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Original Article

Anti-obesity Effects of Ginsenosides in High-Fat Diet-Fed Rats*

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ABSTRACT **Objective**: To examine the anti-obesity effects of ginsenosides in Korea Red Ginseng (KRG, *Panax ginseng*) in rats fed with a high-fat diet (HFD). **Methods**: Twenty-five 4-week-old obesity rats after receiving an HFD for 5 weeks; subsequently, they were additionally treated with ginsenosides Rb1, Rd, Rg1, or Re (10 mg/kg, intraperitoneal injection) for a further 3 weeks (n=5 in each group). The control rats were fed a normal diet. The food consumption, body weight, locomotor activity, serum lipids, adipose tissues, nitric oxide (NO) expression, leptin, neuropeptide Y (NPY), cholecystokinin (CCK) in the brains were measured. **Results**: In the HFD-fed rats, body weight, body fat mass, serum levels of leptin and NO were significantly higher than in the control rats (P<0.05 or P<0.01). However, the treatment of Rd, Re, and Rb1 markedly decreased body fat mass and body weight (P<0.05). The serum level of leptin and NO in ginsenoside-treated rats were markedly lower than the control group (P<0.01). The expression of NPY and CCK in the hypothalamic nuclei showed insignificant difference among groups. However, the expression of NPY immunoreactive neurons in the hypothalamus was significantly reduced in the Rb1-treated group (P<0.05). **Conclusion**: PD-type ginsenoside Rb1 from the crude saponins of KRG may be a useful compound for the treatment of obesity and related disorders through the modulation of peripheral and central appetite-regulating signals.

KEYWORDS *Panax ginseng*, ginsenosides, hypothalamus, obesity

In recent years, the incidence of obesity has reached epidemic proportions, with the World Health Organization reporting that there are 1 billion overweight individuals and 300 million obese individuals. Obesity may induce variety organ damage through metabolic dysfunction.[1] Overweight and obesity are defined, respectively, as the abnormal or excessive accumulation of fat presents a risk to health.[2] It has been proven that overweight and obesity may increase malignancies.[3] In addition, they are associated with notably increased morbidity through higher incidences of diabetes mellitus, cardiovascular diseases, stroke, and heart failure.[4] Therefore, many researchers have focused on obesity management.

Persuasive evidence exists to indicate that gastrointestinal factors, cholecystokinin (CCK), and neuropeptide Y (NPY) release provide feedback that slows gastric emptying, and regulates energy intake in response to combinations of intradermal fat and/or carbohydrate.[5-7] *Panax ginseng* has been used as a supplemental drug for physical and mental voiding symptoms to recover homeostasis. It is neither merely a tonic or a remedy for a certain disease; for example, Patel, et al[8] reported the action of ginseng as adaptogen. Liu, et al[9] called ginseng a harmony drug, and Cha, et al[10] and Schwarz, et al[11] showed that ginsenoside Rb1 was a central nervons system (CNS)-sedative and Rg1 was CNS-stimulant. Numerous reports have been published on the pharmacological and biological activities of Rx ginsenosides.[8,10,11] Ginsenosides Rb1 and Rg1, and other members of ginseng saponins, are reported to have multifunctional activities.[10] However, the anti-obesity mechanisms of ginsenosides have not yet been reported.

In the present study, the anti-obesity effects of ginsenosides Rb1, Rd, Rg1, and Re were investigated in rats fed with a high-fat diet (HFD) through evaluation of changes in body weight, food consumption, serum

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lipid concentration, and physical activity during the development of response-related obesity. More specifically, to identify the anti-obesity mechanism of the effective ginsenosides, the complicated central and peripheral networks were examined through the analysis of serum leptin and nitric oxide (NO), and the expression of hypothalamic neuropeptides such as NPY and CCK.

