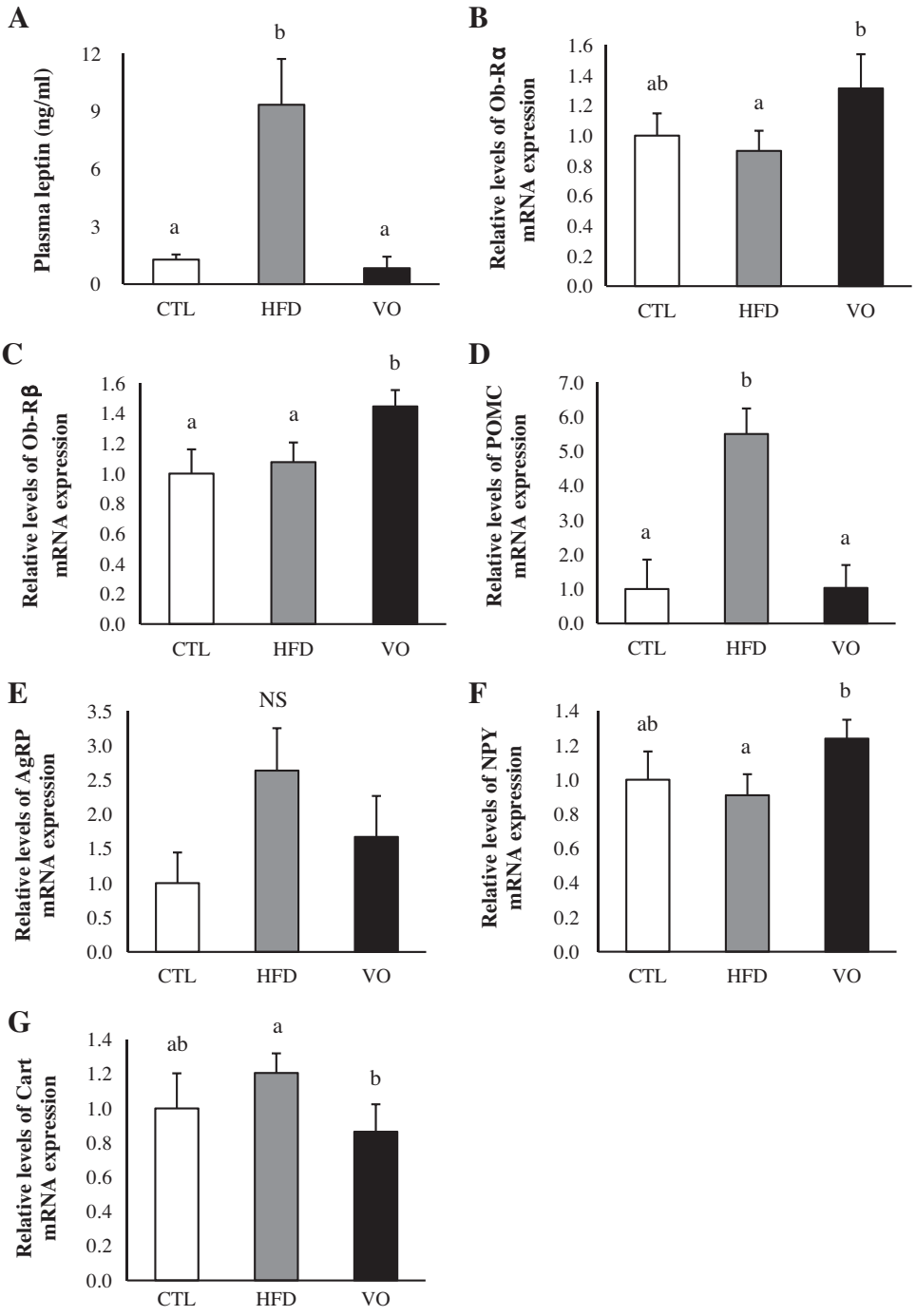

Fig. 3. Effect of administration of voglibose (VO) (1 mg/kg orally once daily) on plasma leptin levels (A) and the expression of hypothalamus OB-Rα (B), OB-Rβ (C), POMC (D), AgRP (E), NPY (F), and Cart (G) mRNA levels. CTL (n = 10): normal control diet, HFD (n = 10): high fat diet, VO (n = 10): high fat diet supplemented with VO. The results were expressed as means ± SE. Tested by one-way ANOVA with Bonferroni's post hoc test. Values with the same superscript letter are not significantly different (a, b).

showed that epididymal mRNA abundance of GLUT4 was significantly increased by the VO group compared with that in the CTL group (Fig. 4E). Hepatic mRNA abundance of GLUT4 was also significantly increased in the VO group compared with that in the CTL and HFD groups (Fig. 4F).

