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Panax red ginseng extract regulates energy expenditures by modulating PKA dependent lipid mobilization in adipose tissue

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ABSTRACT

Regulation of balance between lipid accumulation and energy consumption is a critical step for the maintenance of energy homeostasis. Here, we show that Panax red ginseng extract treatments increased energy expenditures and prevented mice from diet induced obesity. Panax red ginseng extracts strongly activated Hormone Specific Lipase (HSL) via Protein Kinase A (PKA). Since activation of HSL induces lipolysis in WAT and fatty acid oxidation in brown adipose tissue (BAT), these results suggest that Panax red ginseng extracts reduce HFD induced obesity by regulating lipid mobilization.

1. Introduction

Maintenance of energy homeostasis requires adequate sensing of energy level stores in adipose tissue, transduction of these signals, and coordinate regulation of energy intake and expenditure. Disruption of the balance between energy intake and expenditure causes metabolic disorders, and when calorie intake continuously exceeds that of energy consumption, excess energy is stored as triglycerides in adipose tissue, resulting in obesity.

Ginseng extract, mainly composed of polysaccharides, minerals, vitamins, and ginsenosides, has been used for more than 2000 years as one of the most popular traditional medicines in oriental societies [1,2]. Historically, Panax ginseng has been used as a tonic, stress reliever, anti-aging agent, and enhancer of brain and sexual function. Recently, a couple of studies have shown the effect of ginseng extracts on metabolic syndrome. Ginseng extract or ginsenoside Rb2 treatment decreased circulating blood glucose levels in the streptozotocin-induced type I diabetes model [3–5], and treatment with Panax ginseng for 8 weeks or longer decreased circulating glucose levels in human [6]. Moreover, recent studies revealed the anti-obesity activity of ginseng [7].

Although these studies suggest that ginseng extract can affect the regulation of energy metabolism, the underlying mechanism of their action remains unclear. For example, there are contradictory results about the effect of ginseng on the regulation of food intake. Two groups observed a suppressive effect [8,9], whereas Lee et al. did not observe any change in food intake [10], suggesting that appetite regulation is not a major contributing factor for anti-obesity effect of ginseng. Furthermore, there are as yet no reports on the effect of ginseng extracts on energy expenditure.

In this study, we treated HFD induced obese mice with Panax red ginseng extract, and examined the effect of ginseng extract on food intake, adipose tissue, and energy expenditures. Our data suggest that ginseng extract prevents obesity by enhancing lipolysis in white adipose tissue (WAT) and energy expenditure in brown adipose tissue (BAT).

2. Materials and methods

2.1. Panax red ginseng extracts

Panax red ginseng extract was supplied by Korea Ginseng Corporation (KGC). Panax red ginseng extract was produced by steaming fresh 6-year-old *Panax ginseng C. A. Meyer* at 90–100 °C for 3 h and then drying at 50–80 °C. The final Panax ginseng extract contained 34.41 mg/g of water, 7.53 mg/g of Rb1, 2.86 mg/g of Rb2, 2.98 mg/g of Rc, 0.89 mg/g of Rd, 1.90 mg/g of Re, 1.12 mg/g of Rf,

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1.78 mg/g of Rg1, 1.12 mg/g of Rg2s, 1.37 mg/g of Rg3s, 0.72 mg/g of Rg3r, and 0.84 mg/g of Rh1.

2.2. Animal studies

C57BL6/J mice were housed in a temperature-controlled environment under a 12-h light:dark cycle (light on at 8 a.m. and light off at 8 p.m.) with free access to water and normal chow diet (Purina Rodent chow, 38057). When mice were 6–8 weeks old, normal chow diet was replaced with 60% HFD (Research Diets, D12492). Control groups of mice were given regular drinking water while experimental groups were given 2 mg of Panax red ginseng extract/ml of drinking water. The body weight of each mouse was measured weekly. Food and water intake was measured manually every 2–3 days, and weekly calorie intake was calculated based on the information provided from Research Diet (60% HFD) and KGC (Panax red ginseng extract). Experiments were performed at least twice, with independent groups. All animal studies were performed by following an approved protocol from the Asan Life Science Institute, Asan Medical Center.

