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Research article

Central irisin administration suppresses thyroid hormone production but increases energy consumption in rats

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ABSTRACT

Irisin, which is secreted from the skeletal muscle in response to physical exercise and defined as a thermogenic peptide, may play an important role in energy metabolism. Thyroid hormones, which are one of the other influential factors on the metabolic status, increase heat production and are the main regulators of energy metabolism. This study was conducted to determine the possible effects of irisin administration on thyroid hormones.

Forty adult male *Wistar albino* rats were used in the study. The rats were equally divided into 4 groups (n = 10). The brain infusion kit was implanted in the groups, and irisin (or solvent as control) was centrally administered to the rats *via* osmotic mini pumps for 7 days. During the experiment, food consumption, body weights, and body temperatures of the animals were recorded.

Food intake was significantly increased in the groups treated with irisin ($p < 0.05$), but their body weights were not changed. Hypothalamic TRH gene expression, serum TSH, fT3, and fT4 levels were significantly lower in the groups treated with irisin as compared to the naive and control groups ($p < 0.05$). In addition, irisin increased UCP1 mRNA expression in white and brown adipose tissue and UCP3 mRNA expression in muscle tissue in rats and also raised their body temperature ($p < 0.05$).

Consequently, although central irisin administration has inhibitory effects on the hypothalamic-pituitary-thyroid axis, it seems to be an important agent in the regulation of food intake and energy metabolism.

1. Introduction

Exercise has been shown as an important approach to the regulation of metabolism and for the elimination of metabolic disorders [19,24]. It has been thought that irisin mediates the physiological effects of exercise, which is released into the blood circulation from the skeletal muscle during exercise [4]. Irisin is produced by the breakdown of fibronectin type III domain containing protein 5 (FNDC5), which is a membrane protein. It increases the expression of uncoupling protein 1 (UCP1), which leads to increased energy expenditure. The increased expression of UCP1 in white adipocytes leads to “browning” of white adipose tissue, thus it supports the protection of metabolic homeostasis [4,22]. Central irisin administration also increases locomotion and oxygen consumption as well as carbon dioxide and heat production [13,37]. Some researchers suggest that irisin may be effective on adipose tissue metabolism by improving muscle tissue [16]. In addition to these physiological effects of irisin, demonstration of irisin/FNDC5 presence in tissues such as hypothalamus [25], skeletal muscle [11], adipose tissue, pancreas, and liver [16], which plays key roles in the regulation of nutrition and energy metabolism, suggests that this peptide can play a role in regulating metabolic homeostasis and energy use in the body. Recent studies have shown that the changes in circulating levels of irisin may be associated with diseases such as obesity, diabetes, and metabolic syndrome [22,28]. Although it is thought that irisin may be a peptide that has therapeutic potential against these diseases closely related to the energy metabolism [27], there is a need for more

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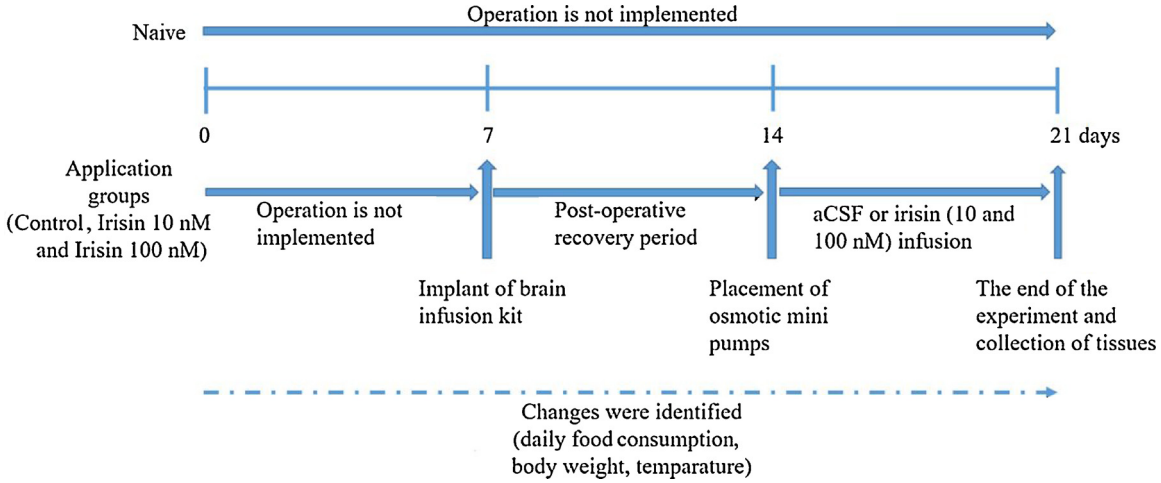