4. Discussion

The effects of the α-glucosidase inhibitors such as acarbose and VO on hyperglycemia and insulin sensitivity in T2DM have been consistently reported [3,13–17]. This is mainly attributed to the fact that α-glucosidase inhibitors delay the digestion of carbohydrates by inhibiting α-glucosidases within the intestinal brush border, which leads to a reduction of glucose absorption [18]. In addition to hypoglycemic effects, a meta-analysis [4] has reported that treatment with acarbose resulted in small but significant reductions in body mass index by 0.17 kg/m^2 in patients with T2DM, indicating multiple roles of these agents in the management of cardiovascular risks.

In the present study, 12 weeks VO supplementation prevented diet-induced obesity and also, remarkable reductions in food intakes were observed. Furthermore, VO supplementation influenced

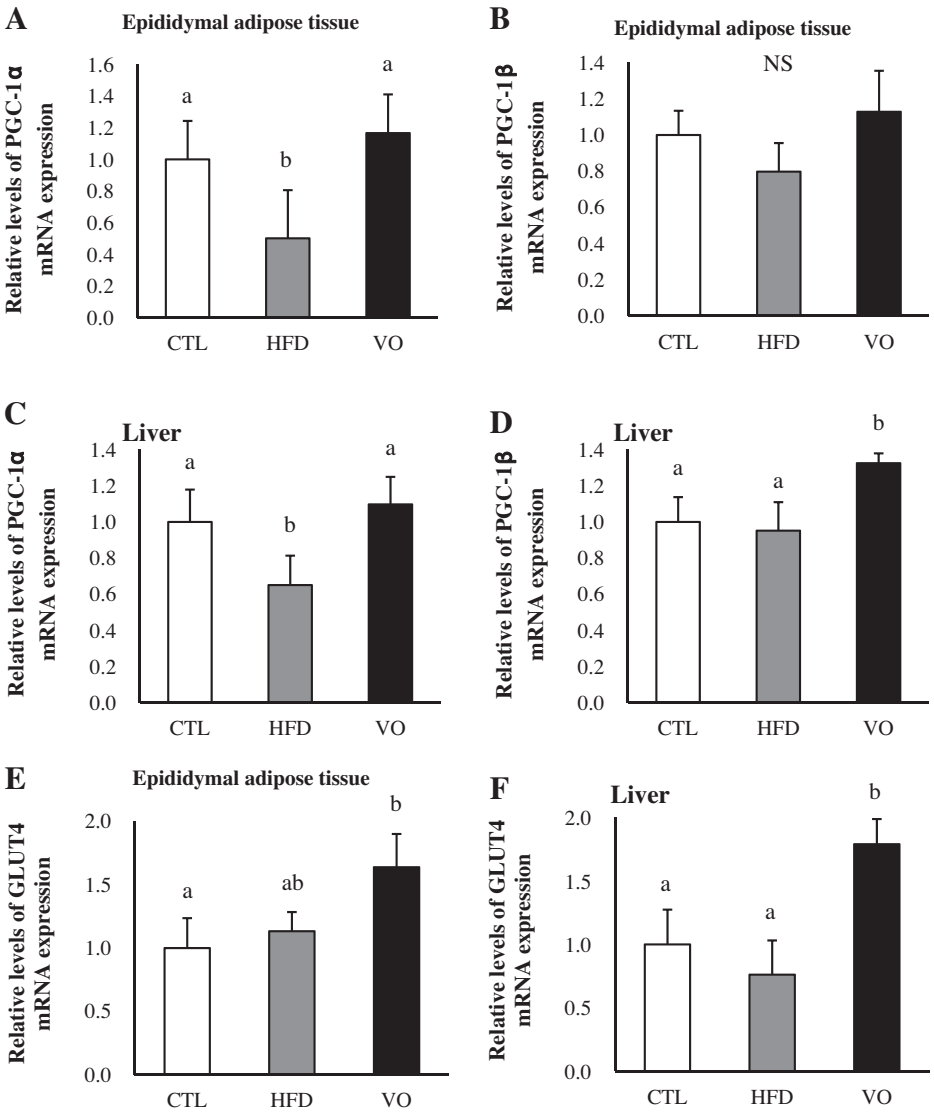

Fig. 4. Effect of administration of voglibose (VO) (1 mg/kg orally once daily) on PGC-1α (A and C), PGC-1β (B and D), and GLUT4 (E and F) mRNA expression in epididymal adipose tissue and liver. CTL ($n = 10$): normal control diet, HFD ($n = 10$): high fat diet, VO ($n = 10$): high fat diet supplemented with VO. The results were expressed as means ± SE. Tested by one-way ANOVA with Bonferroni's post hoc test. Values with the same superscript letter are not significantly different (a, b).