2.3. Histology

Immediately after dissection, mouse tissues were fixed in 10% formaldehyde and embedded in paraffin blocks. Sections (5 um-thick) were evaluated by H&E staining and immunohistochemical (IHC) analysis. F4/80 antibodies (Abcam) were used for IHC analysis, and visualized by DAB staining using the avidin–biotin method according to the manufacturer's instructions (Vector Labs).

2.4. Metabolic cage studies

Mice were individually housed for acclimation before experiments. Individually housed mice were monitored for O_2 consumption, CO_2 production, heat (energy expenditure), and locomotor activity using indirect calorimeter (Columbus). After acclimation, saline or Panax red ginseng extract was administered intraperitoneally in control and experimental groups respectively. Data were collected over a period of 2–3 days. Respiratory exchange ratio (RER) was automatically calculated based on the ratio of O_2 consumption and CO_2 production.

2.5. Western blot

Immediately after dissection, mouse tissues were deep frozen with liquid N_2. Frozen mouse tissues were grinded in liquid N_2 followed by homogenization in lysis buffer (Tris–Cl, ph7.4, 150 mM NaCl, 5 mM EDTA, proteinase inhibitor (Roche), and phosphatase inhibitor). Phospho-Hormone Specific Lipase (HSL), HSL, phosphor-AMPK, AMPK, and phospho-PKA substrate antibodies (Cell signaling) were used for immunoblots as described previously [11].

2.6. Statistics

Statistical analysis was performed using unpaired *t* test with Graph Pad Prism software. Data are presented as means ± s.e.m. Statistical significance is indicated as $^{*}P < 0.05$ and $^{**}P < 0.01$.

3. Results

3.1. Ginseng extract protects mice from HFD induced obesity

We examined the effect of ginseng extracts on HFD (60%) induced obese mice. HFD induced weight gain in both control groups and Panax red ginseng extract treated groups, however weight gain of Panax red ginseng extract treated groups was attenuated and after 8 weeks of HFD treatment, the weight gain of the experimental group was 20% less than that of the control group. After 16 weeks of HFD treatment, experimental groups gained 24% less body weight than control groups (Fig. 1A). Overall, groups treated with ginseng extract weighed approximately 15% less than control groups (38 g vs. 45 g).

We asked whether the protective effect of ginseng extract in diet induced obesity (DIO) is caused by a lower amount of food intake, and monitored the food intake during the study period. Although, compared to control groups, the groups treated with ginseng extract showed slightly lower calorie intake, the difference between the groups was relatively small and did not reach statistical significance (Fig. 1B).

3.2. Ginseng treatment attenuates HFD induced adipose hyperphagia

To examine the reasons behind the weight difference between ginseng extract treated and control groups, heart, liver, WAT, BAT, and gastrogmus and quadriceps tissues were dissected out, and the weight of each individual tissue was measured. The weight of heart muscle tissue was comparable between control and ginseng treated groups; however, ginseng treated groups showed lower liver, skeletal muscle tissue, and particularly low adipose tissue mass (Table 1). When we examined WAT by H&E staining, the size of white adipocytes from ginseng treated groups was smaller than that from control groups (Fig. 2A and B). Interestingly, the WAT from control groups showed signs of more extensive macrophage infiltration, with typical crown structures more frequently found in control groups than ginseng treated groups. Staining with

