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Basic nutritional investigation

Lipolysis and thermogenesis in adipose tissues as new potential mechanisms for metabolic benefits of dietary fiber

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ABSTRACT

Objective: Dietary fiber consumption is associated with reduced risk for the development of noncommunicable diseases. The aim of the present study was to evaluate the effects of cereal dietary fiber on the levels of proteins involved in lipolysis and thermogenesis in white adipose tissue (WAT) and brown adipose tissue (BAT) of C57 BL/6 J mice fed a high-fat diet (HFD).

Methods: Male C57BL/6 J mice were fed normal chow diet (Chow), HFD, HFD plus oat fiber (H-oat), or HFD plus wheat bran fiber (H-wheat) for 24 wk. Body weight and food intake were recorded weekly. Serum adiponectin was assayed by an enzyme-linked immunosorbent assay kit. Western blotting was used to assess the protein expressions of adipose triacylglycerol lipase (ATGL), cAMP protein kinase catalytic subunit (cAMP), protein kinase A (PKA), perilipin A, hormone-sensitive lipase (HSL), uncoupling protein 1 (UCP1), fibroblast growth factor 21 (FGF-21), β3-adrenergic receptor (β3AR), and proliferator-activated receptor gamma coactivator-1 α (PGC-1 α) in the WAT and BAT.

Results: At the end of the feeding period, body and adipose tissues weight in both H-oat and H-wheat groups were lower than in the HFD group. Mice in the H-oat and H-wheat groups showed an increasing trend in serum adiponectin level. Compared with the HFD group, cereal dietary fiber increased protein expressions involved in the lipolysis and browning process. Compared with the H-wheat group, H-oat was more effective in protein expressions of PKA, PGC-1 α, and UCP1 of the WAT samples. Compared with the H-oat group, H-wheat was more effective in protein expressions of PKA, ATGL, UCP1, β3AR, and FGF-21 of the BAT samples.

Conclusions: Taken together, our results suggested that cereal dietary fiber enhanced adipocyte lipolysis by the cAMP–PKA–HSL pathway and promoted WAT browning by activation of UCP1, and consequently reduced visceral fat mass in response to HFD feeding.

Introduction

Obesity develops from an imbalance between energy intake and energy expenditure [1], which is a risk factor for development of several clinical conditions including cardiovascular disease, cancers, and diabetes [2–4]. There is a growing interest in the development of various strategies including dietary interventions that could treat or prevent obesity by promoting fat mobilization or increasing energy expenditure [5,6]. Adipose tissues play different roles in adaptation to changes in nutrient availability, with white adipose tissue (WAT) storing chemical

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energy as triacylglycerol (TG)-enriched lipid droplets and brown adipose tissue (BAT) dissipating chemical energy by heat production through uncoupling protein 1 (UCP1) to protect against hypothermia and obesity [7]. Several studies also revealed the presence of a subset of cells in WAT that could be induced by environmental or hormonal factors to become "brown-like" cells and this "beigeing" process has been suggested to have strong antiobesity and antidiabetic benefits [8,9]. The expression of UCP1 is driven by several transcriptional components, including proliferator-activated receptor gamma coactivator-1α (PGC-1α), which is strongly induced by β3-adrenergic signaling [10,11]. β3-adrenergic receptor (β3AR) activation of the cAMP/protein kinase A (PKA) pathway elevates intracellular fatty acids. UCP1 and PGC-1α are highly expressed in BAT, which contains multilocular adipocytes enriched with mitochondria. Recently, BAT has received much attention as a target of treating obesity [12,13].

A growing body of evidence supports that higher dietary fiber consumption substantially lowers the risk for the development of major obesity-related metabolic diseases, such as cardiovascular disease, diabetes, and certain types of cancer, and plays a role in body weight management [14–16]. Recent animal studies including ours have largely focused on the mechanism of dietary fiber on insulin resistance and hepatic lipid accumulation [17–20]. Also, high-fat diet (HFD)-induced obesity is strongly promoted by lack of soluble fiber, which supports microbiota-mediated intestinal tissue homeostasis that prevents inflammation driving obesity and the metabolic syndrome [21]. However, the mechanism by which cereal dietary fiber exerts its beneficial effects on lipolysis and thermogenesis in adipose tissues is not fully understood. Consequently, the present study aimed to explore the effects of oat fiber or wheat bran fiber on browning of white adipocytes by activation of UCP1 in C57BL/6 J mice fed an HFD. Additionally, we observed the effects of oat or wheat bran fiber on lipolysis by activation of the cAMP–PKA–HSL signaling pathway. The efficacy of oat and wheat bran fiber also was compared.