obesity induced metabolic abnormalities as shown by the improvements in glucose and lipid metabolism. To elucidate the underlying mechanism, we measured the plasma leptin levels known to influence body weight through the control of appetite and energy expenditure and hypothalamic expressions of appetite-related genes. The results showed that the elevated levels of circulating leptin in mice fed a HFD were significantly reduced with VO supplementation; furthermore, VO supplementation modulated the hypothalamic expressions of OB-Rs and appetite related genes. In addition, VO supplementation resulted in up-regulated expression of PGC-1 in the liver and epididymal adipose tissue, implicating that VO may have elicited improved mitochondrial dysfunction.

The exact mechanism by which VO reduces body weight remains unclear; several pathways may be involved in the observed effects. First, weight reduction seems to result from remarkable reductions in food intake, possibly associated with changes in the secretion of glucagon-like peptide 1 (GLP-1). GLP-1 is an incretin that is secreted from the lower gastrointestinal tract by local action of the unabsorbed nutrients [19] and functions physiologically to mediate satiety and produce the cessation of eating [20]. The action of GLP-1 to reduce hunger and increase satiety is likely to be mediated through prolonging gastric emptying or an interaction with appetite-regulating centers in the central nervous system [21–23]. Since body weight is normally maintained by a balance between energy intake and energy expenditure, the weight-lowering effect of VO supplementation shown in the present study might be achieved through reductions in energy intake. Specifically, it is possible that VO increases intestinal GLP-1 secretion and induces satiety [24] and subsequently reduces total food intakes. This can be further supported by previous findings [20] that short-term treatment with an α-glucosidase inhibitor showed increased GLP-1 secretion in patients with T2DM. However, this hypothesis cannot be fully supported in the absence of data available for postprandial GLP-1 and/or dipeptidyl peptidase-4 activity.

Alternatively, the neuroendocrine system involving leptin can be activated. It is well known that leptin controls energy balance and body weight by regulating neuronal activity in the hypothalamus [25]. The action of adipose tissue-derived leptin is mediated

by its receptor (OB-Rβ) in the brain in regulating energy balance and neuroendocrine function [26] and OB-Rβ activates numerous signaling pathways that act as a network to mediate the action of leptin [25]. On the other hand, leptin resistance resulting from defects in leptin transport into the brain [27], leptin signaling [28], and/or the hypothalamic neural circuitry [29,30] has shown to be associated with the imbalances between energy intake and expenditure, ultimately resulting in obesity. In the present study, the elevated plasma leptin levels in mice fed a HFD were significantly reversed by VO supplementation. Furthermore, up-regulations in hypothalamic OB-Rα and OB-Rβ mRNA were observed in mice in the VO group. It is likely that VO improved leptin resistance in the mice fed HFD through either reductions in circulating leptin levels or up-regulations of receptors mediating leptin's action to the brain. We further tested whether VO modulates hypothalamic expression of genes regulating energy balance because leptin is reported to directly target hypothalamic appetite-regulating genes [31,32]. The results showed that VO reversed elevations in hypothalamic POMC and CART levels induced by a HFD; in contrast, NPY mRNA levels were significantly increased in mice in the VO group compared with that in the HFD group. This is in contrast to the facts that POMC and CART are anorexigenic genes and NYP is an orexigenic gene stimulating feeding behavior [33] of which hypothalamic expressions are modulated by central leptin. Our results imply feedback effect of hypophagia induced by VO administration rather than the direct regulation of genes involved in appetite. It seems that the satiety derived from increased GLP-1 levels by VO supplementation, but not satiety from direct modulation of the hypothalamic genes, can explain the reduced consumption of food in the mice fed a HFD in this study.

