MDG-1, a polysaccharide from Ophiopogon japonicus, prevents high fat diet-induced obesity and increases energy expenditure in mice

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A B S T R A C T

MDG-1, a water-soluble polysaccharide extracted from Ophiopogon japonicus, has potent hypoglycemic and weight control effects. We investigated the impact of MDG-1 on body weight, indirect calorimetry, body composition, plasma biochemical indices and obesity-related mitochondrial activity in diet-induced obese mice. Obese C57BL/6 mice induced by a high fat diet were given either vehicle or vehicle plus MDG-1 at 300 mg per body weight for 16-weeks. MDG-1 could evoked weight loss and reduce adipose tissue mass (by up to ~50%) in the obese animals by increasing oxygen consumption and energy expenditure without inhibiting appetite or increasing physical activity. In addition, MDG-1 could ameliorate plasma lipid profiles, decrease leptin secretion, attenuate hepatic lipid accumulation and increased the expressions of genes related to lipid and energy metabolism in the liver. MDG-1 is a promising candidate drug to treat obesity-related metabolic diseases.

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1. Introduction

Over recent decades, the prevalence of obesity has steadily risen in the majority of the developed world, as well as in developing countries, with the adoption of a sedentary lifestyle combined with excessive caloric intake. Currently, it is estimated that more than 1.5 billion adults are overweight and at least 500 million of them are clinically obese, with a body mass index (BMI) over 25 kg/m² and 30 kg/m², respectively (Flegal, Carroll, Ogden, & Curtin, 2010).

To highlight the related threat to public health, the World Health Organization has declared obesity a global epidemic, and stressed that it remains an under-recognized problem of the public health agenda (Flegal, Carroll, Kit, & Ogden, 2012; Ogden, Carroll, Kit, & Flegal, 2012; Puhl & Heuer, 2009).

Notably, obesity can cause and/or exacerbate a wide spectrum of comorbidities, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular disease, liver dysfunction, respiratory and musculoskeletal disorders, sub-fertility, psychosocial problems and certain types of cancer (Deitel & Shikora, 2002). Actually, short-term dietary control or physical practice in obese humans can lower their metabolic rate (Larson-Meyer et al., 2006), reduce their bodyweight and improve insulin sensitivity (Timmers et al., 2011). However, dietary management and exercise are not always successful, underscoring the need to find more efficient medication to treat obesity-related metabolic diseases. Therefore, the use of pharmacological agents may be indispensable for the long-term treatment of obesity.

Ophiopogon japonicus (Thunb.) Ker-Gawl, widely distributed in South-east Asia, is a typical traditional Chinese medicine that has been widely used in clinics to treat cardiovascular and chronic inflammatory diseases for thousands of years (Zhou et al., 2003). Our previous reports demonstrated that MDG-1, a polysaccharide extracted from the roots of O. japonicus, is a water-soluble inulin-type β-α-fructan with an average molecular weight of 3400 Da, including a backbone composed of Fruf (2 → 1) and a branch of Fruf.
(2 \rightarrow 6)\text{Fruf\text estimated as \textnormal{MDG-1} of 2.}\text{ of average 2.8 of main chain residues; it also contains trace of \textnormal{MDG-1}}\text{, which may be connected to its reducing terminal (Fig. 1). Recent research has suggested that MDG-1 could reduce hyperglycemia, hyperinsulinemia and hyperlipidemia in the spontaneous model of type 2 diabetes in ob/ob mice or KKA\text{Y} mice (Wang et al., 2012; Xu et al., 2011). Our previous pharmacokinetic study showed that MDG-1 was hardly absorbed into the blood and had a poor bioavailability of 1.7% after oral administration (Lin et al., 2010). Up to now, the underlying mechanism of MDG-1 against diabetes or obesity remains a mystery.

In this study, we firstly tested whether MDG-1 could prevent weight gain in obese mice induced by a high fat diet (HFD). We also assessed energy expenditure and circadian activity. On this basis, we explored the effects of MDG-1 on obesity-related metabolic disorders, such as T2DM and dyslipidemia via the analysis of plasma glucose and lipid indices and obesity-related hormones, combined with the histopathological observations of the liver and white adipose tissue. Furthermore, we analyzed the hepatic transcript profile via quantitative real-time polymerase chain reaction (qPCR) analysis to elucidate the possible mechanism of the anti-obesity effects of MDG-1.