Methods and materials

Animals and diets

All studies were carried out using 7-wk-old male C57BL/6 J mice (n = 48) purchased from SLAC Laboratory Animal Company (Shanghai China) and maintained on an artificial 12/12-h light/dark cycle at 22 ± 2°C with 60% relative humidity. Mice were acclimated to the animal housing facility for 1 wk before the start of cereal dietary fiber intervention. At 8 wk of age, animals were randomly divided into the following four dietary groups (n = 12 in each group): chow group (Chow), high-fat diet group (HFD), HFD plus oat fiber intervention group (H-oat), and the HFD plus wheat bran fiber intervention group (H-wheat). Chow group mice were allowed a normal chow diet that contained 11.5% fat, 67.7% carbohydrates, and 20.8% protein, which was purchased from Research Diets Inc (New Brunswick, NJ). HFD mice were allowed an HFD that contained 46% fat, 34.4% carbohydrates, and 19.6% protein, which was purchased from Research Diets Inc. H-oat and H-wheat mice were allowed an HFD supplemented with 0.8% oat fiber or 0.8% wheat bran fiber, respectively. Oat fiber (OatWell®22) was granted from DSM Nutritional Products Ltd (Shanghai, China). Wheat bran fiber was obtained from Shanxi Aote Food Science and Technology Company (Taiyuan, China). Dietary fiber was directly mixed with the HFD according to the above recipe. The animals were allowed access to water and four different experimental diets ad libitum during the whole experimental periods. After 24 wk, the mice were deprived of food overnight and sacrificed by decapitation. All of the animal studies were treated in accordance with the guidelines in the Care and Use of Animals and with the approval of the Soochow University Animal Welfare Committee. All possible efforts were made to minimize the suffering and the number of animals used in the present study.

Sample preparation

After 24 wk of feeding, blood samples was taken from the retrobulbar vein and separated by centrifugation, subpackaged, and stored at −80°C until assayed. Serum adiponectin were measured by a commercial enzyme-linked immunosorbent assay kit (Merck Millipore Bioscience Corporation). All of the assays were performed according to the manufacturer's protocols. All samples were run in duplicate. The coefficient of variation for duplicate samples was <5% in the experiments. After the mice were sacrificed, interscapular BAT and visceral fat pads (including the perirenal and epididymal fat pads) were immediately dissected, weighted, fixed or frozen in liquid nitrogen and stored at −80°C for further analysis.

Analysis of cell size and volume in WAT

The WAT samples from epididymal adipose tissue were fixed in 10% neutral buffered formalin overnight and stained with hematoxylin and eosin dye (Beyotime Institute of Biotechnology, Nantong, China). The relative size and volume of fat cells within a microscopic field were determined by quantitation of cells in three different randomly chosen fields of from six mice.

Western blotting

WAT and BAT samples were lysed with radio immunoprecipitation assay (RIPA) lysis buffer (Beyotime Institute of Biotechnology, Nantong, China). The lysates were homogenized and centrifuged at 13 000*g* for 15 min at 4°C. The supernatants were collected and the protein concentrations were determined according to the bicinchoninic acid protein assay kit (Beyotime Institute of Biotechnology, Nantong, China). Equal amounts of protein (50–100 μg) were analyzed by Western blotting. Antibodies against PKA and β3AR were purchased from ImmunoWay Biotechnology Company (Plano, TX, USA). Antibodies against perilipin A, hormone-sensitive lipase (HSL), UCP1, fibroblast growth factor (FGF21), PGC-1α, and cAMP protein kinase catalytic subunit (cAMP) were purchased from Abcam Company (United Kingdom). Antibodies against p-HSL (Ser563), p-HSL (Ser660), and adipose triacylglycerol lipase (ATGL) were purchased from Cell Signaling Technology (Danvers, MA, USA). Antibodies against Peroxidase AffiniPure goat antimouse or antirabbit immunoglobulin G were purchased from Jackson ImmunoResarch Laboratories (West Grove, PA). Signals were visualized using Immobilon western chemiluminescent horseradish peroxidase substrate (Merck Millipore Bioscience, Billercia, MA, USA) and captured using a Syngene chemi-imaging system. Subsequently, bands were quantified using Gene Tool according to the manufacturer's instructions (SynGene, ChemiGenius 2, PerkinElmer, Shelton, CT, USA). The intensity of the bands was normalized using each corresponding β-actin density as an internal control.

Statistical analysis

Results are expressed as means ± SD. A one-way analysis of variance (ANOVA) was performed for the differences in the four groups, followed by the least significant difference post hoc test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS statistical software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Body and white adipose tissues weights

The H-wheat group tended to have higher average food intake compared with the of HFD and H-oat groups for the duration experiment (Fig. 1A; $P < 0.05$). Final body weight did not differ between the H-oat and H-wheat groups, but were lower than in the HFD group (Fig. 1B; $P < 0.01$). Compared with the HFD group, the H-oat and H-wheat groups had lower perirenal (Fig. 1C; $P < 0.01$) and epididymal (Fig. 1D; $P < 0.01$) fat mass. Although perirenal and epididymal fat masses tended to be less in the H-oat group than in the H-wheat group, the difference was not statistically significant.

Analysis of cell size and volume in WAT

Histologic analysis of WAT showed that the relative size and volume of adipocytes were considerably smaller in the H-oat and H-wheat groups than in the HFC group (Fig. 2; $P < 0.05$).