Fig. 1. Experimental design of the study. The rats in the naive group were not subjected to any surgical procedure during the experiment. The brain infusion kits were placed in the right lateral ventricles of the animals in the treatment groups. The animals were expected to recover after the operation. Subsequently (day 14), osmotic mini pumps were attached to the cannulas of the brain infusion kits, and irisin (or solvent) infusion was performed. During the experiment (0–21 days), the changes in the body temperatures before and during infusion in addition to the changes in the food consumption and body weights of the animals were recorded.

comprehensive studies to explain the mechanism in order to illuminate the process.

Thyroid hormones, which are regulated by the hypothalamus-pituitary-thyroid (HPT) axis, maintain baseline energy expenditure by acting primarily on the carbohydrate and lipid catabolism and play a critical role in thermogenesis by increasing uncoupling protein 3 (UCP3) mRNA expression in muscle tissue [8,17]. Thyroid dysfunction is one of the common endocrine disorders and is associated with many pathological processes −primarily metabolic imbalance and abnormal energy homeostasis [5,12,27,35]. When it is considered that irisin and thyroid hormones are related to the energy expenditure, metabolism, and muscle physiology in the body [27], it comes to mind that there may be an interaction between irisin and thyroid hormones. A small number of studies in the literature examined the relationship between circulating levels of irisin and thyroid hormones [15,31]. Ruchala et al. showed that there was a negative correlation between irisin and TSH in patients with thyroid dysfunction [26]. However, Samy et al. reported that circulating level of irisin was not associated with TSH in the experimental model of thyroid dysfunction [27]. The results of the present study are incompatible and insufficient to explain the relationship between thyroid hormones and irisin. Moreover, some studies aim to link circulating levels of irisin and thyroid hormones, but do not reveal the possible effects of irisin on the HPT axis. The purpose of this study was to determine the effects of central irisin administration on the HPT axis and to explain the effects of irisin on energy metabolism by associating with UCP1 in adipose tissue and UCP3 in muscle tissue, which are considered as an indicator of energy expenditure.

2. Materials and methods

2.1. Experimental animals

Forty adult male *Wistar albino* rats (250–280 g) were used in the present study. The hostage of the animals and all implementations were carried out according to the approval taken from the Experimental Animal Ethics Committee of Inonu University Faculty of Medicine (Date: 28.11.2014, Protocol No: 2014/A-93). During the experiment, the animals were kept under standard laboratory conditions (22 ± 1 °C, 12 h light/12 h dark cycle) and were fed *ad libitum* with standard rat diet.

2.2. Experimental design

In order to adapt to the cage stress and the experimental environment, the animals were placed in single cages 7 days before the start of the experiment [10]. Then, while taking into account the body weight, the rats were randomly assigned into 4 groups, including naive, control, irisin 10 nM, and irisin 100 nM (n = 10). The process was not implemented on the rats in the naive group during the experiment. At the end of the 7th day, the rats in the treatment groups were anesthetized with the combination of ketamine and xylazine. The brain infusion kits (ALZET Brain Infusion Kit 1; DURECT Corporation, CA, USA) were attached to the right lateral ventricles of the animals fixed to a stereotaxic device [23] using dental cement [34]. After the cannulas of the kits were closed in such a way that the tips did not catch air, they were placed under the neck skin of the rats. The rats were anesthetized again at the end of 14th day after this process. Osmotic mini pumps (ALZET 2ML1 osmotic pumps, DURECT Corporation, CA, USA) were attached to the cannulas of the brain infusion kits. The solvent (artificial cerebrospinal fluid, aCFS; 124 mM NaCl, 5.0 mM KCl, 1.2 mM KH_2PO_4, 2.4 mM $CaCl_2$, 1.3 mM $MgSO_4$, 26 mM $NaHCO_3$, and 30 mM glucose, pH:7.2) was administered to the rats in the control group for 7 days. Irisin prepared in the solvent (Catalog#067-16, Phoenix Pharmaceuticals Inc., CA, USA) was administered to the rats in the groups treated with irisin for 7 days at 10 nM and 100 nM concentrations (240 µL/h) [21,34]. During the experiment, the changes in the food consumption and body weights of the animals were recorded. In addition, body temperatures of the animals were measured using rectal probe. After infusion (day 21), the animals in the groups were decapitated, and their hypothalamus, blood, muscle and intrascapular white fat tissues (WAT) and brown fat tissues (BAT) were obtained. The tissues were transferred into DNase/RNase-free tubes and were stored at −80 °C until analyses. The experimental design is summarized in Fig. 1.