2. Material and methods

2.1. Chemicals

MDG-1 was extracted from the radix of O. japonicus and purified as previously described (Wang et al., 2010). Briefly, MDG-1 was prepared from the tuberous root of O. japonicus (Cixi, Zhejiang, China) with water, followed by ethanol precipitation, chromatographic purification via DEAE Sephrose Fast Flow and Sephadex G-25 columns (Pharmacia, Uppsal, Sweden), and finally lyophilized. MDG-1 was dried in a vacuum oven at 60 °C for 8 h prior to use.

Mouse leptin ELISA kit (EZML-82K) and Mouse insulin ELISA kits (EZRL-13K) were purchased from Millipore Research (Billerica, MA, USA). ACCU-CHEK® active glucose test strips were from Roche Diagnostics (Mannheim, Germany). High fat diet (HFD; D12492) was from Research Diets Inc. (New Brunswick, NJ, USA). All aqueous solutions were prepared in ultrapure water produced by a Milli-Q system (18.2 mΩ; Millipore, Bedford, MA, USA). A high capacity cDNA reverse transcription kit and fast SYBR® green master mix were purchased from ABI Applied Biosystems (Carlsbad, CA, USA), and Ambion trizol reagent were obtained from Life Technologies (Carlsbad, CA, USA). Other reagents used in this study were of the highest quality available from commercial vendors.

2.2. High fat diet-induced obesity model construction and regimen experiments

Sixty male C57BL/6j mice at 8 weeks old, with body weights ranging from 18.0 to 20.0 g on arrival, were purchased from Shanghai Laboratory Animal Co. Ltd (Shanghai, China). Mice were housed a three per cage with bedding under controlled temperature (22 ± 3 °C), noise, humidity (50 ± 20%) and lighting cycle (12 h lights-on at 7:00 and 12 h lights-off at 19:00). The Institutional Animal Care and Use Committee, Shanghai University of Traditional Chinese Medicine (Shanghai, China) approved the animal facilities and protocols, and all procedures were in accordance with the National Institute of Heath’s guidelines regarding the principles of animal care.

After 1-week acclimation, mice were fed with the HFD for 7 consecutive weeks. Following another 1-week of acclimation to oral gavage, 24 HFD mice were finally selected based on the baseline values of body weight and food intake. They were randomly divided into two groups (n = 12): the MDG-1 group and HFD group.

The MDG-1 group was treated with HFD and supplemented with MDG-1 (at a dose of 300 mg/kg by oral gavage); the HFD group was treated with HFD only. In addition, 12 male C57BL/6j mice were fed with normal diet as the lean control group during the whole obesity model construction and regimen experiments. Animals were dosed daily between 9 a.m. and 10 a.m., and were kept on the respective diets for 16 consecutive weeks. Body weight and cumulative food intake were recorded daily. Before the end of MDG-1 treatment, 12 mice from the MDG-1 group and HFD group (n = 6 per group) were used for indirect calorimetry analysis and body composition measurement on day 110. At the end of the experiment, each group of mice was exsanguinated under anesthesia at regular intervals after 6 h fasting. Blood samples were obtained from each mouse under anesthesia for biochemical index analysis, while tissues were collected for RNA isolation and histological examination.

2.3. Indirect calorimetry and body composition measurement

In brief, the animals were maintained in a comprehensive lab animal monitoring system (Oxymas/CLAMS, Columbus Instruments, Columbus, OH, USA) for 24 h, according to the manufacturer’s instructions. Volume of O2 consumption (VO2, mL/kg/h) and CO2 production (VCO2, mL/kg/h), and physical activity were continuously recorded over a 24-h period. The respiratory exchange ratio (RER) was calculated as the ratio of carbon dioxide output to oxygen uptake (VCO2/VO2). Energy expenditure was calculated according to the following formula, provided by the manufacturer: energy expenditure = (3.815 + 1.232 VO2/VCO2) × VO2 (Kim et al., 2004). Meanwhile, the body composition of fat mass, lean mass and free fluid was determined according to the manufacturer’s instructions.