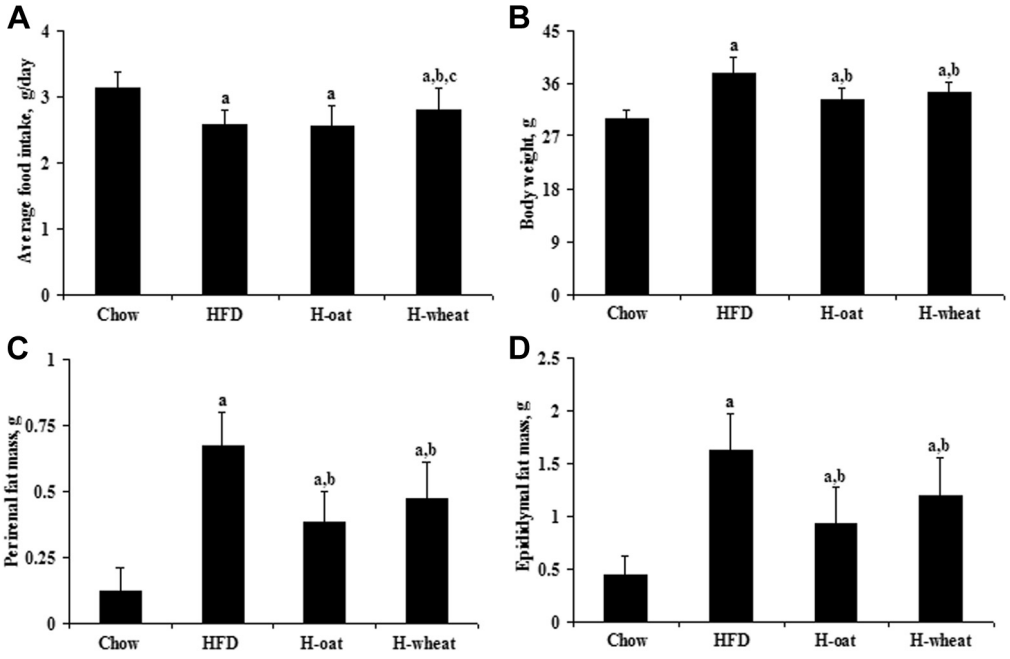

Fig. 1. (A) Average food intake, (B) final body weight, (C) perirenal fat mass, and epididymal fat mass in male C57 BL/6 J mice fed a normal chow diet or an HFD without or with 0.8% oat fiber or wheat bran fiber for 24 wk. Values are means ± SD (n = 12). [a]$P < 0.05$, versus mice fed with normal chow diet; [b]$P < 0.05$, versus mice fed with HFD diet; [c]$P < 0.05$, versus mice fed an H-oat diet. HFD, high-fat diet; H-oat, high-fat diet supplemented with 0.8% oat fiber; H-wheat, high-fat diet supplemented with 0.8% wheat bran fiber.

Serum adiponectin level

The HFD group had a lower concentration of serum adiponectin than the Chow group ($P < 0.05$). Compared with the HFD group, concentrations of serum adiponectin showed an increasing trend in the H-oat and H-wheat groups, but there were no significantly statistical differences among the three groups (Fig. 3; $P > 0.05$).

cAMP–PKA–HSL signaling pathway

Protein expressions of ATGL in both BAT and WAT samples, protein expression of PKA in the BAT samples, and protein expression of p-HSL (660) in the WAT samples was much lower in the HFD group than in the H-oat and H-wheat groups (Fig. 4A, B; $P < 0.05$), but it was lower in the H-oat group than in the H-wheat group (Fig. 4A, B; $P < 0.05$). Protein expressions of perilipin A and cAMP in the WAT samples, and protein expressions of p-HSL(660) and p-HSL(563) in the BAT samples did not differ in the H-oat and H-wheat groups, but was much greater than in the HFD group (Fig. 4A, B; $P < 0.05$). There were no effects from oat and wheat bran fiber on protein expression of perilipin A in the BAT samples. Protein expression of PKA in the WAT samples was lower in the HFD group than in the H-oat and H-wheat groups (Fig. 4A, B; $P < 0.05$), but it was higher in the H-oat group than in the H-wheat group (Fig. 4A, B; $P < 0.05$).

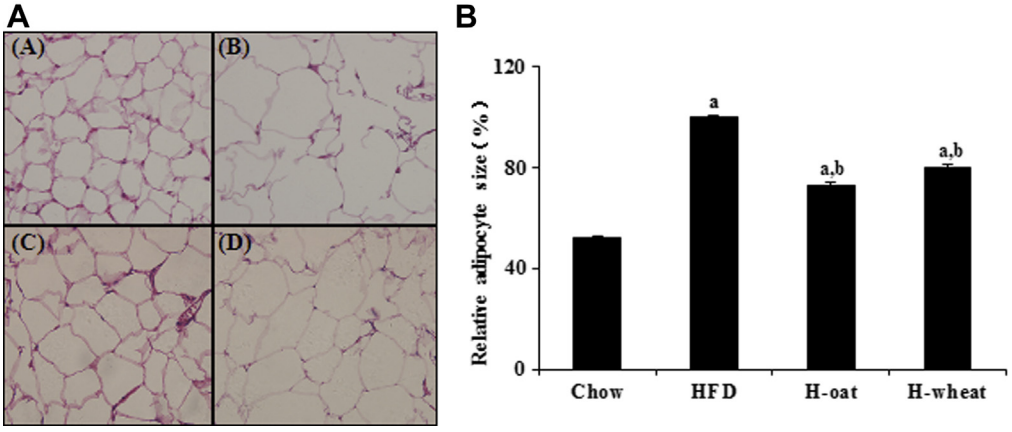

Fig. 2. (A) Histologic examination of WAT (400×) and (B) relative adipocyte size from C57 BL/6 J mice fed a normal chow diet or an HFD without or with 0.8% oat fiber or wheat bran fiber for 24 wk. Values are means ± SD (n = 5). [a]$P < 0.05$, versus mice fed with normal chow diet; [b]$P < 0.05$, versus mice fed with HFD diet. (A), chow diet; (B), high-fat diet (HFD); (C), high-fat diet supplemented with 0.8% oat fiber (H-oat); (D), high-fat diet supplemented with 0.8% wheat bran fiber (H-wheat).