2.3. Quantitative real-time PCR analyses

2.3.1. Hypothalamic TRH mRNA levels

Total RNA isolation from the hypothalamus tissue was performed using the High Pure RNA Tissue Kit (Roche, USA; Lot no: 10156400). cDNA was synthesized from isolated RNA using the Transcriptor First Strand cDNA Synthesis Kit (Roche, USA; Lot no: 14585924). Hypothalamic TRH mRNA analysis was performed using the primers and hydrolysis probes with the Fast Start Essential DNA Probes Master Kit (Roche, USA; Lot no: 10048800) and the Real Time Ready Assay (β-

Actin; Lot no: 90015222, TRH; Lot no: 90015384) on the Roche Light Cycler 96 Real-time PCR System. To determine the change in TRH gene expression among the groups, the β-Actin gene was selected as housekeeping gene, and relative mRNA expression levels were calculated according to housekeeping genes using the $2^{-\Delta\Delta Ct}$ method.

2.3.2. Muscle and adipose tissue UCP mRNA levels

The Pure Link RNA Mini Kit (Invitrogen, USA; Catalog No. 12183018A) was used for total RNA isolation from the muscle, WAT and BAT. The kit procedure was followed during the process. cDNA synthesis was performed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA). The real-time PCR analysis was performed with the ABI Prism 7500 Fast Real-Time PCR Instrument (Applied Biosystems, USA) using Tag Man Master Mix (Applied Biosystems, USA). All results were standardized to the levels of GAPDH (housekeeping). The samples were quantified for UCP-1 (Rn-00562126-m1, Applied Biosystems, USA), UCP-3 (Rn00565874_m1, Applied Biosystems, USA), using the $2^{-\Delta\Delta Ct}$ method.

2.4. Western Blot analysis

The hypothalamus tissue lysate was obtained using lysis buffer. Total protein concentration was determined using the Protein Assay Kit (Bio-Rad, Hercules, CA). 30 μg of total protein from each sample was run on 15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Then, it was transferred to PVDF membranes. The membranes were blocked with 5% dry milk prepared with TBS buffer. After washing steps, it was incubated at 4 °C during overnight hours with an antibody specific to rat TRH within 2.5% dry milk. After the membranes were washed with TBS-T, it was incubated for 1 h with HRP conjugated anti-rabbit or anti-mouse secondary antibody. Mouse anti-beta-actin antibody was used as loading control.

Chemiluminescent screening was performed with chemi-glow screening agents. The Blots were visualized with the UVP ChemiDoc-It 2 imager, and densitometry measurements were performed with the ImageJ program. All experiments were repeated independently three times [32,33]. Tissue protein level measured in the assay was divided by β-actin.

2.5. Serum TSH, T3 and T4 levels

The blood samples were centrifuged for 10 min at 4500 rpm and the serum was obtained from blood. Moreover, the levels of serum TSH (USCN Life, Catalog#E0463r; China), free T3 (fT3), and free T4 (fT4) (Elabscience, Catalog#E-EL-R1097 and E-EL-R0390, respectively; China) were determined using ELISA kits.

2.6. Statistical analyses

The compliance with the normal distribution was examined through Shapiro Wilk test. In the comparison of quantitative variables among groups, Kruskal Wallis H test was used. When the significant difference was determined among groups, multiple comparisons were performed through Bonferroni Corrected Mann Whitney *U* test. The values were expressed as mean ± SD. The value of $p < 0.05$ was accepted as statistically significant. During the analyses, IBM SPSS Statistics 22.0 for Windows package program was used.

3. Results

3.1. Food consumption

The changes in the food consumption of the rats during the experiment are shown in Fig. 2. According to the findings, the food consumption of the animals in the pre-operative period (days 0–7) was similar. Placement of the brain infusion kits in the treatment groups reduced the food consumption of the rats compared with the naive group ($p < 0.05$). 10 nM and 100 nM concentrations of irisin increased the food consumption of the rats during the infusion (days 14–21) compared with the naive and control groups (Fig. 2; $p < 0.05$).