2.4. Plasma biochemical indexes assay

Blood glucose, plasma levels of insulin, plasma lipid/sterol profiles (total cholesterol, total triglyceride and low-density lipoprotein cholesterol), and leptin were measured using commercial kits according to the manufacturers’ instructions.

2.5. Histopathological observations

Liver and epididymal white adipose were weighted and then fixed in 10% formalin and embedded in paraffin. Sections were obtained and stained with hematoxylin and eosin (HE) using standard protocols. Stained slides were viewed under a microscope (Leica, Solms, Germany) at ×200 magnification and an Olympus C4000 zoom digital camera (Nikon DS-L1, Nikon, Tokyo, Japan).
captured the images. In total, 500 adipocytes from five areas, with a size of approximately 1 mm² each, were analyzed for the size of adipocytes per sample. Image analyses were performed with Image-Pro Plus 6.0.0.260 Image Analysis Software (Media Cybernetics, Bethesda, MD, USA).

2.6. RNA extraction and qPCR analysis

The Trizol reagent (Life Technology, USA) was used to isolate total RNA from about 100 mg liver tissue, which was subjected to chloroform extraction and isopropanol precipitation. A High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Invitrogen, Life technology, USA) reverse transcribed the total RNA according to the manufacturer’s instructions. A SmartSpec™ Plus spectrophotometer (Bio-Rad, Hercules, CA, USA) quantified the extracted RNA.

Primers were designed by Shanghai Generay Biotech Co. Ltd (Shanghai, China) and their sequences are shown in Table 1. Real time PCR for the selected genes was performed on an ABI 7500 Fast Real-Time PCR System using a Fast SYBR® Green Master Mix and the following parameters: one cycle at 50 °C for 20 s and 95 °C for 20 s, followed by 40 cycles at 95 °C for 3 s and 60 °C for 30 s. Dividing the amount of target gene by the amount of internal control (GAPDH) normalized all expression data.

2.7. Data analysis

Data were expressed as mean value ± standard error of the mean (S.E.M.). Student’s t-test was used to analyze the differences between two groups. Dunnett’s multiple comparison test was used for comparisons between multiple groups. P values < 0.05 were considered significant. Statistical analyses were performed using the SPSS 17.0 software package for Windows.

Table 1: Sequence of the primers used in real-time PCR.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward primer</th>
<th>Reverse primer</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAD</td>
<td>TGATAGCAGACGACCTACAGT</td>
<td>TCTCAACTCTCAGCCATT</td>
</tr>
<tr>
<td>PDK1</td>
<td>TGTCATGGTGACGACATGTC</td>
<td>CTTGTCAGAGCTGGAAGA</td>
</tr>
<tr>
<td>CPT1</td>
<td>TACGAGGAGGAGACGATGT</td>
<td>ATAGCCGACACTTTGAGA</td>
</tr>
<tr>
<td>SOD2</td>
<td>TCTGGCAGAAGCTGACCTAA</td>
<td>TATGGAAGCCAAGACGCC</td>
</tr>
<tr>
<td>NRF1</td>
<td>TTTGAGAATTGCTGAAAAAGT</td>
<td>TTCTGGGATAATGCCAGGAC</td>
</tr>
<tr>
<td>TEAM</td>
<td>CATCTCCTCCTTACGGCTTAC</td>
<td>TTTCCTGTCGTTGGTCCCTC</td>
</tr>
<tr>
<td>ERK1A</td>
<td>CATCTGCTGGTTGGTGA</td>
<td>CTTGGACAGCTAGGAGAAG</td>
</tr>
<tr>
<td>PGC1A1</td>
<td>TGTCACCACAGCAGAACGCTCC</td>
<td>GCCACTCGGTTGCTATGGG</td>
</tr>
<tr>
<td>GAPDH</td>
<td>AGAAGCTGGGCTATTGG</td>
<td>AGGGGCTTACACAGTCTTC</td>
</tr>
</tbody>
</table>