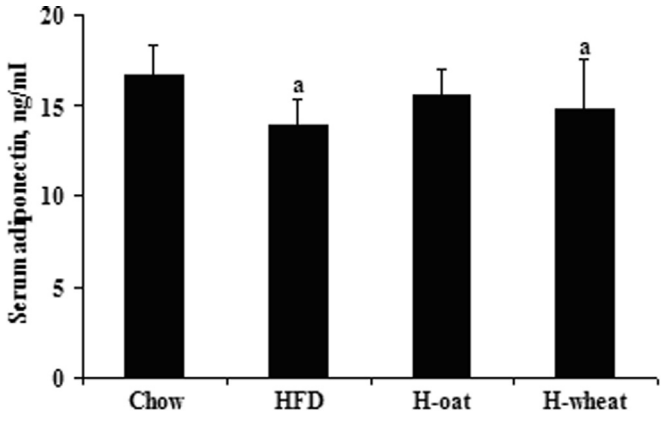

Fig. 3. Serum adiponectin concentration in male C57 BL/6 J mice fed a normal chow diet or an HFD without or with 0.8% oat fiber or wheat bran fiber for 24 wk. Values are means ± SD (n = 12). [a]$P < 0.05$, versus mice fed with normal chow diet. HFD, high-fat diet; H-oat, high-fat diet supplemented with 0.8% oat fiber; H-wheat, high-fat diet supplemented with 0.8% wheat bran fiber.

Relative protein expressions in browning process

Protein expression of UCP1 in the WAT samples did not differ between the HFD and H-wheat groups, but were much less than in the H-oat group (Fig. 5A, B; $P < 0.05$). Protein expression of β3AR in the BAT and WAT samples did not differ between the HFD and H-oat groups, but were much less than in the H-wheat group (Fig. 5A, B; $P < 0.05$). Protein expression of UCP1 in the BAT samples and FGF-21 in the BAT and WAT samples was lower in the HFD group than in the H-oat and H-wheat groups, but these were lower in the H-oat group than in the H-wheat group (Fig. 5A, B; $P < 0.05$). Protein expression of PGC-1α in the BAT and WAT samples were lower in the HFD group than in the H-oat and H-wheat groups. It was lower in the H-wheat group than in the H-oat group on protein expression of PGC-1α from BAT samples, and there was no statistical difference between the H-oat and H-wheat groups in protein expression of PGC-1α from WAT samples (Fig. 5A, B; $P < 0.05$).

Discussion

Cereal dietary fiber has received widespread attention in the scientific community. Although some mechanisms have been proposed for the health benefit of cereal dietary fiber, its effects on lipolysis and thermogenesis in adipose tissues remain unclear. In the present study, we used obese mice induced by an HFD whose body weight gain was >70% more than those fed a chow diet. At organ and molecular levels, we found that cereal dietary fiber from oat or wheat bran inhibited HFD-induced obesity by activation of the cAMP–PKA–HSL signaling pathway and increasing browning of white adipocytes.

It has been established that dietary fiber plays an important role in the regulation of metabolism [17–21]. The direct link between dietary fiber and lipid metabolism is demonstrated by a previous study [17] and current work, which showed that cereal dietary fiber resulted in significant reduction in relative size and volume of adipocytes in HFD-induced obesity. This is in line with a previous study demonstrating that adipocyte volume was determined by the content of intracellular lipids [22]. There were no significant differences in the indexes of body weight, perirenal, and epididymal fat mass between the two intervention groups, but the average food intake and energy intake (H-wheat, 13.29 ± 1.63 kcal/d versus H-oat, 12.09 ± 1.44 kcal/d) in the H-wheat group were significantly higher than in the H-oat group. Whether the food intake difference was caused by different satiety effect warrants future investigation. Our results also demonstrated that ATGL as a rate-limiting enzyme for lipolysis in adipocytes [23], was substantially activated by oat or wheat bran fiber to increase mobilization of intracellular fat. The effect was more effective in the H-wheat group.

Adiponectin is an adipocyte-secreted hormone that suppresses energy expenditure and enhances energy conservation [24]. Results from the present study demonstrated that HFD resulted in reduction in serum adiponectin, compared with the chow diet. Although neither oat nor wheat bran fiber was effective for serum adiponectin, there was an increasing trend in the two intervention groups, compared with the HFD group. Some animal and population investigation also demonstrated that intake of dietary fiber did not affect plasma adiponectin [19,25].