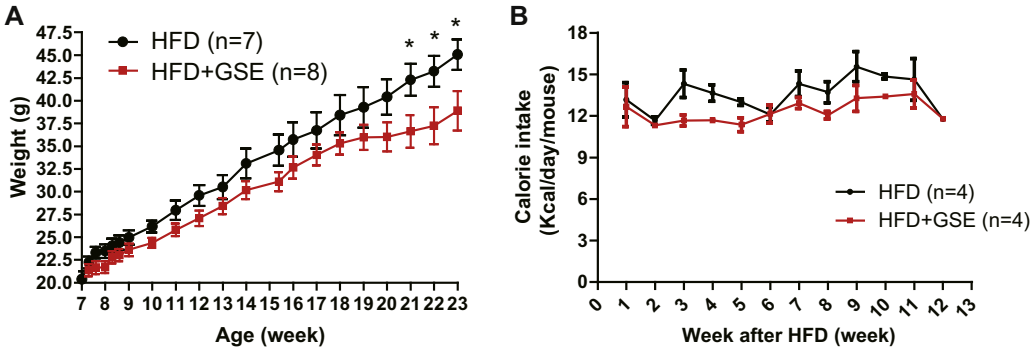

Fig. 1. Effect of Panax red ginseng extract on HFD induced obesity. (A) Normal chow fed 7-week-old C57BL6/J mice were switched to 60% HFD. Panax red ginseng extract was supplied in drinking water (2 mg/ml) to experimental groups (HFD + GSE, $n = 7$), and regular drinking water was supplied to control groups (HFD, $n = 8$). Body weight was monitored weekly. (B) Calorie intake was monitored and recorded weekly. All values were expressed as mean ± s.e.m. *Indicates $P < 0.05$.

Table 1
Tissues weight of HFD and HFD supplemented with Panax red ginseng groups.

	HFD			HFD + GS		
	Mean	s.e.m.	*N*	Mean	s.e.m.	*N*
Heart	0.160	0.020	4	0.170	0.004	4
Liver	0.512	0.042	4	0.368	0.011	4
EpiWAT	2.120	0.105	4	1.783	0.292	4
BAT	0.155	0.019	4	0.125	0.019	4
Quad	0.380	0.018	4	0.355	0.060	4
Gastroc	0.438	0.027	4	0.395	0.023	4

F4/80, a macrophage marker, confirmed that the control groups had more extensive macrophage infiltration in WAT (Fig. 2C).

3.3. Ginseng extract regulates lipid mobilization in WAT

Previous studies demonstrated that ginseng extract or ginsenosides activated AMPK. Similarly, in this study, western blot analysis with an antibody against phospho-Thr172 AMPK showed increased AMPK activity in WAT from ginseng treated groups compared to control groups (Fig. 2D).

Adrenaline signaling maintains energy homeostasis by regulating lipid mobilization in adipose tissues [11,12]. In WAT, adrenaline signaling stimulates lipolysis via ADRB3 (Adrenoreceptor beta 3) mediated PKA (Protein Kinase A) dependent signaling pathway. HSL, which is a key molecule in the lipolysis pathway, is a direct substrate of PKA, and phosphorylation of Ser660 site of HSL by PKA initiates lipolysis. Western blot analysis with an antibody against phospho-Ser660 HSL revealed increased phosphorylation at serine 660 site of HSL in WAT from ginseng treated mice. In addition, western blot analysis with antibodies specific for phospho-PKA substrate and phosphor-CREB confirmed that PKA activity is more active in WAT of ginseng treated mice (Fig. 2D).

3.4. Ginseng extract treatment increases energy expenditures

As ginseng extract showed a protective effect in DIO without a significant reduction of energy intake (Fig. 1B), we investigated the effect of ginseng on energy expenditure. O_2 consumption and CO_2 production rates in control and Panax red ginseng extract treated groups were measured using indirect calorimeter. Panax red ginseng extract treated groups showed higher O_2 consumption and CO_2 production rates than control groups, suggesting that ginseng treatment increases the metabolic rate and energy expenditures (Fig. 3A and B). The difference in O_2 consumption and CO_2 production rates between the control and ginseng treated groups was maximal immediately after the IP injection of ginseng extract, and gradually decreased 1 day after the injection. These findings suggest that ginseng extract plays a direct role in the regulation of energy expenditure. The higher metabolic rate of ginseng treated mice was not accompanied by increased physical activity (Fig. 3C). The physical activity of ginseng extract treated groups was slightly lower compared with that of control groups, suggesting that the enhancing effect of ginseng on energy expenditure involves a mechanism other than increased physical activity. The RER of ginseng extract injected groups was significantly lower than that of control groups (Fig. 3D).