3. Results and discussion

3.1. MDG-1 prevents the body weight gain of HFD mice

During the 16-week experiment, no abnormal clinical signs were observed. HFD rats showed significantly higher body weight gain than normal diet-fed rats throughout the experimental period (Fig. 2A); however, treatment with MDG-1 significantly suppressed the increase in body weight gain from 6 weeks after administration. Net body weight gains after 16 weeks of treatment with vehicle and MDG-1 were 12.0 ± 2.18 and 8.32 ± 2.73 g, respectively. Interestingly, we found that the HFD had an inhibitory effect on the appetite of animals, as the food intake in the HFD or MDG-1 groups was significantly lower than those of lean mice. However, the food intake was almost comparable between the animals in the HFD and MDG-1 groups (Fig. 2B), indicating that MDG-1 was well tolerated in the animals.

3.2. MDG-1 elevates the fat metabolic rate of HFD mice

Obesity is a multifactorial and complex condition characterized by long-term intake of excess energy above energy consumption (Fukuda-Tsuru, Kakimoto, Utsumi, Kiuchi, & Ishii, 2014). No difference in food intake for the MDG-1-treated group suggested that factors other than energy intake contributed to the resistance of weight gain by MDG-1. We conducted indirect calorimetric studies to ascertain whether the resistance to weight gain was associated with an increase in energy expenditure. Surprisingly, we found that the 24-h O₂ consumption was markedly increased for the animals in the MDG-1 group (P < 0.05 vs. the HFD group, Fig. 3A), suggesting an increased oxidative capacity of the mice in the MDG-1 group. In addition, the RER values of obese mice treated with MDG-1 were close to 0.7, especially during the dark phase (P < 0.05 vs. the HFD group, Fig. 3B), indicating a preference for fat oxidation over carbohydrate metabolism. Consistent with these data, a significant elevation in energy expenditure in the MDG-1 treated mice was also observed (P < 0.05 vs. the HFD group, Fig. 3C). To confirm this hypothesis, we further evaluated the effects of MDG-1 on the free fluid of mice. The fat mass was 7.2 ± 3.3 g in the MDG-1 group and a fat reduction of nearly 50% was observed (P < 0.05 vs. the HFD group, Fig. 3D) after the treatment. At the same time, a significant decrease in free fluid was also observed in the MDG-1 group. Collectively, these results further showed that MDG-1 could elevate the fat metabolic rate of obese mice, leading to weight loss. Meanwhile, MDG-1 did not alter the physical activity of mice, as no obvious change in the locomotor

Fig. 2. Effects of MDG-1 on (A) cumulative body weight gain, and (B) food intake in high fat diet-induced obesity mice. Data are expressed as mean values and S.E.M. (n = 12). Lean, C57BL/6j mice fed with a normal chow diet; HFD, mice fed with high fat diet; MDG-1, mice fed with high fat diet and treated with 300 mg/kg MDG-1 daily. Significance: * P < 0.05 vs. the HFD group.
activity was observed between the MDG-1 and HFD mice ($P>0.05$ vs. the HFD group, Fig. 3E).

3.3. **MDG-1 ameliorates the biochemical parameters of HFD mice**

Diet-induced obesity has detrimental effects on glucose homeostasis and plasma lipid profiles; therefore, we analyzed whether MDG-1 could normalize these parameters. Consistent with our previous studies, treatment with MDG-1 showed an inhibitory effect on fed blood glucose and plasma insulin in the HFD animals (Fig. 4A and B). In addition, plasma lipid profiles (Fig. 4D–F) showed that the levels of total triglyceride and low-density lipoprotein cholesterol (LDL-C) were significantly reduced following treatment with MDG-1 ($P<0.05$ vs. the HFD group), whereas the total cholesterol was unaffected. This hypotriglyceridemia effect was consistent with some previous reports that inulin or oligofructose, as dietary fibers, could modify the hepatic metabolism of lipids in several animal models (Fiordaliso et al., 1995; Kok, Taper, & Delzenne, 1998; Trautwein, Rieckhoff, & Eebersdobler, 1998). However, compared with the dose of oligofructose (10% in the diet), the consumption of MDG-1 was much lower. Leptin is an adipocyte-derived hormone that plays a pivotal role in regulating food intake, energy expenditure and neuroendocrine function. It can also stimulate the oxidation of fatty acids and the uptake of...
glucose (Minokoshi et al., 2002). In this study, we found that the levels of plasma leptin were significantly reduced after treatment with MDG-1 (P < 0.05, vs. the HFD group, Fig. 4C). Thus, it is possible that the decreased body adiposity was related to the lower leptin level.