The mobilization of metabolic energy from adipocytes depends on a tightly regulated balance between hydrolysis and resynthesis of TGs. Hydrolysis is stimulated by β-adrenergic signaling to activate the cAMP–PKA pathway [26], which mediates phosphorylation and activation of lipolytic enzymes, including HSL, ATGL, and perilipin [27,28]. HSL was once thought to be the major enzyme responsible for the lipolytic breakdown of cellular fat stores. Phosphorylation of HSL occurs on multiple sites, including Ser-660, which stimulates catalytic activity and Ser-563, which is believed to be mutually exclusive with phosphorylation of HSL at the non-PKA site Ser-565 [29]. Thus, hormonal cues that signal systemic energy induce HSL phosphorylation at Ser-563 by PKA, which contributes to adipocyte lipolysis to maintain whole-body energy homeostasis. The present study found that oat or wheat bran fiber also increased levels of cAMP and PKA substrates including ATGL and p-HSL, suggesting that cereal dietary fiber-induced fat mobilization is mediated by the cAMP–PKA–HSL pathway. Consistent with these results, the expression of perilipin A, which regulates lipid storage and hydrolysis [30], was dramatically upregulated by cereal dietary fiber.

BAT is enriched in mitochondria that use UCP1-mediated uncoupling to convert significant amounts of chemical energy to heat. UCP1, the major isoform expressed in brown adipocytes, plays an important role in thermogenesis regulation of body weight [7]. Furthermore, upregulation of UCP1 level results in increased thermogenesis and energy expenditure, which helps to protect from fat accumulation and obesity [31]. In the present study, both oat and wheat bran fiber increased the protein expression of UCP1 in BAT and WAT of HFD-induced obese mice, suggesting increased thermogenesis. Additionally, wheat bran fiber increased the protein expression of β3AR in WAT, whereas oat fiber did not. Brown-like cells can emerge in most white fat depots upon prolonged cold exposure or β-adrenergic receptor activation [32]. β3AR and cold exposure can induce a subset of cells in WAT to become “brown-like” cells and this “beigeing” process has been suggested to have strong antiobesity and antidiabetic benefits [8,9]. We speculated that increased β3AR in the H-wheat group could account for increased thermogenesis and energy expenditure, to control obesity.

PGC-1α is a critical transcriptional regulator of oxidative metabolism and adaptive thermogenesis [33]. Also, PGC-1α is highly expressed in BAT, which contains multilocular adipocytes enriched with mitochondria. Studies showed that upregulation of UCP1 was mediated by the transcription factor PGC-1α [34]. In