METHODS

Animals and Diets

All experimental procedures performed on the animals were conducted with the approval of the Ethics Committee of the Kyung Hee University and in accordance with the US National Institutes of Health "Guide for the care and use laboratory animals" (NIH Publication No. 80–23, revised 1996). Twenty-five male Sprague-Dawley rats (Orient Animal Corp, Kyunggido, Korea) with a body weight of 90–100 g were used for the experiment. The rats were fed commercial rat chow for 1 week before the switched to a HFD containing lard and cholesterol for 5 weeks. For the final 3 weeks, the rats received daily intraperitoneal injections (i.p.) of ginsenosides Rb1, Rd, Rg1, or Re at 10 mg/kg or saline at 1 mL/kg. The rats were maintained in a temperature-controlled room (18–26 ℃, 30%–70% relative humidity) with a 12:12 light-dark cycle and given free access to food and tap water. The experimental diets contained either normal fat (11.7% of calories as fat, AIN-76A diet #100000, Dyets Inc., Bethlehem, PA, USA), or high fat (40% of calories as fat, ANI-76A diet #100496, Dyets Inc., Bethlehem, PA, USA, Appendix 1).

Ginsenoside Purification

Ginsenosides purified from Korean Red Ginseng (KRG) were kindly provided by the Korea Ginseng Corporation (Daejon, Korea). KRG was manufactured by the Korea Ginseng Corporation from the roots of 6-year-old fresh *Panax ginseng* Meyer. The yield of the crude saponin from 100% ethanol extract of KRG was 4.76%. The main components of the crude saponin were ginsenosides Rb1 (20.14%), Rb2 (10.19%), Rc (11.34%), Rd (4.63%), Re (12.27%), Rf (3.01%), Rg1 (16.44%), Rg2 (2.01%), and Rg3 (2.64%); other minor ginsenosides were also present.

Experimental Designs

The experiment was designed to investigate the effect ginsenosides Rb1, Rd, Rg1, and Re on the HFD-induced model of obesity. After 5 weeks, the rats were randomly divided into 6 groups of 5 rats each. The rats were fed either a normal diet (N diet group, *n*=5) or an HFD. The HFD group comprised rats fed an HFD that received no ginsenoside treatment. The remaining HFD-fed rats were administered ginsenoside Rb1, Rd, Rg1, and Re (Rb1, Rd, Rg1, Re groups, respectively).

Isolation of Ginsenosides from Crude Saponin

The crude saponin (10 g) was dissolved in methanol, separated by using silica gel (70–230 mesh, Merck, Darmstadt, Germany) column chromatography with $CHCl_3$-MeOH-H_2O (7:3:1, v/v, lower layer), and assayed by using thin layer chromatography (TLC). The TLC plates were silica gel 60F254 (0.25 mm, Merck, Darmstadt, Germany) and the developing solvent was $CHCl_3$-MeOH-H_2O (63:35:10, v/v, lower layer). The plates were stained by spraying with MeOH-H_2SO_4 (95:5, v/v) and heated. The stained plates were then analyzed by using a TLC scanner. The ginsenosides Rg1 (1 g, Rf = 0.46), Rd (200 mg, Rf = 0.31), Re (400 mg, Rf = 0.30) and Rb1 (1.2 g, Rf = 0.16) were isolated in accordance with their polarity. To isolate the Rd + Re fraction further, silica gel column chromatography was repeated with BuOH-EtOAc-H_2O (50:20:30, v/v, higher layer). The ginsenosides Rd and Rb1 were protopanaxadiol-type ginsenosides and Rg1 and Re were protopanaxatriol-type ginsenosides.

Measurement of Food Intake, Body Weight, and Weight of Regional Fat

Food intake and body weight of rats were recorded twice per week. The food cups were removed at 8:00 am and returned to animals with fresh food at 5:00 pm. In each group, the rats were collected randomly and weighed.

Locomotor Activity

Locomotor behavior was measured by using the S-MART program (Pan Lab, Spain). The system consisted of a black, ventilated test chamber (26 cm × 30 cm × 45 cm), lit with a ceiling mounted video camera. The camera's image was transmitted to a contrast-sensitive tracker which mapped the point of highest contrast and relayed the digitalized coordinates to a personal computer. The software stored the information and simultaneously displayed an arbitrary unit for the tracked subject. The animals were permitted to adapt to the contained for 1 h and the distance traveled was recorded for 1 h in baseline

conditions and for 1 h in treatment conditions.