Finally, we propose a beneficial effect of VO on mitochondrial dysfunction in obesity, which leads to improved energy utilization and metabolic abnormalities. It has been accepted that mitochondrial dysfunction could be one of the underlying defects linking obesity to diabetes, both by decreasing insulin sensitivity and by compromising β-cell function [34]. Along with body weight loss, in the present study, VO supplementation remarkably improved metabolic status measured by TG content, FFA, and glucose levels in mice fed a HFD. In addition, improvement of peripheral insulin action and insulin secretory dynamics was observed, as measured by a HOMA-IR and HOMA-β cell function effect. In this study, we observed that VO supplementation up-regulated PGC-1α and PGC-1β in the liver and epididymal adipose tissue of mice fed a HFD. PGC-1 is a central transcriptional regulator of mitochondrial biogenesis [35], and defects in mitochondrial energy metabolism have been suggested to cause hepatic steatosis, insulin resistance, and T2DM [36]. In line, reduced PGC-1α expression and mitochondrial dysfunction in the adipose tissue, have been associated with obesity and insulin resistance [37–39]. Considering that PGC-1α is importantly involved in increased mitochondrial function and oxidative metabolism, the observed metabolic benefits of VO in the present study are likely mediated by transcriptional activity of PGC-1α targeted for downstream genes in glucose transport and hepatic lipid metabolism. Indeed, enhanced expression of GLUT4 in adipose tissue and the liver further support this hypothesis.

In summary, 12 weeks of treatment with VO, an α-glucosidase inhibitor, remarkably regulated body weight and reduced total energy intakes. In addition, beneficial metabolic effects in obesity were achieved by VO supplementation, including plasma glucose levels, plasma FFA levels, and insulin sensitivity. At this point, the exact underlying mechanisms are not known but they may involve the incretin effect of VO, the activation of neuroendocrine linked to leptin, and stimulation of genes responsible for enhanced energy metabolism. Further studies are required to elucidate the mechanism of the observed results.

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References

[1] American Diabetes Association, J. Beck, C.E. Cox, et al., Clinical practice recommendations, Diabetes Care 36 (2013) S1–S110.
[2] Look AHEAD Research Group, R.R. Wing, P. Bolin, et al., Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes, N. Engl. J. Med. 369 (1998) 145–154.
[3] K. Matsumoto, M. Yano, S. Miyake, et al., Effects of voglibose on glycemic excursions, insulin secretion, and insulin sensitivity in non-insulin-treated NIDDM patients, Diabetes Care 21 (1998) 256–260.
[4] F.A. van de Laar, P.L. Lucassen, R.P. Akkermans, et al., Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis, Diabetes Care 28 (2005) 154–163.
[5] R.V. Kumar, V.R. Sinha, Newer insights into the drug delivery approaches of α-glucosidase inhibitors, Expert Opin. Drug Deliv 9 (2012) 403–416.
[6] E. Standl, O. Schnell, Alpha-glucosidase inhibitors, cardiovascular considerations and trial evaluation, Diab. Vasc. Dis. Res. 9 (2012) (2012) 163–169.
[7] J.L. Chiasson, R.G. Josse, R. Gomis, et al., Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial, Lancet 359 (2002) 2072–2077.
[8] R. Kawamori, N. Tajima, Y. Iwamoto, et al., Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance, Lancet 373 (2009) 1607–1614.
[9] Y. Liao, S. Takashima, H. Zhao, et al., Control of plasma glucose with alpha-glucosidase inhibitor attenuates oxidative stress and slows the progression of heart failure in mice, Cardiovasc. Res. 70 (2006) 107–116.
[10] T. Narita, H. Yokoyama, R. Yamashita, et al., Comparisons of the effects of 12-week administration of miglitol and voglibose on the responses of plasma incretins after a mixed meal in Japanese type 2 diabetic patients, Diabetes Obes. Metab. 14 (2012) 283–287.
[11] J. Folch, M. Lees, G.H. Sloane-Stanley, A simple method for the isolation and purification of total lipids from animal tissues, J. Biol. Chem. 226 (1957) 497–509.
[12] D.R. Matthews, J.P. Hosker, A.S. Rudenski, et al., Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man, Diabetologia 28 (1985) 412–419.
[13] R.F. Coniff, J.A. Shapiro, T.B. Seaton, Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus, Arch. Intern. Med. 154 (1994) 2442–2448.
[14] P. Segal, P.U. Feig, G. Schernthaner, et al., The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone, Diabetes Care 20 (1997) 687–691.
[15] T. Kawagishi, Y. Nishizawa, H. Taniwaki, et al., Relationship between gastric emptying and an alpha-glucosidase inhibitor effect on postprandial hyperglycemia in NIDDM patients, Diabetes Care 20 (1997) 1529–1532.
[16] H. Laube, T. Linn, P. Heyen, The effect of acarbose on insulin sensitivity and proinsulin in overweight subjects with impaired glucose tolerance, Exp. Clin. Endocrinol. Diabetes 106 (1998) 231–233.
[17] K. Shinozaki, M. Suzuki, M. Ikebuchi, et al., Improvement of insulin sensitivity and dyslipidemia with a new alpha-glucosidase inhibitor, voglibose, in nondiabetic hyperinsulinemic subjects, Metabolism 45 (1996) 731–737.
[18] S. Matthaei, M. Stumvoll, M. Kellerer, et al., Pathophysiology and pharmacological treatment of insulin resistance, Endocr. Rev. 21 (2000) 585–618.
[19] M.J. Dailey, T.H. Moran, Glucagon-like peptide 1 and appetite, Rev. Diabet. Stud. 24 (2013) 85–91.
[20] A. Lee, P. Patrick, J. Wishart, et al., The effects of miglitol on glucagon-like peptide-1 secretion and appetite sensations in obese type 2 diabetics, Diabetes Obes. Metab. 4 (2002) 329–335.
[21] R.S. McIntyre, A.M. Powell, O. Kaidanovich-Beilin, et al., The neuroprotective effects of GLP-1: possible treatments for cognitive deficits in individuals with mood disorders, Behav. Brain Res. 237 (2013) 164–171.
[22] J.N. Roberge, P.L. Brubaker, Regulation of intestinal proglucagon-derived peptide secretion by glucose-dependent insulinotropic peptide in a novel enteroendocrine loop, Endocrinology 133 (1993) 233–240.
[23] R.A. Reimer, C. Darimont, S. Gremlich, et al., A human cellular model for studying the regulation of glucagon-like peptide-1 secretion, Endocrinology 142 (2001) 4522–4528.
[24] R. Moriya, T. Shirakura, J. Ito, et al., Activation of sodium-glucose cotransporter 1 ameliorates hyperglycemia by mediating incretin secretion in mice, Am. J. Physiol. Endocrinol. Metab. 297 (2009) E1358–E1365.
[25] D.L. Morris, L. Rui, Recent advances in understanding leptin signaling and leptin resistance, Am. J. Physiol. Endocrinol. Metab. 297 (2009) E1247–E1259.
[26] S. Arora, Anubhuti, role of neuropeptides in appetite regulation and obesity – a review, Neuropeptides 40 (2006) 375–401.