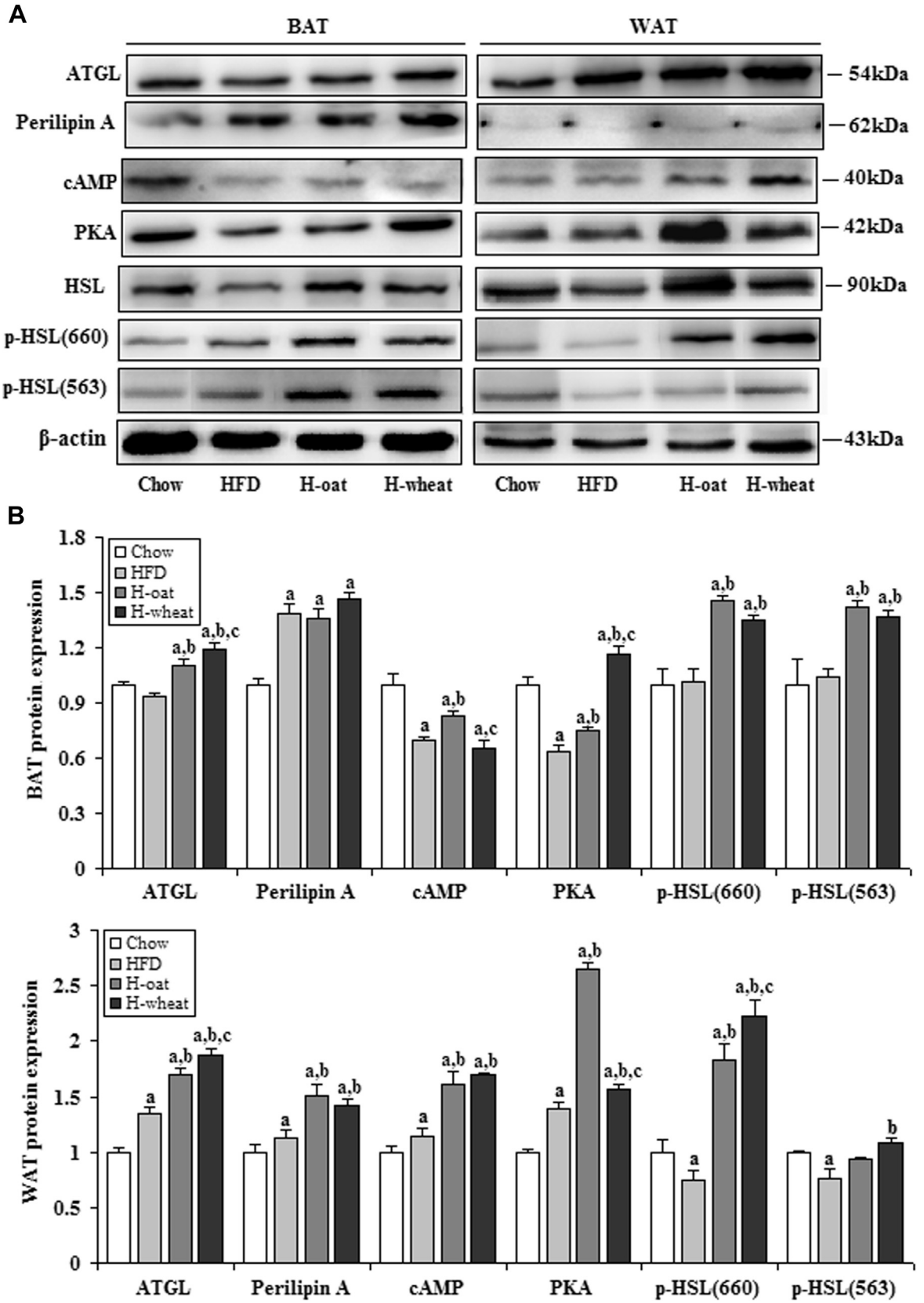

Fig. 4. Protein expressions of ATGL, perilipin A, cAMP, PKA, and HSL (Western blotting image [A] and statistical analysis [B]) in BAT and WAT of male C57 BL/6 J mice fed a normal chow diet or an HFD without or with 0.8% oat fiber or wheat bran fiber for 24 wk. Values are means ± SD (n = 5). $^{a}P < 0.05$, versus mice fed with normal chow diet; $^{b}P < 0.05$, versus mice fed with HFD diet; $^{c}P < 0.05$, versus mice fed with H-oat diet. ATGL, adipose triacylglycerol lipase; BAT, brown adipose tissue; cAMP, cAMP protein kinase catalytic subunit; HFD, high-fat diet; H-oat, high-fat diet supplemented with 0.8% oat fiber; H-wheat, high-fat diet supplemented with 0.8% wheat bran fiber; HSL, hormone sensitive lipase; PKA, protein kinase A; WAT, white adipose tissue.