Enzyme-Linked Immunosorbent Assay

Following 4–5 h feed deprivation of feed, blood was drawn from the heart under sodium pentobarbital anesthesia (60 mg/kg, i.p.) and centrifuged (3,000 × *g* for 15 min at 4 ℃). Subsequently, the epididymal fat, perirenal fat, and peritoneal fat pads were immediately excised, weighed, and frozen in liquid N2. Serum and tissue samples were frozen at –70 ℃ until used for the measurement of biochemical parameters. The serum leptin and NOx concentrations were determined by using an enzyme-linked immunosorbent assay (ELISA) kit (DuoSet ELISA development system, R&D Systems, Inc., Minneapolis, MN, USA) with sensitivity of detection level 7.8 pg/mL. The concentration of stable NO metabolites [nitrate (NO_3^-) + nitrite (NO_2^-), NOx] present in plasma at the time of sacrifice was determined. After the conversion of plasma nitrate to nitrite by using nitrate reductase (10 U/mL in 100 μm Tris buffer, pH 7.6), the total concentration of nitrite was determined at 560 nm by using a spectrophotometric method based on the Griess reaction. All serum samples were analyzed in duplicate in one assay and intra- and inter-assay variation was below 10%.

Immunohistochemistry of NPY and CCK

After behavioral testing was completed, all rats were deeply anesthetized with sodium pentobarbital (80 mg/kg, i.p.) and the ascending aorta was perfused with normal saline followed by 500 mL formalin. The brains were removed, post-fixed in the same fixative for 2 h at 4 ℃, and then placed overnight at 4 ℃ in phosphate buffered saline (PBS) containing 20% sucrose, and sliced into 30-μm thick coronal sections through the hypothalamic areas by using a microtome (Leica, CM 1850, Germany). The sections were incubated with rabbit anti-NPY antibody (1:2000; Immunostar, WI; USA) or rabbit anti-CCK antibody (1:500; Immunostar, WI) for 72 h at 4 ℃ with constant agitation. The sections were rinsed in PBS containing 0.3% Triton X-100 (PBST), incubated for 2 h at room temperature in biotinylated goat anti-rabbit serum (Vector Lab., Burlingame, CA, USA) diluted 1:200 in PBST containing 2% normal goat serum, and placed in Vectastain Elite ABC reagent (Vector Lab., Burlingame, CA) for 2 h at room temperature. After further rinses with in PBS, the tissue was developed by using 3,3-diaminobenzidine as the chromogen, with nickel intensification. The sections were mounted on gelatine-coated slides, air-dried, and cover-slipped for microscopic observation.

Images were captured by using an Axio Vision 3.0 imaging system (Zeiss, Oberkochen, Germany) and processed in Adobe Photoshop. NPY or CCK immunoreactivity was counted at 200 × magnification by using a microscope rectangle grid measuring (100 μm × 100 μm). To measure the number of NPY or CCK immunoreactive cells, the grid was placed on the arcuate nucleus (ARC), lateral hypothalamus (LH), ventromedial hypothalamus (VMH) and paraventricular nucleus (PVN) according to a stereotaxic atlas.[11]

Statistical Analysis

The values of the experimental results were expressed as the mean ± standard error median (*SEM*). Differences between groups were analyzed by analysis of variance (ANOVA) with or without repeated measures (time) as applicable. Individual comparisons among groups were analyzed by one-way ANOVA followed by Tukey's *post hoc* test. For all results, values of $P<0.05$ were considered to indicate statistical significance. Analyses were computed by using SPSS statistical software (version 15.0 for Windows).

RESULTS

Body Weight

The body weight, food intake, and food efficiency ratio of rats fed experimental diets after the treatment of ginsenosides are shown in Figure 1 and Appendixes 2–3. Over time, body weight gradually increased, and it was higher in the HFD group than in the normal diet group. Compared with rats in the HFD group, the body weight gain was 27%, 23%, and 17% lower in the Rb1, Re, and Rd groups, respectively ($P<0.01$).