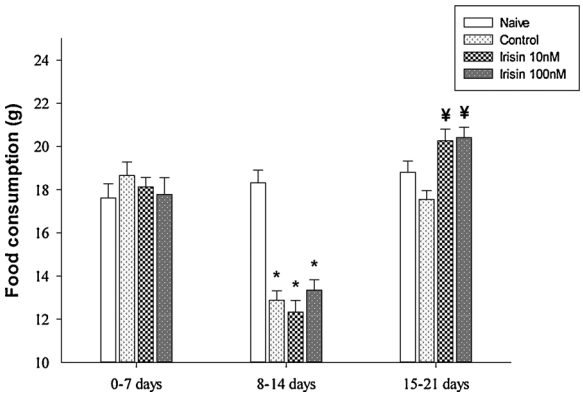

Fig. 2. Food consumption change of the groups before and after experiment. Irisin infusion significantly increased food consumption. (The values were expressed as mean ± SD. *$p < 0.05$ *vs* naive group; ¥$p < 0.05$ *vs* naive and control groups).

3.2. Body weight and body temperature

The changes in the body weights of the animals before and after the operation were determined (Fig. 3a). According to the findings, the body weights of the animals in the pre-operative period (days 0–7) were similar. However, the body weights of the rats implanted with the brain infusion kit showed a decrease in the days following the operation (Fig. 3a; $p < 0.05$). It was determined that central irisin administration did not change the weights of the rats compared with the naive and control groups.

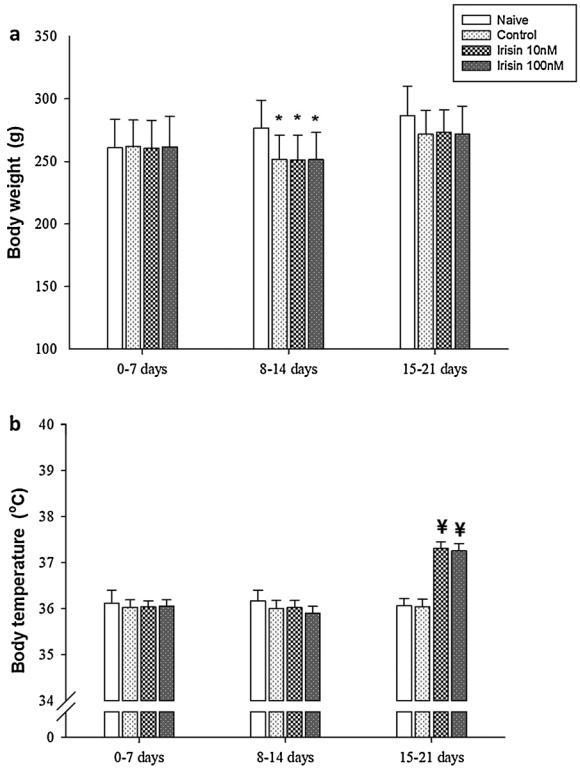

Fig. 3. (a) Body weight and (b) body temperature changes of the groups before and after central irisin infusion. Treatment with two different concentrations of irisin caused a significant increment body temperature. (The values were expressed as mean ± SD. *$p < 0.05$ *vs* naive group; ¥$p < 0.05$ *vs* naive and control groups).