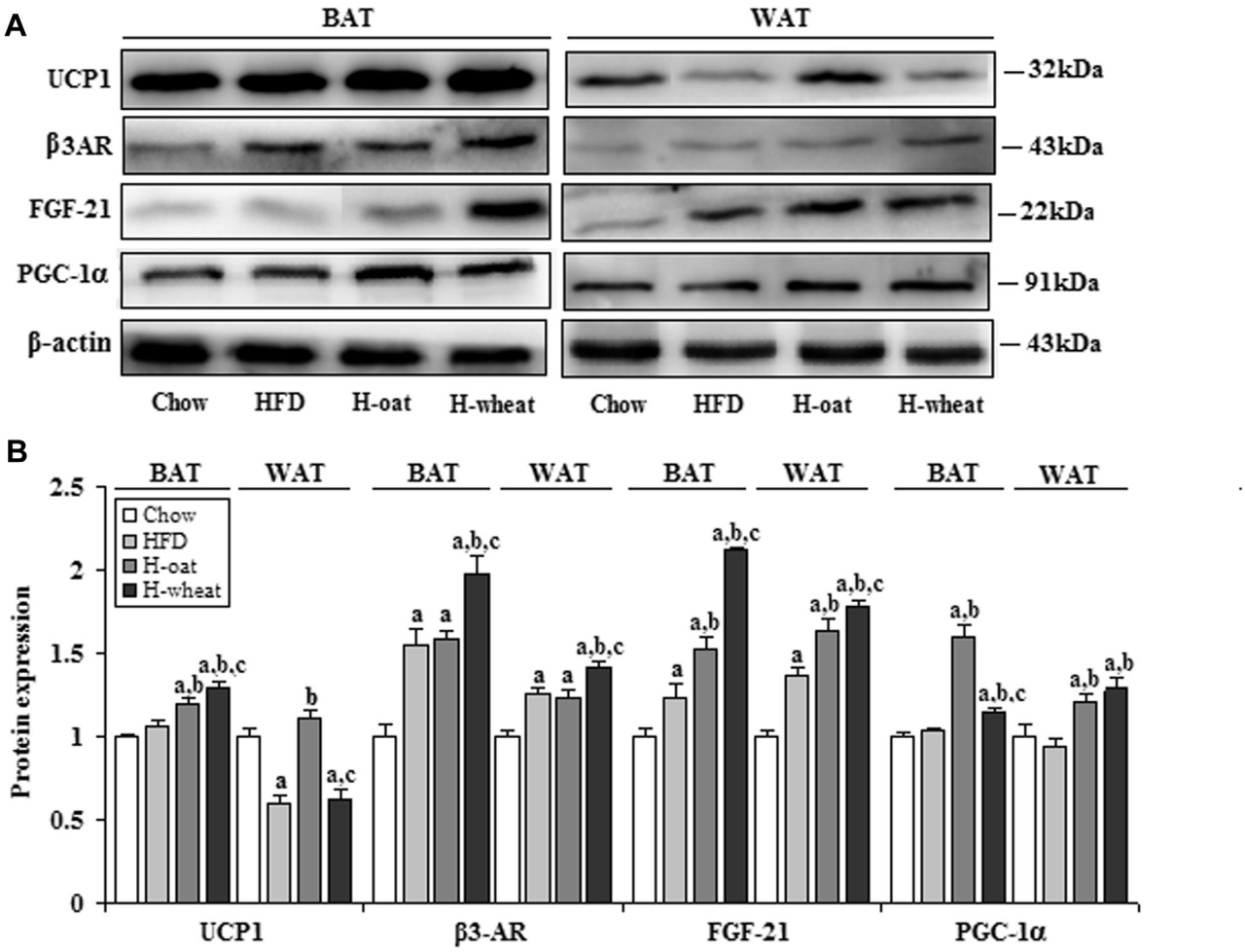

Fig. 5. Protein expressions of UCP1, β3AR, FGF-21, and PGC-1α (Western blotting image [A] and statistical analysis [B]) in BAT and WAT of male C57 BL/6 J mice fed a normal chow diet or an HFD without or with 0.8% oat fiber or wheat bran fiber for 24 wk. Values are means ± SD (n = 5). $^{a}P < 0.05$, versus mice fed with normal chow diet. $^{b}P < 0.05$, versus mice fed with HFD diet. $^{c}P < 0.05$, versus mice fed with H-oat diet. BAT, brown adipose tissue; β3AR, β3-adrenergic receptor; FGF-21, fibroblast growth factor 21; HFD, high-fat diet; H-oat, high-fat diet supplemented with 0.8% oat fiber; H-wheat, high-fat diet supplemented with 0.8% wheat bran fiber; PGC-1α, proliferator-activated receptor gamma coactivator-1 α; UCP1, uncoupling protein 1; WAT, white adipose tissue.

the present study, we observed that the protein expression of PGC-1α is also increased in H-oat and H-wheat mice, suggesting that increased UCP1 expression is mediated by transcription factor PGC-1α. Animal research demonstrated that FGF21 can regulate PGC-1α and browning of WAT in adaptive thermogenesis [9]. And FGF21 plays a physiologic role on regulating lipolysis in WAT [35,36], as well as increasing substrate utilization by increasing fatty acid oxidation in the liver [37]. The beneficial effects of FGF21 on glucose metabolism and body weight have evoked a substantial interest in FGF21 as a potential treatment for diseases such as obesity and diabetes [38]. Our data suggest that cereal dietary fiber from oat and wheat bran increased the protein expression of FGF21, which regulates PGC-1α levels.

It is important to note that many studies have been performed to evaluate the effects of cereal dietary fiber on insulin resistant and hepatic lipid accumulation [17–20]. The present study aimed to explore the effects of cereal dietary fiber on browning of white adipocytes by activation of UCP1 and on lipolysis by activation of the cAMP–PKA–HSL signaling pathway in C57 BL/6 J mice fed an HFD. Given the fact that cereal fiber intake is far below suggested and noncommunicable diseases are surging in modern societies [39], the present investigation provides a biochemical rationale for promoting adequate cereal dietary fiber intake as a nutritional and lifestyle approach in the prevention and treatment of obesity and associated metabolic diseases.

Conclusion

The present study suggested that cereal dietary fiber reduces high-fat–induced obesity by enhancing adipocyte lipolysis and consequently reduces visceral fat mass in response to HFD feeding. The present study explored the potential mechanisms for the beneficial effects of cereal dietary fiber on lipolysis and thermogenesis. We found that cereal dietary fiber both strengthened fat mobilization by the cAMP–PKA–HSL pathway in WAT, and promoted WAT browning by activation UCP1 and β3AR, PGC-1α, FGF-21, involved in thermogenesis, thereby reducing obesity. Nevertheless, the precise molecular mechanisms of cereal dietary fiber on lipolysis and thermogenesis in adipose tissues in depth remains to be elucidated, to confirm the role of cereal dietary fiber in preventing obesity-associated diseases.