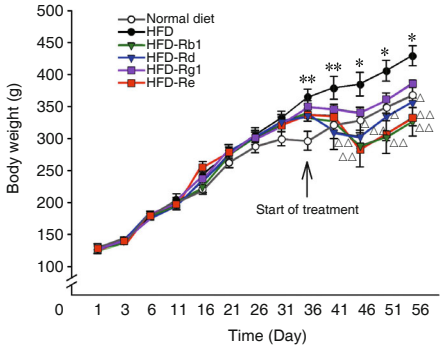

Figure 1. Change in Rats Body Weight in Experimental Groups ($\bar{x} \pm SEM$, n=5)

Notes: $^{*}P<0.05$, $^{**}P<0.01$ *vs*. normal diet group; $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$ *vs*. HFD group

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The mass of various adipose tissues (epididymal, perirenal, and peritoneal) is shown in terms of body weight. Similar to the body weight change, the weight of regional fat masses was higher in the HFD group than the normal diet group. PD-type ginsenosides, such as Rb1 and Rd, significantly reduced the relative epididymal, perirenal, and peritoneal fat mass compared with the HFD-fed rats. Significant differences among groups in the epididymal fat, perirenal, and peritoneal fat were observed (P<0.05 or P<0.01). In addition, Rb1 showed significantly decreased fat mass compared to the HF group (P<0.01).

Locomotor Activity

The locomotor activity was not different between the normal diet and HFD groups for the entire experimental period. In contrast, Rb1 treatment between 1 and 5 days after treatment increased locomotor activity relative to the HFD group (P<0.05), but significant differences were not found among groups on the other experimental days (Figure 2).

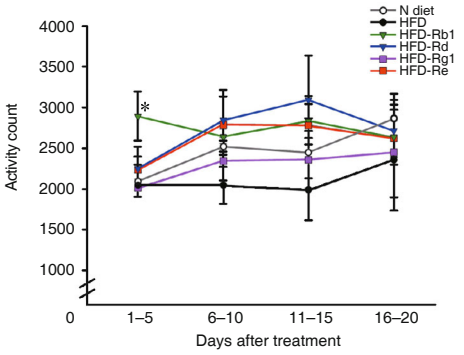

Figure 2. Change in Locomotor Activity of Rats in Groups ($\bar{x} \pm SEM$, n=5)

Note: *P<0.05 *vs*. HFD group

Serum Leptin

In the HFD group, serum leptin was significantly higher than in normal diet group (P<0.01), which suggested the development of hyperleptinemia. In contrast with the level in HFD-fed rats, those treated with Rb1, Rd, and Re had significantly smaller elevations in serum leptin concentration (69%, 63%, and 58%, respectively, P<0.01). The Rb1, Rd, and Re groups showed no difference compared with the normal diet group, but the level in the Rg1 group was higher than the normal diet group (Figure 3).

Serum NO

The concentration of serum NO in the HFD group was significantly higher than in the normal diet group (P<0.01). Treatment with Rb1, Rd, and Rg1 reduced serum NO concentration by 80%, 70%, and 61%, respectively (all P<0.01), but the level in the Rg1 group was not different compared to that in the HFD group (P>0.05, Figure 4).

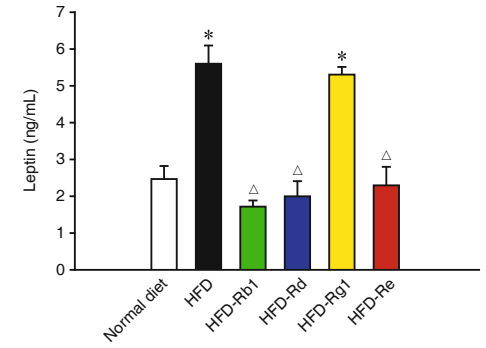

Figure 3. Levels of Leptin in Rat Serum of Groups ($\bar{x} \pm SEM$)

Notes: *P<0.01 *vs*. normal diet group; △P<0.01 *vs*. HFD group; n=5 in each group

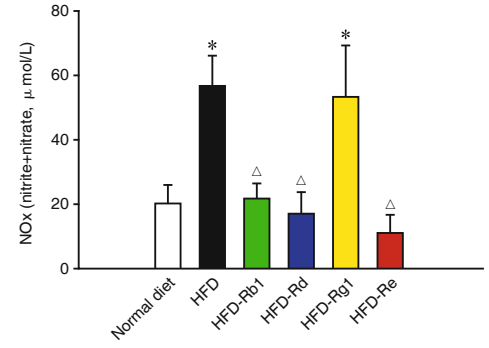

Figure 4. NO Levels in Rat Serum of Groups ($\bar{x} \pm SEM$, n=5)

Notes: *P<0.01 *vs*. normal diet group; △P<0.01 *vs*. HFD group

Expression of Hypothalamic NPY Neurons

More NPY-immunopositive neurons in ARC and PVN were clearly observed than those of LH and VMH in all groups. The NPY expression after treatment with Rb1 in the HFD group was significantly lower in the PVN than both the normal and HFD groups (P<0.05, Figure 5).