3.5. Ginseng extract increases energy expenditure via regulation of brown adipose tissue activity

BAT is a highly active metabolic tissue involved in energy homeostasis by regulating fatty acid oxidation. Examination of BAT tissues by H&E showed that brown adipocytes from ginseng

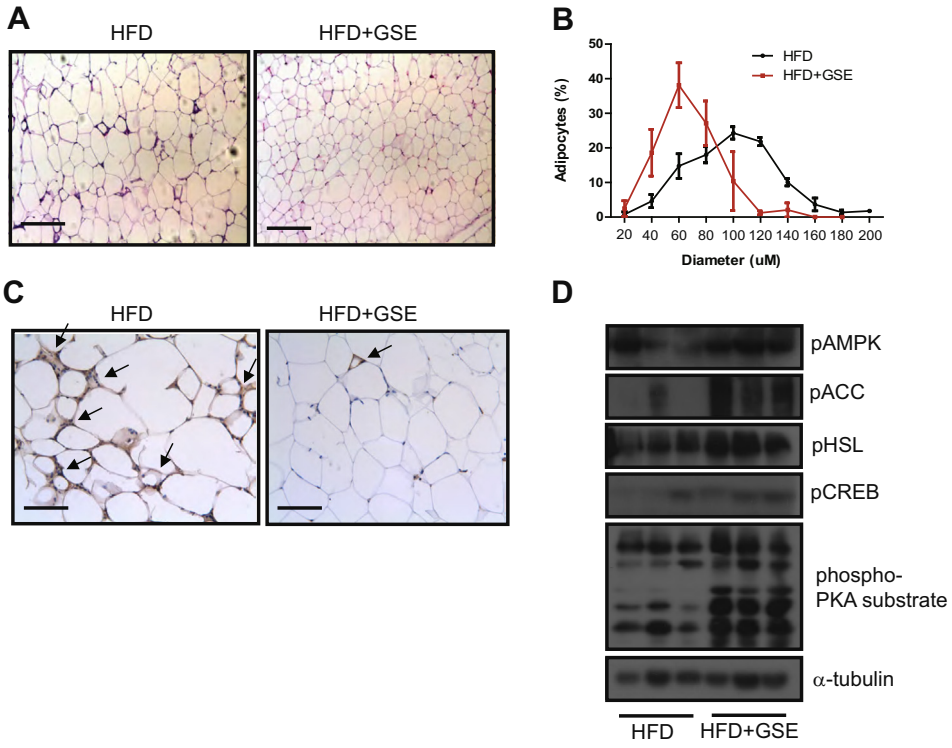

Fig. 2. Panax red ginseng extract regulates lipid metabolism via AMPK and PKA pathway and attenuates HFD induced white adipocyte hypertrophy and macrophage infiltration. (A) Hematoxylin and eosin stained sections of epididymal WAT at 15 weeks following treatment with HFD with (HFD + GSE) or without (HFD) Panax red ginseng. Scale bar represents 100 um. (B) Adipocyte size distribution. (C) Macrophage infiltration in epididymal WAT by F4/80 immunohistochemistry. (D) Western blot analysis shows activation of AMPK, HSL, and PKA induced by Panax red ginseng extract treatment in protein samples of WAT. Scale bar represents 200 um.