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References

[1] Hofbauer KG. Molecular pathways to obesity. Int J Obes Relat Metab Disord 2002;26:S18–27.
[2] Davin C, Vollenweider P, Waeber G, Paccaud F, Marques-Vidal P. Cardiovascular risk factors attributable to obesity and overweight in Switzerland. Nutr Metab Cardiovasc Dis 2012;22:952–8.
[3] Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569–78.
[4] Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–9.
[5] van Dam RM, Seidell JC. Carbohydrate intake and obesity. Eur J Clin Nutr 2007;61:S75–99.
[6] Xu J, Cao K, Li Y, Zou X, Chen C, Szeto IM, et al. Bitter gourd inhibits the development of obesity-associated fatty liver in C57 BL/6 mice fed a high-fat diet. J Nutr 2014;144:475–83.
[7] Feldmann HM, Golozoubova V, Cannon B, Nedergaard J. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. Cell Metab 2009;9:203–9.
[8] Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481:463–8.
[9] Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, et al. FGF12 regulates PGC-1 α and browing of white adipose tissues n adaptive thermogenesis. Genes Dev 2012;26:271–81.
[10] Barbera MJ, Schluter A, Pedraza N, Iglesias R, Villarroya F, Giralt M. Peroxisome proliferator-activated receptor alpha activates transcription of the brown fat uncoupling protein-1 gene. A link between regulation of the thermogenic and lipid oxidation pathways in the brown fat cell. J Biol Chem 2001;276:1486–93.
[11] Chang JS, Fernand V, Zhang Y, Shin J, Jun HJ, Joshi Y, et al. NT-PGC-1 α protein is sufficient to link β3-adrenergic receptor activation to transcriptional and physiological components of adaptive thermogenesis. J Biol Chem 2012;287:9100–11.
[12] Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med 2009;360:1518–25.
[13] Mund RA, Frishman WH. Brown adipose tissue thermogenesis: β3-adrenoreceptors as a potential target for the treatment of obesity in humans. Cardiol Rev 2013;21:265–9.
[14] Cho SS, Qi L, Fahey GC Jr, Klurfeld DM. Consumption of cereal fiber, mixtures of whole grains and bran, and whole grains and risk reduction in type 2 diabetes, obesity, and cardiovascular disease. Am J Clin Nutr 2013;98:594–619.
[15] Wang CH, Qiao C, Wang RC, Zhou WP. Dietary fiber intake and pancreatic cancer risk: A meta-analysis of epidemiologic studies. Sci Rep 2015;5:10834.
[16] Slavin JL. Dietary fiber and body weight. Nutrition 2005;21:411–8.
[17] Han SF, Jiao J, Zhang W, Xu JY, Wan ZX, Zhang WG, et al. Dietary fiber prevents obesity-related liver lipotoxicity by modulating sterol-regulatory element binding protein pathway in C57 BL/6 J mice fed a high-fat/cholesterol diet. Sci Rep 2015;5:15256.
[18] Tsai CEM, Tsai YL. Effect of dietary fiber on the prevention of liver lipid accumulation induced by high polyunsaturated oil. J Food Lipids 1999;6:75–89.
[19] Zhou AL, Hergert N, Rompata G, Lefevre M. Whole grain oats improve insulin sensitivity and plasma cholesterol profile and modify gut microbiota composition in C57 BL/6 J mice. J Nutr 2014;2:222–30.
[20] Kim H, Bartley GE, Young SA, Davis PA, Yokoyama W. HPMC supplementation reduces abdominal fat content, intestinal permeability, inflammation, and insulin resistance in diet-induced obese mice. Mol Nutr Food Res 2012;56:1464–76.
[21] Chassaing B, Miles-Brown JP, Pellizzon M, Ulman E, Ricci M, Zhang L, et al. Lack of soluble fiber drives diet-induced adiposity in mice. Am J Physiol Gastrointest Liver Physiol 2015;309:G528–41.
[22] Goldrick RB. Morphological changes in the adipocyte during fat deposition and mobilization. Am J Physiol 1967;212:777–82.
[23] Zechner R, Zimmermann R, Eichmann TO, Kohlwein SD, Haemmerle G, Lass A, et al. Fat Signals: lipases and lipolysis in lipid metabolism and signaling. Cell Metab 2012;15:279–91.
[24] Saito K, Arata S, Hosono T. Adiponectin plays an important role in efficient energy usage under energy shortage. Biochim Biophys Acta 2006;1761:709–16.
[25] Li S, Guerin-Deremaux L, Pochat M, Wils D, Reifer C, Miller LE. NUTRIOSE dietary fiber supplementation improves insulin resistance and determinants of metabolic syndrome in overweight men: a double-blind, randomized, placebo-controlled study. Appl Physiol Nutr Metab 2010;35:773–82.
[26] McKnight GS, Cummings DE, Amieux PS, Sikorski MA, Brandon EP, Planas JV, et al. Cyclic AMP, PKA, and the physiological regulation of adiposity. Recent Prog Horm Res 1998;53:139–59.
[27] Schweiger M, Schreiber R, Haemmerle G, Lass A, Fledelius C, Jacobsen P, et al. Adipose triglyceride lipase and hormone-sensitive lipase are the major enzymes in adipose tissue triacylglycerol catabolism. J Biol Chem 2006;281:40236–41.
[28] Ducharme NA, Bickel PE. Lipid droplets in lipogenesis and lipolysis. Endocrinology 2008;149:942–9.
[29] Watt MJ, Holmes AG, Pinnamaneni SK, Garnham AP, Steinberg GR, Kemp BE, et al. Regulation of HSL serine phosphorylation in skeletal muscle and adipose tissue. Am J Physiol Endocrinol Metab 2006;290:E500–8.
[30] Sztalryd C, Kimmel AR. Perilipins: lipid droplet coat proteins adapted for tissue-specific energy storage and utilization, and lipid cytoprotection. Biochimie 2014;96:96–101.
[31] Li B, Notle LA, Ju JS, Han DH, Coleman T, Holloszy JO, et al. Skeletal muscle respiratory uncoupling prevents diet-induced obesity and insulin resistance in mice. Nat Med 2000;6:1115–20.
[32] Cousin B, Cinti S, Morroni M, Raimbault S, Ricquier D, Penicaud L, et al. Occurrence of brown adipocytes in rat white adipose tissue: molecular and morphological characterization. J Cell Sci 1992;103:931–42.
[33] Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell 1999;98:115–24.
[34] Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. Nature 2000;404:652–60.
[35] Arner P, Pettersson A, Mitchell PJ, Dunbar JD, Kharitonenkov A, Rydén M. FGF21 attenuates lipolysis in human adipocytes: a possible link to improved insulin sensitivity. FEBS Lett 2008;582:1725–30.
[36] Li X, Ge H, Weiszmann J, Hecht R, Li YS, Véniant MM, et al. Inhibition of lipolysis may contribute to the acute regulation of plasma FFA and glucose by FGF21 in ob/ob mice. FEBS Lett 2009;583:3230–4.
[37] Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab 2007;5:426–37.
[38] Coskun T, Bina HA, Schneider MA, Dunbar JD, Hu CC, Chen YY, et al. Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 2008;149:6018–27.
[39] Institute of Medicine of the National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academies Press; 2002:339–61.