Expression of Hypothalamic CCK Neurons

The CCK immunoreactivities were unaffected after normal diet or HFD intervention. The CCK expression after treatment with Rb1 was significantly higher in the VMH and PVN than the normal diet group (P<0.05); for rats treated with Rb1, the expression of CCK was significantly higher in the PVN than that of rats in the HFD group (P<0.05, Figure 6).

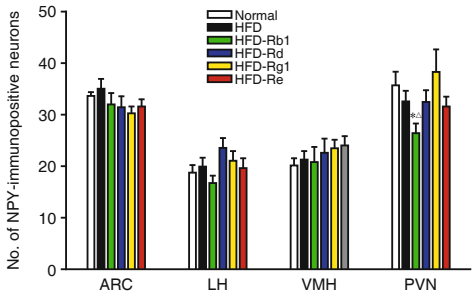

Figure 5. Expression of NPY Immunopositive Neurons in Rat Hypothalamus ($\bar{x} \pm SEM$, n=5)

Notes: $^{*}P$<0.05 *vs*. normal diet group; $^{\triangle}P$<0.05 *vs*. HFD group; ARC: arcuate nucleus; LH: lateral hypothalamus; VMH: ventromedial hypothalamus; PVN: paraventricular nucleus; the same below

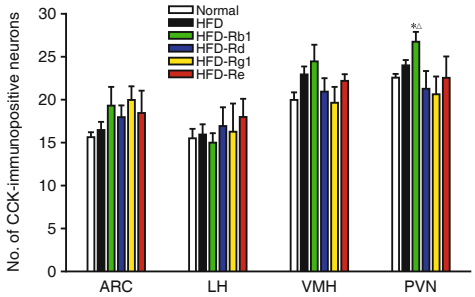

Figure 6. Expression of CCK Immunopositive Neurons in Rat Hypothalamus ($\bar{x} \pm SEM$, n=5)

Notes: $^{*}P$<0.05 *vs*. normal diet group; $^{\triangle}P$<0.05 *vs*. HFD group

Food Intake and Food Efficiency Ratio

Daily food intake was not significantly different in the normal diet and HFD groups, but the daily food intake in the Rb1, Rd, or Re groups continued to diverge from the control group in HFD (P<0.01). Diarrhea was not observed in the HFD groups, in the presence or absence of ginsenosides, throughout the experiment. The total food consumption during the whole experimental period was significantly different among groups (P<0.01). The food efficiency ratio [FER, body weight gain (g) × total food intake $(g)^{-1}$] was significantly different among groups (P<0.05). The FER of HFD-fed rats was higher than that of normal diet-fed rats and was reduced by 9% in HFD-fed rats treated with Rb1 (Appendixes 2–3).

DISCUSSION

The present study demonstrated that certain ginsenosides (Rb1, Rd, Rg1, and Re) reduced HFD-induced obesity. Body weight, total food intake, and serum leptin were reduced in the groups treatment with Rb1, Re, Rd, Rg1 and total regional fat storage was reduced in the group treated with Rb1, Rd, Re, Rg1 in order. Serum NO was reduced in the groups treated with Re, Rd, Rb1, Rg1, in that order. In addition, Rb1 reduced NPY-immunoreactive neurons of the PVN and increased CCK-immunoreactive neurons of the PVN, relative to the HF diet group, even though there were no significant differences in the other hypothalamic areas among groups. Rb1 tended to increase physical activity in the early period after treatment. In general, these results suggested that Rb1 may have the most effective anti-obesity activity.