[27] K. El-Haschimi, D.D. Pierroz, S.M. Hileman, et al., Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity, J. Clin. Invest. 105 (2000) 1827–1832.

[28] J.K. Howard, B.J. Cave, L.J. Oksanen, et al., Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3, Nat. Med. 10 (2004) 734–738.

[29] I.S. Farooqi, J.M. Keogh, G.S. Yeo, et al., Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene, N. Engl. J. Med. 348 (2003) 1085–1095.

[30] I.S. Farooqi, G.S. Yeo, J.M. Keogh, et al., Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency, J. Clin. Invest. 106 (2000) 271–279.

[31] C.C. Cheung, D.K. Clifton, R.A. Steiner, Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus, Endocrinology 138 (1997) 4489–4492.

[32] M.L. Håkansson, A.L. Hulting, B. Meister, Expression of leptin receptor mRNA in the hypothalamic arcuate nucleus – relationship with NPY neurons, Neuroreport 7 (1996) 3087–3092.

[33] M.W. Schwartz, R.J. Seeley, L.A. Campfield, et al., Identification of targets of leptin action in rat hypothalamus, J. Clin. Invest. 98 (1996) 1101–1106.

[34] R.H. Eckel, S.E. Kahn, E. Ferrannini, et al., Obesity and type 2 diabetes: what can be unified and what needs to be individualized?, J Clin. Endocrinol. Metab. 96 (2011) 1654–1663.

[35] P.J. Fernandez-Marcos, J. Auwerx, Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis, Am. J. Clin. Nutr. 93 (2011) 884S–890S.

[36] Z. Wu, P. Puigserver, U. Andersson, et al., Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1, Cell 98 (1999) 115–124.

[37] S. Kleiner, R.J. Mepani, D. Laznik, et al., Development of insulin resistance in mice lacking PGC-1α in adipose tissues, Proc. Natl. Acad. Sci. USA 109 (2012) 9635–9640.

[38] A. Hammarstedt, P.A. Jansson, C. Wesslau, et al., Reduced expression of PGC-1 and insulin-signaling molecules in adipose tissue is associated with insulin resistance, Biochem. Biophys. Res. Commun. 301 (2003) 578–582.

[39] P. Puigserver, Z. Wu, C.W. Park, et al., A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis, Cell 92 (1998) 829–839.