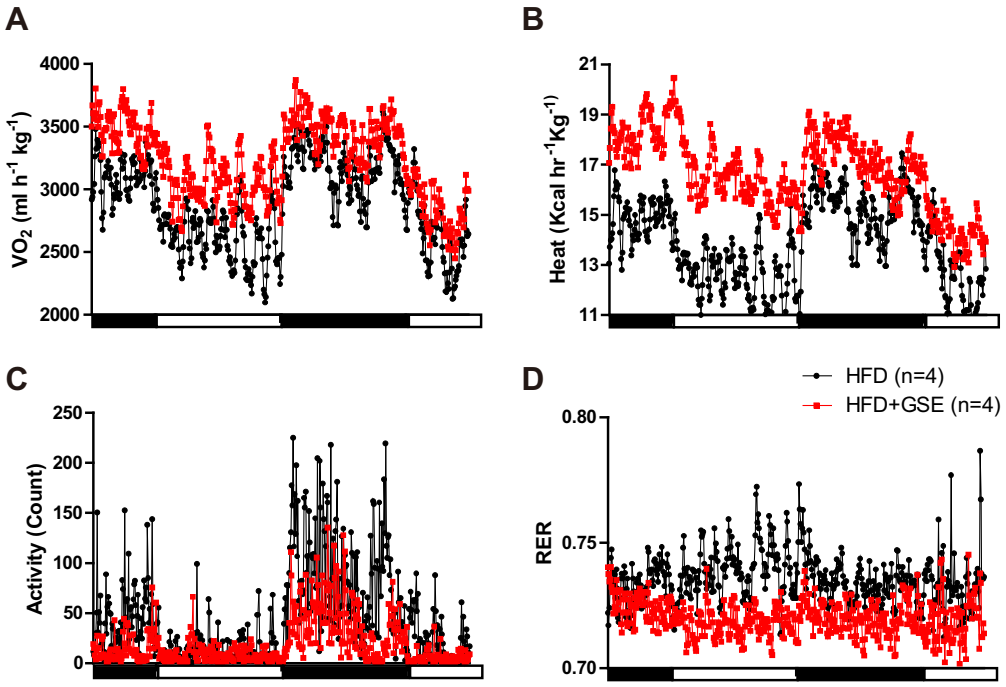

Fig. 3. Panax red ginseng extract increases energy expenditure in mice. *In vivo* energy metabolism analysis of control and Panax red ginseng extract treated groups by metabolic cage study. Panax red ginseng extract was introduced by ip injection at the beginning of the study. (A) Oxygen consumption rate. (B) Energy expenditure. (C) Physical activity, and (D) RER (respiratory exchange ratio). Black and white bars represent night and light cycle, respectively. Values are displayed as means for 4 mice per group.

treated mice contain less lipid droplets than those of control mice resulting in smaller brown adipocytes (Fig. 4A). Adrenaline stimulates fatty acid oxidation in BAT, as it does in WAT, through activation of PKA [13]. In parallel with the increased HSL and PKA activity observed in WAT, the phosphorylation of HSL and PKA activity was elevated in BAT of ginseng treated mice (Fig. 4B).

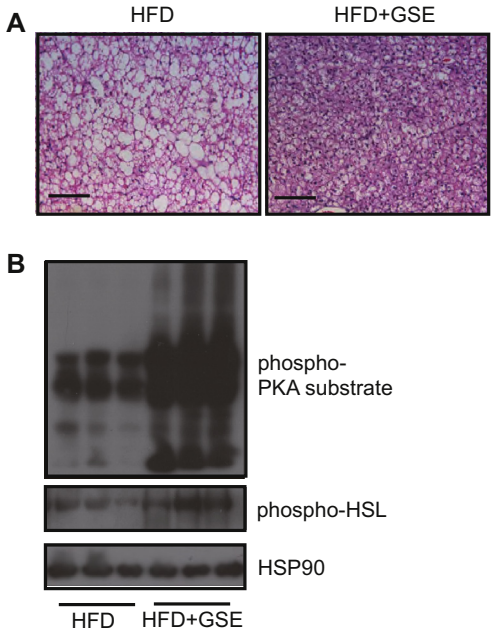

Fig. 4. Enhanced brown adipose tissue activity by Panax red ginseng treatment. (A) Hematoxylin and eosin stained section of BAT in control and Panax red ginseng treated mice (15-week treatment). Scale bar represents 100 um. (B) Western blot analysis showing HSL and PKA activity is elevated in BAT following Panax red ginseng extract treatment.

4. Discussion

Since the identification of the adipose derived hormone leptin, there has been a tremendous advancement in our understanding of the molecular mechanisms of energy homeostasis regulation. However, the anti-obesity drugs developed so far, are often accompanied by side effects. *Panax ginseng* is a natural herbal medicine that has been in use for more than 2000 years, and although using the right dose is important, this medicine has been proven to be safe.