The HFD (40% of calories as fat) used in this study induced obesity through increased body weight and fat accumulation. Although cumulative food intake over the experimental period was similar in both groups, the HFD resulted a marked increase in body weight and body fat mass after 8 weeks relative to the N diet group. These results were similar to those of our previous study.[12] Many studies have documented a similar pattern of food consumption in high-fat-fed animals compared with low-fat-fed animals.[13,14] These showed that the HFD group had a higher energy intake than the normal diet group and that the HFD contributed to the progression of obesity.[15-17] In this study, parallel to the change in body weight, the weights of regional (epididymal, perirenal, and peritoneal) fat mass were higher in the HFD group than in the normal diet group. However, the treatment of ginsenosides (Rb1, Re, Re) normalized the body weight and the fat mass in the rats. Previously, it was reported that the ginsenoside Rb1 reduced fatty liver through the activation of AMP activated protein kinase (AMPK) in obese rats.[13] The activation of AMPK indicated an increase in ATP usage. Xiong, et al[18] reported the anti-obesity and anti-hyperglycemic effect of ginsenoside Rb1 in rats. Collectively, these data suggested that the ginsenoside Rb1 may be helpful in the prevention of diet-induced obesity and metabolic syndrome.

Food intake is regulated through the CNS pathway, mediated by various neurotransmitters including NPY and CCK. Hypothalamic NPY potentially stimulates food intake[19] and CCK has been reported to reduce appetite and inhibits food intake Add Reference. In this study, there were few differences between the HF and normal diets with respect to the hypothalamic NPY and CCK expression, but there was a tendency for lower NPY levels and higher CCK levels in the HFD group through diet composition, leptin, and NO level. In this study, it is more likely that decreased serum leptin and NO after the treatment of ginsenoside Rb1 resulted from decreased body fat. In contrast, leptin acts partly through interactions with NPY in the hypothalamus.[20] The lower

NPY level in rats hypothalamus of the HFD group than the normal diet group was closely associated with an increase in circulating leptin levels. The decreased expression of NPY in the HFD group after treatment with ginsenoside Rb1 may also reflect the reduced leptin levels related to body fat mass.

As leptin is known to act on the ARC-PVN feeding regulatory pathway, the inhibition of the signal that produces a balance involving NPY arcuato-paraventricular projection by leptin may be one of the potential mechanisms underlying anti-obesity action of ginsenoside Rb1.[21] Leptin has been documented to regulated food intake, body temperature, energy expenditure,[22] and blood pressure,[23] and thus, it may play a role in metabolic syndrome. In this study, the treatment of ginsenoside Rb1 reduced the NPY-immunoreactive neurons of the LH and the VMH; the Rb1 group had significantly lower expression of NPT-immunopositive neurons in the PVN. In our previous study, we proved that the PD type saponins more effectively reduced NPY expression in the brain than the PT-type saponins. Shen, et al[24] showed that the infusion of Rb1 decreased food intake. Xiong, et al[18] also reported the anti-obesity and antihyperglycemic effects of ginsenoside Rb1 in rats. These results suggested that anti-obesity therapeutics during growth, especially the PD-type ginsenoside Rb1, were the most effective for the treatment of obesity.

CCK is a peptide found throughout the CNS and in neurons and endocrine cells of the gastrointestinal tract that elicits a satiating effect and regulates feeding behavior.[25] Postprandial plasma concentration of CCK, which stimulates pancreatic enzyme secretion, was higher in HFD-fed rats than those fed a low-fat diet.[26] CCK has been shown to enhance the effect of leptin in other experimental paradigms.[27,28] The hypothalamus is well recognized for its importance in the regulation of sympathetic activity and energy balance.[29-31] A few discrete nuclei in the basal hypothalamus are crucial for the regulation of daily energy homeostasis, especially those sites connected with the neural mechanisms affecting appetite. The inference that hypothalamic sites, such as the ARC, LH, VMH, PVN, and other nuclei, contain neural mechanisms that affect the ingestive behavior was based on the results of numerous studies employing either discrete lesions in the hypothalamus or surgical transection of neural pathways.[32,33] Previous studies also demonstrated that the LH was a feeding and parasympathetic center opposing the VMH as a satiety and sympathetic center.[28,29] The ARC contains a high density of neurons that produce the orexigenic and anorexigenic peptides and the terminal fields of neurons in the ARC extend into various hypothalamic sites, such as LH, VMH, and PVN.[32,33] In the HFD-fed rats, increased CCK-immunoreactive neurons of the ARC, VMH, and PVN were shown. The treatment of ginsenoside Rb1 significantly increased the CCK immunoreactive neurons in the VMH and PVN. Consistent with behaviors as food intake and locomotor activity, the treatment of ginsenoside Rb1 acts as an obesity-related neuromodulator.