3.4. MDG-1 suppresses HFD-induced adipocyte hypertrophy

Obesity causes adipocyte hypertrophy, which is correlated with altered metabolic functions, such as reduced insulin sensitivity and elevated lipolysis (Attie & Scherer, 2009). We measured the epididymal fat weight and the size of adipocytes to confirm whether treatment with MDG-1 is associated with changes in the morphology of adipose tissue. Compared with the HFD treatment, MDG-1 reduced the epididymal fat weight significantly (Fig. 5E). Hypertrophy of adipocytes in epididymal white adipose was observed in the HFD group and was inhibited in the MDG-1-treated group, providing further evidence that leanness correlated with MDG-1 treatment (Fig. 5D).

3.5. MDG-1 improves HFD-induced hepatic lipid accumulation

Feeding an HFD to rodents leads to hepatic steatosis (Buettner, Scholmerich, & Bollheimer, 2007). Compared with the lean mice group, the liver weight in the HFD group was significantly higher (P < 0.05 vs. lean group) and MDG-1 tended to lower the liver weight of the mice (Fig. 6D). Histological analysis of the liver sections from HFD groups showed extensive intracellular vacuolization and significant lipid accumulation in both the perivenular and periportal area (Fig. 6B). By contrast, only scattered small lipid droplets were detected in the livers from the MDG-1 treated animals (Fig. 6C), indicating that MDG-1 could prevent lipid accumulation, which might contribute to the decreased fat accumulation.

3.6. MDG-1 affects the mitochondrial activity of HFD mice

To test the hypothesis that mitochondrial activity of HFD mice was affected by MDG-1 treatment, and to further understanding the molecular basis of the weight loss, elevated fat metabolic rate and restored glucose and lipid metabolism induced by MDG-1, we analyzed the expressions of related genes liver tissues (Fig. 7).

Mitochondrial β-oxidation is the dominant oxidative pathway for the fatty acids under normal physiological conditions (Lee et al., 2006). Long and very long chain fatty acids are activated by acyl-CoA synthetases on the mitochondrial outer membrane. However, transport of long and very long fatty acids into the mitochondria requires carnitine O-palmitoyltransferase I and II.

Fig. 5. Effects of MDG-1 on white adipose tissue in high fat diet-induced obesity mice. Hematoxylin and eosin (HE) staining of adipocytes in (A) lean mice, (B) high fat diet mice and (C) high fat diet mice treated with MDG-1 were prepared. (D) Mean adipocyte cell size and (E) epididymal fat weight of normal or high fat diet-induced obese mice treated with vehicle or MDG-1 for 16 weeks were measured. Data are expressed as mean values and S.E.M. (n = 12). Significance: * P < 0.05 vs. the HFD group.

Fig. 6. Effects of MDG-1 on hepatic lipid accumulation in high fat diet-induced obesity mice. Hematoxylin and eosin (HE) staining of liver specimens from (A) lean mice, (B) high fat diet mice and (C) high fat diet mice treated with MDG-1 were prepared. (D) Hepatic weights were measured. Data are expressed as mean values and S.E.M. (n = 12). Significance: * P < 0.05 vs. the HFD group.
(CPT-1 and CPT-2), which combine fatty acyl-CoAs with carnitine to form acylcarnitines, which can enter into β-oxidation (Bartlett & Eaton, 2004). Notably, the expression of the CPT-1 gene was increased in the liver tissue of the obese animals treated with MDG-1 (Fig. 7A), demonstrating that augmented fatty acid oxidation occurred in the MDG-1 treated animals. In addition, although a tendency was observed for medium-chain acyl-CoA dehydrogenase (MCAD) mRNA levels to increase under MDG-1 treatment, the differences were not significant. Overall, increased mRNA of genes related to fatty acid oxidation may indicate increased fat oxidation and decreased fat accumulation in the livers of the MDG-1–treated group, which would explain our histological analysis of liver sections and correlates with our previous result that MDG-1 could decrease triglyceride content in the liver in ob/ob mice (Xu et al., 2011).

