UCP2 KO mice exhibit ameliorated obesity and inflammation induced by high-fat diet feeding

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Uncoupling protein 2 (Ucp2) was first introduced as a member of Uncoupling protein family and a regulator of ROS formation; however, its role in adipose tissue is not fully understood. The present study, we have investigated the role of Ucp2 against high-fat diet (HFD)-induced obesity in epididymal white adipose tissue (eWAT) and browning of inguinal white adipose tissue (iWAT). Diet-induced obesity is closely related to macrophage infiltration and the secretion of pro-inflammatory cytokines. Macrophages surround adipocytes and form a crown-like-structure (CLS). Some reports have suggested that CLS formation requires adipocyte apoptosis. After 12 weeks of HFD challenge, Ucp2 knockout (KO) mice maintained relatively lean phenotypes compared to wild-type (WT) mice. In eWAT, macrophage infiltration, CLS formation, and inflammatory cytokines were reduced in HFD KO mice compared to HFD WT mice. Surprisingly, we found that apoptotic signals were also reduced in the Ucp2 KO mice. Our study suggests that Ucp2 deficiency may prevent diet-induced obesity by regulating adipocyte apoptosis. However, Ucp2 deficiency did not affect the browning capacity of iWAT. [BMB Reports 2022; 55(10): 500-505]

INTRODUCTION

Uncoupling protein 2 (Ucp2) is encoded by a mitochondrial gene and was first reported as a regulator of mitochondrial proton leakage, ATP production, and insulin secretion (1). Although the exact mechanisms underlying these functions have not yet been understood, many researchers have agreed that Ucp2 expression is negatively correlated with ROS and NO production (2, 3). In addition, the lifespan of Uncoupling protein 2 (Ucp2) knock-out (KO) mice is shorter than that of wild-type (WT) mice (4). However, Ucp2 displays a wide tissue expression range (5), and its roles in various tissues and cell types have not been covered.

Adipose tissue is a major metabolic organ that stores energy in the form of triglycerides (6-8). Its function in energy homeostasis of the whole body has been studied for decades and it is now considered an endocrine organ that secretes various adipokines and lipid metabolites (9, 10). Another key aspect of adipose tissue is the thermogenic capacity (11-13) of brown adipose tissue (BAT), which means dissipation of excess energy in the form of heat. The activation of BAT and recruitment of beige adipocytes from white adipocytes occur in an uncoupling protein 1 (Ucp1)-dependent manner (14-16). Recently, a study has revealed that macrophage-specific deletion of Ucp2 does not affect adipose tissue inflammation or weight gain after a high-fat diet (HFD) (17). To study the role of Ucp2 in adipose tissue, we have examined HFD-induced obesity and β3 adrenergic stimulation in Ucp2 KO mice. We have demonstrated that Ucp2 deletion dysregulates adipose tissue homeostasis under diet-induced obesity (DIO), but does not affect the browning of white adipose tissue (WAT).

Our study also showed that Ucp2 deletion alleviates HFD-induced weight gain and adipose tissue inflammation by blocking adipocyte apoptosis, an event preceding the recruitment of macrophages and pro-inflammatory cytokine secretion. We also establish the role of Ucp2 in thermogenesis and browning of inguinal white adipose tissue (iWAT), a well-known function of Ucp1, from the same family. Under β3-specific stimulation or 4°C cold exposure, browning capacity of iWAT of Ucp2 deficient mice was comparable to that of WT mice.