Collectively, ginsenoside Rb1 was found to exert anti-obesity effects in the rats fed a HFD through the reduction of their body weight, food intake, and fat storage. It was also effective in the regulation of serum leptin and NO secretion, and CCK and NPY expression in the hypothalamus. Rb1 may be a useful agent for the control of obesity via the peripheral and central appetite modulators.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Shim IS, KIM JH and Park HJ designed the study. Park HJ and Kim JH acquired and analyzed the data. Park HJ, Kim JH and Shim IS wrote the article, which all other authors reviewed.

Electronic Supplementary Material: Supplementary material (Appendixed 1–3) are available in the online version of this article at https://doi.org/10.1007/s11655-019-3200-x.

REFERENCES

1. Che Y, Wang ZP, Yuan Y, Zhang N, Jin YG, Wan CX, et al. Role of autophagy in a model of obesity: a long-time high fat diet induces cardiac dysfunction. Mol Med Rep 2018;18:3251-3261.
2. Qin C, Li J, Tang K. The paraventricular nucleus of the hypothalamus: development, function, and human diseases 2018;159:3458-3472.
3. Berger NA. Obesity and cancer pathogenesis. Ann N Y Acad Sci 2014;1311:57-76.
4. van Baak MA. Nutrition as a link between obesity and cardiovascular disease: how can we stop the obesity epidemic? Thromb Haemost 2013;110:689-696.
5. Luscombe-Marsh ND, Seimon RV, Bollmeyer E, Wishart JM, Wittert GA, Horowitz M, et al. Acute effects of oral preloads with increasing energy density on gastric emptying, gut hormone release, thermogenesis and energy intake, in overweight and