The pyruvate dehydrogenase complex (PDC) catalyzes the conversion of pyruvate to acetyl-CoA in mitochondria and is a key regulatory enzyme in the oxidation of glucose to acetyl-CoA. Phosphorylation of PDC by pyruvate dehydrogenase kinases (PDK) inhibits its activity. The expression of the pyruvate dehydrogenase kinase 4 (PDK4) gene is increased during fasting and other conditions associated with the switch from the utilization of glucose to fatty acids as an energy source (Connaughton et al., 2010). We found that the expression level of PDK4 mRNA in the HFD group was almost 2-fold higher than that in the lean mice group, and MDG-1 treatment restored the expression level to close to the levels of lean mice (Fig. 7C), suggesting an elevation on glycolysis and inhibition of gluconeogenesis.

Oxidative damage is elevated in obesity and the severity of metabolic dysfunction among obese patients is directly correlated with markers of oxidative stress (Tinalhones et al., 2009). One of the primary sources of pro-oxidants with obesity may be mitochondrial dysfunction, which promotes increased superoxide radical production as a byproduct during mitochondrial respiration. Superoxide dismutases (SOD) represent the primary cellular defense against superoxide radicals. In mammals, there are two intracellular forms of SOD: copper zinc superoxide dismutase (SOD1), which is located primarily in the cytoplasm, and manganese superoxide dismutase (SOD2), which is located in the mitochondria (Okado-Matsumoto & Fridovich, 2001). A previous report suggested sulfated heteropolysaccharide fractions from O. japonicus had a strong antioxidant activity (Xiong, Li, Huang, Lu, & Hou, 2011). The data in Fig. 7D indicated that the expression of SOD2 mRNA was significantly upregulated in the MDG-1 group (P < 0.05 vs. the HFD group). SOD2 catalyzes the conversion of superoxide to hydrogen peroxide, which is subsequently converted to water by other antioxidants to reduce oxidative stress/damage (Liu et al., 2013); therefore, these results demonstrated that MDG-1 could ameliorate the mitochondrial dysfunction induced by oxidative damage in vivo.

The transcription factors peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) and estrogen-related receptor α (ERRα) regulate much of the fatty acid metabolism; therefore, we observed their expression levels in mouse livers. MDG-1 treatment did not change the mRNA level of ERRα, but there was a trend for PGC-1α mRNA to increase in the MDG-1–treated group (Fig. 7E and F). Interestingly, the nuclear regulatory factor NRF-1 (Vernochet et al., 2012), which plays a role in cell adaptation to the energy stress situation by translating a metabolic perturbation into an increased capacity to generate energy, showed a return to near normal expression levels in the MDG-1 group (P < 0.05 vs. the HFD group, Fig. 7G). However, MDG-1 did not affect the expression of mitochondrial transcription factor A (TFAM).

Collectively, we observed that most of the altered genes were involved in energy metabolic activities, such as β-oxidation of fatty acids, glycolysis, antioxidant defense and mitochondrial respiratory chain complex activities. Obesity is also described as an energy imbalance; therefore, these results suggested that the possible mechanism of weight loss induced by MDG-1 might be increased energy expenditure driven by MDG-1’s regulation and improvement of mitochondrial dysfunction.

4. Conclusions

In this paper, we showed, for the first time that MDG-1, a polysaccharide derived from O. japonicas, could evoke gradual weight loss without inhibiting the appetite or increasing the physical activity of obese mice. In addition, the weight loss of obese mice treated with MDG-1 was mainly caused by the reduction of fat mass content without affecting the lean mass content. Furthermore, MDG-1 could ameliorate some plasma biochemical indexes of insulin resistance and altered the expression levels of several
genes related to lipid metabolism, energy metabolism, mitochondrial function and oxidative stress. Consequently, we speculate that MDG-1 increases energy expenditure by elevating metabolic activities such as fatty acid oxidation, thus inducing the reduction of fat mass and resulting in weight loss. Thus, MDG-1 could be an efficient medication to treat obesity and obesity-related metabolic diseases.

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