RESULTS

UCP2 KO mice were protected from HFD-induced obesity

To investigate the role of Ucp2 in adipose tissue under HFD condition, 6-week-old C57BL/7 mice were fed either normal chow diet (NCD) or high-fat diet for 16 weeks. We then isolated adipocytes and stromal vascular fraction (SVF) from epididymal white adipose tissue (eWAT) and measured Ucp2 mRNA levels...
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(Fig. 1A). Ucp2 expression was higher in HFD adipocytes. To confirm Ucp2 expression in adipocytes, we used a 3T3L1 cell line and verified a positive correlation between mRNA levels of Ucp2 and Pparγ, a differentiation marker (Fig. 1B, C). Then, we randomly assigned 6-week-old WT and KO mice to either NCD or HFD for 12 weeks. A chronic access to HFD resulted in significant weight gain in WT mice compared to mice with NCD, whereas the weight gain in HFD KO mice was comparable to that in NCD group (Fig. 1D, E). The net body weight change by the NCD or HFD administration was also significantly less in the KO group (Fig. 1F). Body composition data also coincided with the changes in body weight. Ucp2 KO mice showed significantly lower fat mass and higher lean mass than WT mice (Fig. 1G). WAT in KO mice was lesser than it was in WT mice (Fig. 1H). The WAT weight of HFD KO mice was significantly lower than that of HFD WT mice (Fig. 1I). Serum triglyceride (TG) and glucose levels were also lower in HFD KO mice than in HFD WT mice (Supplementary Fig. 1G, H). The mRNA level of the eWAT glucose uptake marker, Glut4, was increased in HFD KO mice compared to that in NCD KO mice, but the expression level in HFD WT mice was also significantly lower than that in HFD WT mice (Supplementary Fig. 2D). Hematoxylin and eosin (H&E) staining also revealed that adipocytes were smaller in HFD KO mice (Fig. 1J, K).

HFD-induced macrophage infiltration and inflammation were reduced in HFD KO mice
As HFD-induced obesity is closely linked to macrophage infiltration and secretion of pro-inflammatory cytokines (18, 19), we analyzed the macrophages present in epididymal adipose tissue. Localization of antigen F4/80 using immunohistochemistry (IHC) stained showed crown-like-structure (CLS) formation in macrophages (Fig. 2A), and the number of CLSs was comparable in NCD WT and KO mice, while HFD KO mice showed a significant reduction in CLS formation compared to HFD WT (Fig. 2B). The mRNA level of CCL2, a marker for macrophage recruitment to adipose tissue, was significantly reduced in HFD KO mice compared to that in HFD WT mice (Fig. 2E). Additionally, mRNA levels of pro-inflammatory markers, TNFα, IFNγ, and IL-1β were also significantly decreased in KO mice (Fig. 2G, and mRNA level of the anti-inflammatory marker adiponectin in both HFD groups was similarly reduced, compared to that in NCD groups (Fig. 2D). Many studies have shown that in DIO, adipocyte apoptosis is a major cause of and a direct upstream step before CLS formation (20-22). To determine whether deletion of the Ucp2 gene affects CLS formation and secretion of cytokines directly, or an upstream event, we investigated mRNA and protein levels of apoptotic signals in adipose tissue. We observed that caspase 3 (Cas3), caspase 9 (Cas9), and Bax/BCL2, the major apoptosis markers, only increased in the HFD WT group (Fig. 2C), and mRNA level of the anti-inflammatory marker adiponectin in both HFD groups was similarly reduced, compared to that in NCD groups (Fig. 2D). TUNEL assay was also performed, and apoptotic expression was higher in HFD WT mice compared to that in KO mice.