obese men. Asia Pac J Clin Nutr 2013;22:380-390.
6. Montgomery IA, Irwin N, Flatt PR. Beneficial effects of (pGlu-Gln)-CCK-8 on energy intake and metabolism in high fat fed mice are associated with alterations of hypothalamic gene expression. Horm Metab Res 2013;45:471-473.
7. Bi S, Kim YJ, Zheng F. Dorsomedial hypothalamic NPY and energy balance control. Neuropeptides 2012;46:309-314.
8. Patel S, Rauf A. Adaptogenic herb ginseng (*Panax*) as medical food: status quo and future prospects 2017;85:120-127.
9. Liu DY, Li YH, Xu YT, Zhu Y. Anti-aging traditional Chinese medicine: potential mechanisms involving AMPK pathway and calorie restriction based on "medicine-food homology" theory. Chin J Mater Med (Chin) 2016;41:1144-1151.
10. Cha HY, Park JH, Hong JT, Yoo HS, Song S, Hwang BY, et al. Anziolytic-like effects of ginsenosides on the elevated plus-maze model in mice. Bio Pharm Bull 2005;28:1621-1625.
11. Schwarz AJ, Danckaert A, Reese T, Gozzi A, Paxinos G, Watson C, et al. A stterotaxic MRI template set for the rat brain with tissue class distribution maps and co-registered anatomical atlas: application to pharmacological MRI. Neuroimage 2006;32:538-550.
12. Kim JH, Kang SA, Han SM, Shim I. Comparison of the antiobesity effects of the protopanaxadiol- and protopanaxatriol-type saponins of red ginseng. Phytother Res 2009;23:78-85.
13. Shen L, Xiong Y, Wang DQ, Howles P, Basford JE, Wang J, et al. Ginsenoside Rb1 reduces fatty liver by activating AMP-activated protein kinase in obese rats. J Lipid Res 2013;54:1430-1438.
14. Nagatomo F, Fujino H, Kondo H, Takeda I, Tsuda K, Ishihara A. High-fat diet-induced reduction of peroxisome proliferator-activated receptor-gamma coactivator-1alpha messenger RNA levels and oxidative capacity in the soleus muscle of rats with metabolic syndrome. Nutrit Res 2012;32:144-151.
15. Paternain L, Batlle MA, De la Garza AL, Milagro FI, Martinez JA Campion J. Transcriptomic and epigenetic changes in the hypothalamus are involved in an increased susceptibility to a high-fat-sucrose diet in prenatally stressed female rats. Neuroendocrinology 2012;96:249-260.
16. Shin AC, Zheng H, Townsend RL, Patterson LM, Holmes GM, Berthoud HR. Longitudinal assessment of food intake, fecal energy loss, and energy expenditure after Roux-en-Y gastric bypass surgery in high-fat-fed obese rats. Obesity Surg 2012;23:531-540.
17. Togo Y, Otsuka T, Goto M, Furuse M, Yasuo S. Photoperiod regulates dietary preferences and energy metabolism in young developing Fischer 344 rats but not in same-age Wistar rats. Am J Physiol Endocrinol Metabol 2012;303:E777-E786.
18. Xiong Y, Shen L, Liu KJ, Tso P, Xiong Y, Wang G, et al. Antiobesity and antihyperglycemic effects of ginsenoside Rb1 in rats. Diabetes 2010;59:2505-2512.
19. Fan S, Dakshinamoorthy J, Kim ER, Xu Y, Huang C, Tong Q. An indirect action contributes to C-Fos induction in paraventricular hypothalamic nucleus by neuropeptide Y. Sci Rep 2016;19980.
20. Lin S, Storlien LH, Huang XF. Leptin receptor, NPY, POMC mRNA expression in the diet-induced obese mouse brain. Brain Res 2000;875:89-95.
21. Kalra SP, Kalra PS. Neuropeptide Y: a physiological orexingen modulated by the feedback action of ghrelin and leptin. Endocrine 2003;22:49-56.
22. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995;269:540-543.
23. Vecchione C, Maffei A, Colella S, Aretini A, Poulet R, Frati G, et al. Leptin effect on endothelial nitric oxide is mediated through Akt-endothelial nitric oxide synthase phosphorylation pathway. Diabetes 2002;51:168-173.
24. Shen L, Wang DQ, Lo CC, Arnold M, Tso P, Woods SC, et al. Gut vagal afferents are necessary for the eating-suppressive effect of intraperitoneally administered ginsenoside Rb1 in rats. Physio Behav 2015;152:62-67.
25. Akeieda AS, Poleni PE, Date Y. Coinjection of CCK and leptin reduces food intake via increased CART/TRH and reduced AMPK phosphorylation in the hypothalamus. Am J Phsyiol Endocrinol Metab 2014;306:1284-1291.
26. Feinle-Bisset C, Patterson M, Ghatei MA, Bloom SR, Horowitz M. Fat digestion is required for suppresision of ghrelin and stimulation of peptide YY and pancreatic polypeptide secretion by intraduodenal lipid. Am J Physiol Endocrinol Metab 2005;289:E948-E953.
27. Cano V, Ezquerra L, Ramos MP, Ruiz-Gayo M. Regulation of leptin distribution between plasma and cerebrospinal fluid by cholecystokinin receptors. Br J Pharmacol 2003;140:647-652.
28. Guilmeau S, Buyse M, Tsocas A, Laigneau JP, Bado A. Duodenal leptin stimulates cholecystokinin secretion: evidence of a positive leptin-cholecystokinin feedback loop. Diabetes 2003;52:1664-1672.
29. Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. Brain Behav Immune 2014;42:10-21.
30. Bray GA, Inoue S, Nishizawa Y. Hypothalamic obesity. the autonomic hypothesis and the lateral hypothalamus. Diabetologia 1981;20:366-377.
31. Bray GA, York DA. The MONA LISA hypothesis in the time of leptin. Recent Prog Hormone Res 1998;53:95-117.
32. Bischof GN, Park DC. Obesity and aging: consequences for cognition, brain, structure, and brain function. Psychosom Med 2015;77:697-709.
33. Grundmann SJ, Ramkey EA, Cook MM, Wood AL, Rollins RL, King BM. Combination unilateral amygdaloid and ventromedial hypothalamic lesions: evidence for feeding pathway. Am J Physiol Regul Integr Comp Physiol 2005;288:R702-R707.

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