We found that supplementation of drinking water with Panax red ginseng extract significantly attenuated HFD induced obesity in mice. The weight reduction caused by Panax red ginseng appears to be due to decreased fat accumulation in major metabolic tissues, such as WAT, BAT, and liver.

The underlying mechanisms of the anti-obesity effects of ginseng have started to be revealed by recent studies. Karu et al. suggested that concentrated crude ginsenoside extract blocks food absorption by directly inhibiting pancreatic lipase activity [7]. Treatment with Panax white ginseng extract down-regulated mRNA expression of the genes involved in lipogenesis and lipolysis, such as PPARγ2, SREBP-1c, FAS, and DGAT-1 [14]. Another group demonstrated that Panax red ginseng extract's anti-adipogenic activity was mediated through inhibition of angiogenesis [10]. More recently, the regulation of AMPK activity by ginseng was investigated by several groups. Treatment with Panax ginseng extracts [15] or ginsenosides Rb1 [16], Rb2 [17], Rg1 [18], Rg2 [19], or Rg3 [20] enhanced glucose uptake in 3T3L1 and C2C12 cells, and decreased gluconeogenesis in HepG2 cell lines via AMPK activation. We also observed that Panax red ginseng extract activated AMPK, as evidenced by the increased phosphorylation at Thr172 of AMPK and Ser79 of ACC (Acetyl-CoA Carboxylae), which is a direct phosphorylation target site of AMPK. As Ser79 phosphorylated ACC is inactive, we speculate that the reduced WAT mass by Panax red ginseng extract is at least partially due to inhibition of fatty acid synthesis.

Another pivotal signal that controls lipid mobilization in adipose tissue is adrenaline. Adrenaline signaling stimulates lipolysis in WAT and fatty acid oxidation in BAT by directly activating PKA. Interestingly, we found that the activity of HSL, which is acquired by direct phosphorylation by PKA, is elevated in Panax red ginseng treated adipose tissue. In line with this finding, the overall PKA activity in adipose tissue was increased by Panax red ginseng, suggesting that the decreased size of adipocytes in Panax red ginseng treated adipose tissue is also caused by hyper-activation of PKA mediated lipolysis pathway.

Most mechanistic studies aiming to explain the anti-obesity effect of ginseng or ginsenosides have focused on the reduction in WAT mass. However, decreased WAT without accompanying decrease in energy intake or increase in energy expenditure, leads to the development of severe type 2 diabetes, as exemplified by the A-Zip mouse model [21]. In our study, mice treated with ginseng extract showed increased energy expenditure without accompanying increase in physical activity. BAT is a specialized organ involved in non-shivering thermogenesis through dissipation of energy generated from fatty acid oxidation. Inactivation of ACC by AMPK has been shown to decrease malonyl-CoA level facilitating fatty acid translocation into mitochondria, and subsequently leading to the activation of the fatty acid oxidation pathway. In parallel, activation of HSL by PKA also increases fatty acid oxidation rate. In fact, chronic activation of AMPK with AICAR, an AMPK agonist, or selective ADRB3 agonist, CL-316,243, treatment leads to weight loss by increasing lipolysis and fatty acid oxidation in adipose tissues [13,22]. We also observed that Panax red ginseng activates PKA in BAT. Thus, we suggest that fatty acids released from WAT by Panax red ginseng extract flow into BAT, where they enter beta oxidation cycle resulting in increased energy expenditures (Supplementary Fig. 1).

Metabolic syndrome is caused by complex mechanisms involving multiple tissue interactions and signaling pathways, which hinder the development of potent therapeutics. Reflecting this complexity, recent clinical therapies have started to use a combination of drugs for the treatment of obesity and diabetes [23]. We demonstrated that Panax ginseng extract is a dual regulator of AMPK and PKA activity in adipose tissues. Further clinical and mechanical studies are required to validate Panax red ginseng extract as an anti-obesity medicine.

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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.2014.04.056.

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