Under β3 adrenergic receptor stimulation, Ucp2 does not affect the thermogenic capacity
To stimulate the β3 adrenergic receptor, we injected CL 316,243, a β3 adrenergic agonist, intraperitoneally (i.p.) into 7-week-old mice, once a day (1 mg/kg) for three consecutive days. A schematic is shown in Fig. 3A. Body weight gains or losses were measured before the first injection and at the time of euthanasia. Saline-injected WT and KO mice gained comparable weights, whereas CL-injected KO mice lost significantly more weight than CL-injected WT mice did (Fig. 3B). The body compositions were also measured; fat content of CL-injected KO mice tended...
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Fig. 3. No difference was observed in CL 316,243-induced β3 adrenergic stimulation between the two genotypes. (A) Schematic diagram of CL injection experiment. (B) Body weight gain graph, (C) fat composition, (D) lean composition. (E) WAT weight differences normalized by total body weight, and (F) absolute fat weight differences of Saline injected WT, Saline injected KO, CL injected WT, and CL injected KO mice. (G) Relative mRNA expression of browning markers and (H) UCP1 protein expression in iWAT was normalized to the levels of α-actin. (I) H&E staining of eWAT, iWAT, and BAT. Data are presented as the mean ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. 4. Cold-induced browning capacity was comparable between WT and KO mice. (A) Schematic diagram of cold-induced browning. (B) Body weight gain graph. Body composition of (C) fat, (D) lean, (E) weights of WAT normalized by body weight and (F) actual weights are listed. (G) Relative mRNA expression of browning markers was analyzed in iWAT. (H) UCP1 protein expression in iWAT was normalized to the levels of α-actin. (I) H&E staining of eWAT, iWAT, and BAT. Data are presented as the mean ± SEM.

to be lower than that of CL-injected WT mice, but these differences were not statistically significant (Fig. 3C), while lean masses were similar among all groups (Fig. 3D). Their actual WAT masses were measured and normalized by their body weights and actual weights were recorded (Fig. 3E, F). We then measured browning of inguinal iWAT at the molecular level. Saline-injected WT and KO mice showed insignificant levels of Ucp1, whereas CL-injected WT and KO mice both showed high expression of Ucp1, at comparable levels (Fig. 3H). The mRNA levels of the browning markers, Ucp1, Elovl3, CIDEA, and PGC1α, were consistent with the corresponding protein levels (Fig. 3G). Finally, we histologically investigated the browning of adipose tissue and confirmed that adipocyte sizes and lipid droplet accumulations were similar between the two genotypes (Fig. 3I).

Ucp2 deletion does not affect phenotypes or browning of WAT under cold adaptation
To explore the role of Ucp2 in cold adaptation, we exposed 7-week-old mice to warm (30°C) and cold (4°C) conditions for 5 days. A schematic is shown in Fig. 4A. This cold exposure did not affect body weight changes in WT and KO mice (Fig. 4B). Changes in body composition data and actual WAT weight were negligible (Fig. 4C-F). Protein and mRNA levels of browning markers showed similar cold effects in both the WT and KO groups and showed no differences between the two genotypes (Fig. 4G, H). Finally, we compared histological differences, however; we found no evidence that Ucp2 deletion affects adipose tissue remodeling (Fig. 4I).

DISCUSSION
In the past decades, studies have revealed the significance of genes from Ucp family. Ucp1 is specifically expressed in brown and beige adipocytes, Ucp3 expression is distributed in skeletal muscles, and Ucp2 expression has a wide tissue distribution (5). Many studies have studied the roles of Ucp2 in various organs (23-25) and they have demonstrated that Ucp2 negatively regulates ROS formation (2-4). However, the role of Ucp2 in adipose tissue and energy metabolism was not fully investigated.

In 2001, a cross between Ucp2 KO and ob/ob mice was studied, which showed a gain of weight comparable to that of WT mice (1). In 2002, Ucp2 KO mice were reported to have higher body weights than WT mice after the HFD challenge (26). These results contradict our observation that Ucp2 KO mice gained significantly less weight than Ucp2 WT mice did after the HFD challenge. These discrepancies may be attributed to two reasons. Firstly, the Ucp2 KO mice used in each experiment had different backgrounds. In 2009, Pi et al. discovered that the insulin secretion capacities of Ucp2 KO mice differed according to their genetic backgrounds (27). Among 129/B6 mixed, 129 congenic, B6 congenic, and A/J congenic Ucp2 KO mice, only 129/B6 mixed genetic background, the one used in the two previously reported articles, showed a higher insulin secretion compared to WT mice. Secondly, all three studied used different experimental designs. The first group used ob/ob mice with NCD, and the second group fed HFD to 4-month-old mice. We fed HFD to 6-week-old mice for 2 months. We suggest that these two differences may have resulted in the inconsistent results of the studies.