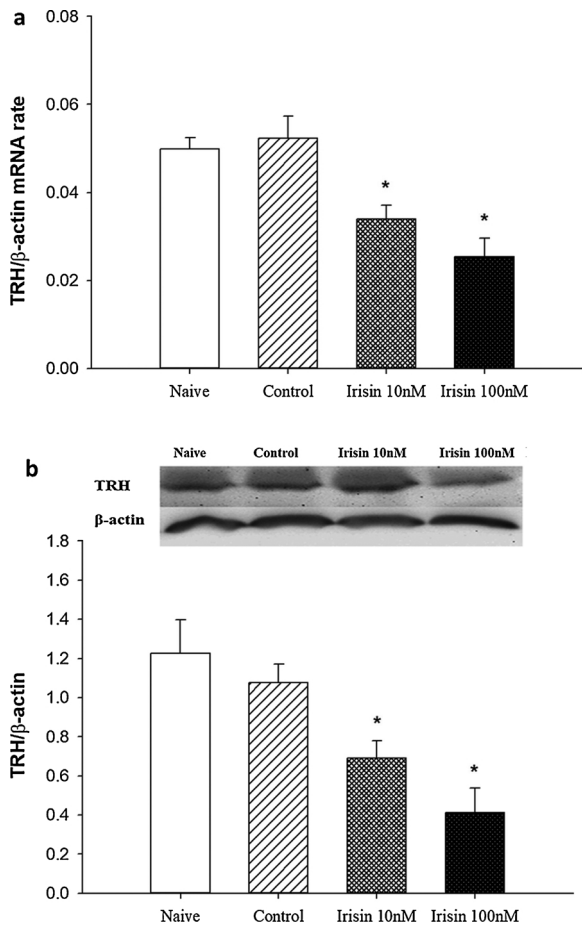

Fig. 4. The levels of TRH in the hypothalamus after the irisin infusion. (a) TRH mRNA level decreased after the irisin infusion. (b) In addition, treatment of irisin causes a decrease in the level of TRH protein. (The values were expressed as mean ± SD. *p < 0.05 *vs* naive and control groups).

The body temperatures of the animals in the pre-operative period were similar. After the attachment of the osmotic mini pumps, the body temperatures of the rats in the groups treated with irisin were significantly higher compared to that of the rats in the naive and control groups (Fig. 3b; $p < 0.05$).

3.3. Hypothalamic TRH level

Hypothalamic TRH mRNA and protein levels were decreased significantly after central irisin administration compared to the other groups (Fig. 4; $p < 0.05$). aCSF administered to animals in the control group did not significantly affect either TRH mRNA or protein levels compared with the naive group.

3.4. Serum TSH, fT3 and fT4 levels

The changes in serum TSH, fT3, and fT4 hormone levels of the animals after central irisin administration are given in Fig. 5. aCSF administered to animals in the control group did not show a significant effect on serum thyroid hormone levels. However, both doses of central irisin administration significantly reduced serum TSH, fT3, and fT4 levels of the animals compared to the other groups ($p < 0.05$).

3.5. UCP1 and UCP3 mRNA levels

The changes in UCP1 mRNA expression in WAT and BAT, and UCP3 mRNA expression in muscle tissue in the animals after central irisin administration are shown in Fig. 6. UCP1 mRNA expression in WAT and