Adipose tissue is a metabolically active and dynamic organ
that comprises heterogeneous cell population (28). Adipocytes, making up the majority of cell populations, store energy in the form of triglycerides (7), whereas the rest of the populations are composed of various cell types, including immune cells (9, 28-30). Recently, a study has reported that macrophage-specific Ucp2 deletion does not affect body weight gain and adipose tissue inflammation after HFD (17), whereas our data demonstrated that Ucp2 null KO mice were protected from DIO. To delineate this matter, we fed 6-week-old C57/BL6 mice HFD for short (2 weeks) and long (16 weeks) terms and isolated them into adipocytes and a SVF from eWAT. Although the Ucp2 mRNA levels in adipocytes and SVF of the NCD group were comparable, after the HFD challenge, adipocytes exhibited significantly higher Ucp2 levels than the SVF (Fig. 1A, Supplementary Fig. 1E). In addition, we used 3T3-L1 murine pre-adipocytes and confirmed that Ucp2 mRNA expression was increased by the PGC1α mRNA level, a marker for differentiation (Fig. 1B, C). Considering the expression levels of Ucp2 in adipocytes, it may play a role in adipocytes but not in SVF, including macrophages, in HFD-induced obesity.

We induced obesity in Ucp2 WT and KO mice through HFD. Surprisingly, HFD treated KO mice exhibited leaner phenotypes compared to WT mice. Weight gain was significantly reduced in Ucp2 KO mice compared to that in WT mice (Fig. 1D-F). Serum TG and glucose levels were significantly lower in the HFD KO group (Supplementary Fig. 1G, H), and the eWAT glucose uptake marker level was also reduced in HFD KO mice (Supplementary Fig. 2D). HFD KO mice had significantly lower fat content (Fig. 1G) and WAT weights (Fig. 1I). Histologically, HFD KO mice showed smaller adipocyte distribution (Fig. 1, K).

Obesity is strongly associated with pro-inflammatory cytokines and adipose tissue macrophages (18, 31). Moreover, deletion of macrophages has been reported to prevent DIO phenotypes in eWAT (32). It has also been reported that adipocyte apoptosis is an upstream event necessary for macrophage infiltration into adipose tissue and CLS formation (20-22). Furthermore, Ucp2 was reported to regulate adipocyte apoptosis in 3T3L1 cell lines when treated with 1alpha,25-dihydroxyvitamin D3 (33). We confirmed that adipose tissue macrophages (Fig. 2A, B) and pro-inflammatory markers (Fig. 2C) were reduced in HFD KO mice than in HFD WT mice. We then compared apoptosis between the two genotypes. Interestingly, HFD KO mice showed significantly reduced mRNA and protein expression of apoptosis markers compared to HFD WT mice (Fig. 2F, Supplementary Fig. 2A, B). TUNEL assay also showed higher apoptotic signals in the HFD WT group (Supplementary Fig. 2C).

Sympathetic nervous system stimulation via β-adrenergic receptors induces multilocular lipid droplets in adipocytes and browning of white adipose tissue. Ucp1, a well-known marker for browning of WAT, dissipates heat by uncoupling the H+ gradient, which would otherwise be used in ATP synthesis. Recently, Caron S et al. reported that Ucp2 KO mice failed to adapt to chronic cold exposure (10°C) (34). This study focused on glucose metabolism in BAT and did not reveal the role of Ucp2 in iWAT and thermogenesis. Here, using stimulation with a β3 adrenergic agonist and 4°C cold exposure, we demonstrated that the browning capacity of iWAT is comparable between WT and KO mice. Ucp2-depleted mice showed a tendency to lose more weight than WT mice (Fig. 3B and 4B), but the actual weights of WAT and adipocyte sizes were comparable (Fig. 3F, I; 4F, I). Moreover, the protein and mRNA expression of major browning markers in iWAT were comparably increased (Fig. 3G, H; 4G, H).

In conclusion, Ucp2 deficiency ameliorated HFD-induced obesity in eWAT but did not alter thermogenic and browning capacities in iWAT. HFD-challenged Ucp2 KO mice showed lean phenotypes in terms of body weight, fat composition, actual fat weight, and smaller adipocytes. Additionally, macrophage infiltration, CLS formation, pro-inflammatory cytokine markers, and apoptosis markers were reduced in the eWAT of the HFD-KO mice. Considering the high expression levels of Ucp2 in HFD adipocytes, we suggest that Ucp2 may regulate apoptotic pathways of adipocytes and eventually prevent HFD-induced obesity.

MATERIALS AND METHODS

Animals

Ucp2 null KO mice were purchased from the Jackson Laboratory, USA (B6.129S4-Ucp2tm1Lowl/J, Strain #:005934). Ucp2 KO mice were obtained by crossing heterozygous breeders. All protocols were performed in accordance with the Guide for Animal Experiments (edited by the Korean Academy of Medical Sciences and approved by the Institutional Animal Care and Use Committee of Seoul National University, Seoul, Korea) (approval number: SNU-201013-2-1). For HFD experiments, 6-week-old male WT and KO mice were randomly assigned (n = 5) to either NCD or a 60% HFD (20% carbohydrate, 60% fat, 20% protein; DI2492; Research Diets Inc.). For CL 316,243 (Sigma, USA) treatment, 7-week-old WT and KO mice were i.p. injected with 1 mg/kg of CL for 3 days (n = 4). For the cold challenge, 7-week-old WT and KO mice were randomly assigned to either thermoneutral (30°C) or cold (4°C) environment conditions for 5 consecutive days (n = 5). At the end of each experiment, the body composition of all animals was determined by nuclear magnetic resonance (Minispec LF-50, Bruke).

Histology

Samples were fixed with 4% paraformaldehyde and embedded in paraffin. They were sliced into 4.5-μm-thin sections and stained with H&E, following a standard protocol. For IHC staining, anti-F4/80 antibody (D259R, Cell Signaling Technology) was used. The samples were then washed and blocked with 2.5% horse serum for 1 h. After another washing with PBS + 0.05% Tween 20 incubation was performed with a 1:500 dilution of primary anti-F4/80 antibody (ImmPRESS,
Vector Laboratories) for 1 h at 24°C. Finally, they were developed using a DAB kit (Vector Laboratories), according to the manufacturer’s protocols. H&E and IHC samples were visualized using a Pannoramic Scanner (3DHISTECH).

Western blotting
Proteins were extracted using RIPA buffer and quantified using the BCA assay protocol. Equal amounts of protein were separated by SDS-PAGE and then transferred to PVDF membranes. Samples were incubated with primary antibodies overnight at 4°C and then incubated with HRP-conjugated secondary antibodies. The blots were visualized using enhanced chemiluminescence and a Chemi-Doc Imaging System (Bio-Rad). Images were quantified and normalized using the ImageJ software (NIH). The primary antibodies used were UCP1 (Abcam), Caspase3 (Cell Signaling Technology), Cleaved caspase 3 (CST), α-tubulin (Sigma), and β-actin (Santa Cruz).

Quantitative real-time PCR
Total RNA was extracted from the tissues using TRizol reagent (Invitrogen) according to the manufacturer’s instructions. cDNA was synthesized using a premix (Bioneer), according to the manufacturer’s instructions. qPCR was performed using the QuantStudio5 (Applied Biosystems). PCR was performed using the SYBR Lo-ROX Kit (Meridian), according to the manufacturer’s protocol. qPCR was performed using the QuantStudio5 (Applied Biosystems). PCR was performed using the SYBR Lo-ROX Kit (Meridian), according to the manufacturer’s instructions. The primer sequences used are shown in the Supplementary Fig. 3.

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CONFLICTS OF INTEREST
The authors have no conflicting interests.

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