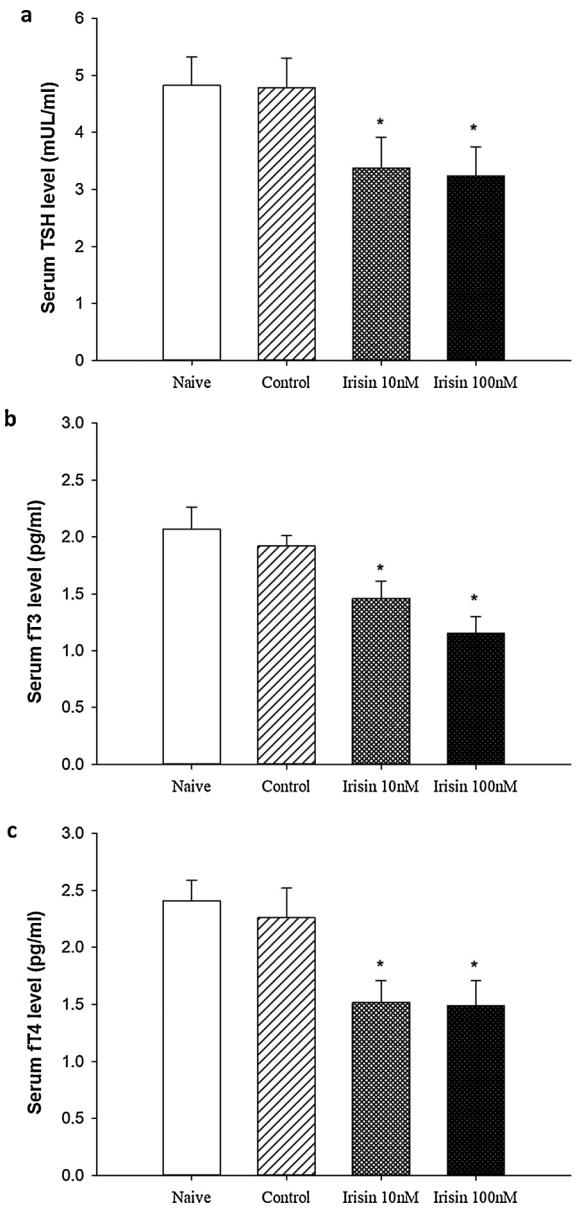

Fig. 5. (a) TSH, (b) fT3, and (c) fT4 levels in serum after treatment with 10 nM and 100 nM concentrations of irisin. Central irisin infusion significantly reduced serum TSH, fT3, and fT4 levels. A difference between naive group and control group applied aCSF was not observed. (The values were expressed as mean ± SD. *p < 0.05 vs naive and control groups).

BAT, and UCP3 mRNA expression in muscle tissue were significantly increased after central irisin administration compared with the naive and control groups ($p < 0.05$). aCSF administered to animals in the control group did not significantly affect either UCP1 or UCP3 mRNA levels compared with the naive group.

4. Discussion

Regulation of nutrient uptake is a complex process that involves the mutual integration of the signals from both the central nervous system and the environment. Circulating hormones and nutrients send peripheral metabolic signals to the brain stem in order to transmit them to the hypothalamus and the brain. The hypothalamus plays a role in short- and long-term regulation of food intake and is a brain center in which a large number of peptides and neurotransmitters are integrated to perform an action [20]. Demonstration of the presence of irisin in the hypothalamus and CSF [11,25] supports the idea that this peptide may

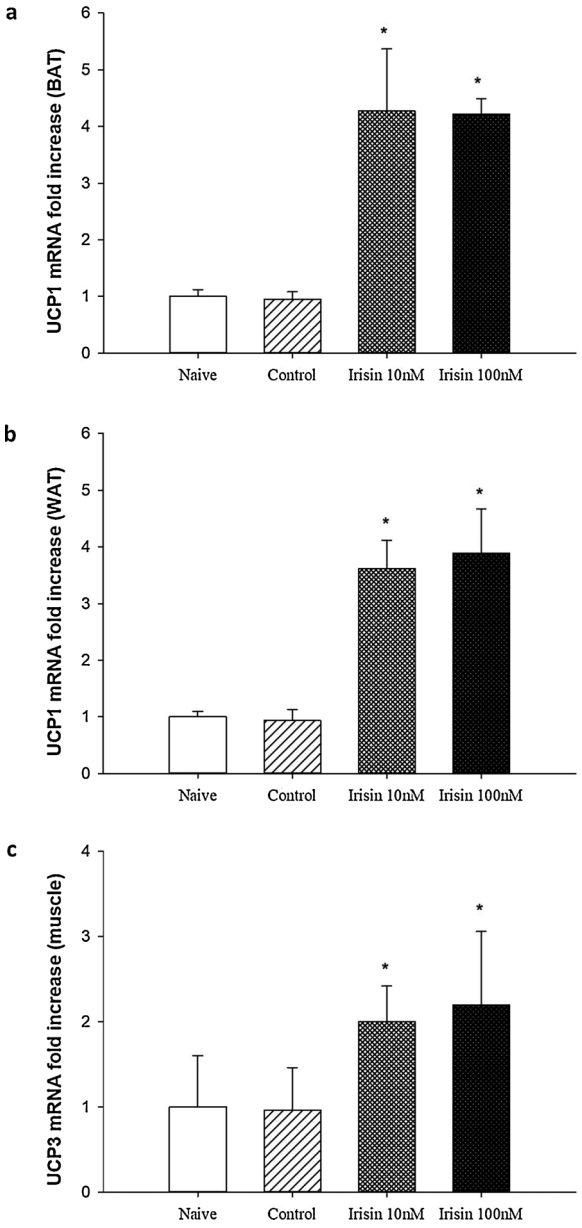

Fig. 6. The amounts of UCP1 and UCP3 mRNA levels in the adipose and muscle tissues after the central irisin infusion. Infusion of 10 nM and 100 nM irisin increased significantly UCP1 mRNA levels in the (a) BAT and (b) WAT, and (c) UCP3 mRNA level in the muscle tissue. A difference between naive group and control group was not observed. (The values were expressed as mean ± SD. *$p < 0.05$ vs naive and control groups).

play a role in regulating food intake and energy metabolism.

A small number of studies have attempted to explain the relationship between irisin, body weight, and food consumption. Some researchers reported that circulating level of irisin was higher in obese subjects than in normal individuals [7]. Stengele et al. reported that the serum irisin level was significantly higher in morbidly obese subjects than in normal individuals and anorexic patients. Thus, this situation led to a correlation between circulating level of irisin and body weight and body mass index [31]. Several studies provided information about the changes in the serum irisin level after feeding. It was reported that circulating level of irisin was decreased in the morning of the day following high-level food consumption [29]. However, another study showed that the serum irisin level was not affected by a standard food consumption and was not associated with calorie level [1]. These studies showed that circulating level of irisin was enhanced due to the increase in body weight especially in obese subjects and that the serum irisin level might be affected following nutrient uptake. In addition to these studies, some experimental models have tried to explain the effects of irisin administration on nutrient uptake. Butt et al. showed that intraperitoneal injection of irisin reduced short-term nutrient uptake in Goldfish (*Carassius auratus*) [6]. Ferrante et al. reported that a single intrahypothalamic injection of irisin in rats reduced food intake by stimulating the pro-opiomelanocortin (POMC)/CART neurons [14]. In contrast to these studies, in our previous study, we reported that central irisin administration stimulated food intake by increasing serum ghrelin level and hypothalamic NPY mRNA expression and by reducing POMC mRNA level [34]. Moreover, in the same study, we showed that the animals' body weights did not change despite the increased nutrient uptake and that irisin administration did not affect water consumption [34]. In the present study, we also showed that long-term central administration of irisin significantly increased nutrient uptake; but did not cause significant changes in body weight. Unlike the studies in the literature (see Ferrante et al. [14] and Butt et al. [6]), we think that our results occurred depending on the application time (long-term infusion) of irisin. In addition, food intake after irisin administration was shortly followed up in the previous studies [6,14]. Long-term consumption of food as shown in our study could help to better understand the possible effects of irisin on nutrition.

The hypothalamus plays a major role in the homeostatic integration of metabolic information and regulation of energy balance. Thyroid hormones, one of the best-known actors of this process, are regulated along the HPT axis and generally stimulate energy use and thermogenesis by increasing the metabolic rate [36]. Both T3 and T4 increase the expression of UCP1 and UCP3, which are considered as the markers of the peripheral energy use and play an important role in thermogenesis [3,9,18,30]. Demonstration of the presence of irisin, which stimulates energy use and identified as a thermogenic peptide [4,13] in the central area [11,25], suggests that it may have effects on thyroid hormones, which are important regulators of basal metabolism.

A small number of studies have been inadequate to explain the relationship between thyroid hormones and irisin. Samy et al. showed that the serum irisin levels of rats with thyroid dysfunction were high and that the increased irisin level was not associated with TSH [27]. Ates et al. reported that the serum irisin level in individuals with hypothyroidism was higher than in healthy controls and that circulating level of irisin showed a positive correlation with TSH and a negative correlation with fT4 [2]. However, another study reported that circulating level of irisin showed a negative correlation with TSH and a positive correlation with fT4 [26]. The results of current studies are inadequate to explain the effects of irisin, which is considered to play a significant role in energy metabolism, on the HPT axis, and consequently, on thyroid hormones. In this study, we showed that central irisin administration significantly suppressed the hypothalamic TRH mRNA and protein levels and the serum TSH, fT3, and fT4 levels. These results are important to show the effect of irisin on the HPT axis because they reveal an entire mechanism. Furthermore, the increases in UCP1 mRNA expression in WAT and BAT, and UCP3 mRNA expression in muscle tissue after central irisin administration (see Fig. 6) show that irisin can stimulate energy expenditure and heat generation independently from thyroid hormones. Consequently, we may claim that irisin mediates the effects of physical exercise on energy metabolism (food intake, energy expenditure, and thermogenesis).

5. Conclusions

This study demonstrates the effects of central irisin administration on HTP axis and energy metabolism. We define a novel physiological effect of irisin infusion on mainly thyroid hormones in energy metabolism. Irisin reduced levels of TRH and thyroid hormone in hypothalamus and blood, respectively, but increased UCP1 and UCP3 mRNA expression in peripheral tissues. In addition, irisin infusion increased the food consumption but not change body weight in animals. Our data

suggest that irisin infusion could stimulated energy use by increasing UCP1 and UCP3 expression and body heat.

Declaration of conflicting interests

The authors declare no conflict of interest.

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