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Research paper

Effects of central irisin administration on the uncoupling proteins in rat brain

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ABSTRACT

Irisin is a thermogenic peptide that enables the development of brown adipose tissue from white adipose tissue by activating the UCP1. This study has been designed to determine the effects of the irisin on UCPs. Sprague Dawley female rats were used in the study. 1, 3 and 10 μM concentrations of irisin were injected intracerebroventricularly to the rats, and the control group was received only vehicle. The animals were killed at the 16, 24, and 48 h time intervals and their brains were taken out. The hypothalamus, pituitary gland, hippocampus, cerebellum, striatum and cortex areas were separated and the UCP2, UCP3, UCP4 and UCP5 mRNA levels were determined. Just before the animals were killed, their body temperatures were recorded.

It was observed that after application of the high dose irisin, UCP5 mRNA level in the all brain areas increased ($p < 0.05$); it was also observed that the three doses decreased the UCP4 expression in all brain areas (except the pituitary gland; $p < 0.05$). The UCP2 and UCP3 mRNA expressions showed significantly increase in cerebellum and striatum ($p < 0.05$). The UCP2 mRNA expression decreased in hypothalamus, pituitary gland, hippocampus and cortex areas ($p < 0.05$). It was also observed that the body temperatures of the rats increased depending on the irisin injection and this increase was the most considerable at the 24 h ($p < 0.05$). The results of this study suggest that the UCP2-5 is expressed in different areas of the brain, and the irisin affects this expression, and may have effective roles in some brain functions.

1. Introduction

Mitochondria convert the oxygen and food (e.g free fat acids, simple sugars and amino acids) into ATP via oxidative phosphorylation to obtain the cellular energy. Oxidative phosphorylation occurs with the transfer of the electrons through the electron transfer chain (ETC) [23]. While the ETC continues, the protons in the mitochondrial matrix are pumped towards the inter-membrane area of the mitochondria. This creates an electrochemical gradient that is known as the proton motive force. The potential energy obtained with this proton gradient is used in the ATP synthesis by the ATP-synthase [26]. The uncoupling proteins (UCPs), which are from the protein family that carries the mitochondrial anions, are located in the inner membrane of the mitochondria [32]. This protein family is transport protons to the mitochondrial matrix and in turn dissipates the proton motive force as heat [38]. Recent studies have showed that the tissue distribution of UCPs regulates different significant biologic functions such as mitochondrial function [19], oxidative phosphorylation [13], hormone secretion [14], neuronal cell survival [57] and calcium regulation [60].

Five different UCPs that are distributed in different tissues have been identified so far [32]. UCP1, also known as real UCPs, is a protein that is specific to the brown adipose tissue [32,53]. UCP2 is distributed in various peripheral tissues including the central nervous system (CNS) [5,21,48–50]. UCP3 is expressed in the neuronal area although it is specific to the skeletal and heart muscles [1,10,62]. UCP4 and UCP5 are expressed in the CNS at high levels (for example hypothalamus, hippocampus and cortex) [36,51]. UCP2 and UCP3 have high sequence identity with UCP1, whereas UCP4 and UCP5 have much lower sequence identity with UCP1 [9,32,35].It is reported that the UCPs in the CNS are important

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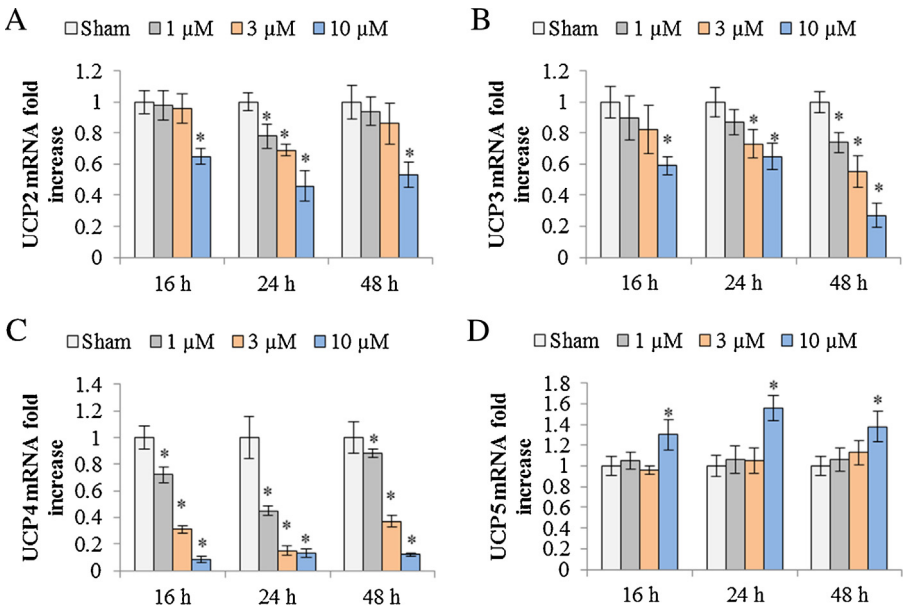

Fig. 1. UCP2 (A), UCP3 (B), UCP4 (C) and UCP5 (D) mRNA levels in hippocampus after treatment with 1, 3 and 10 μM concentrations of irisin. The graph show normalized mRNA levels for indicated genes. Statistical analysis were performed using one-way ANOVA and bar graphs are mean ± SD. *$p < 0.05$ compared to the sham group.

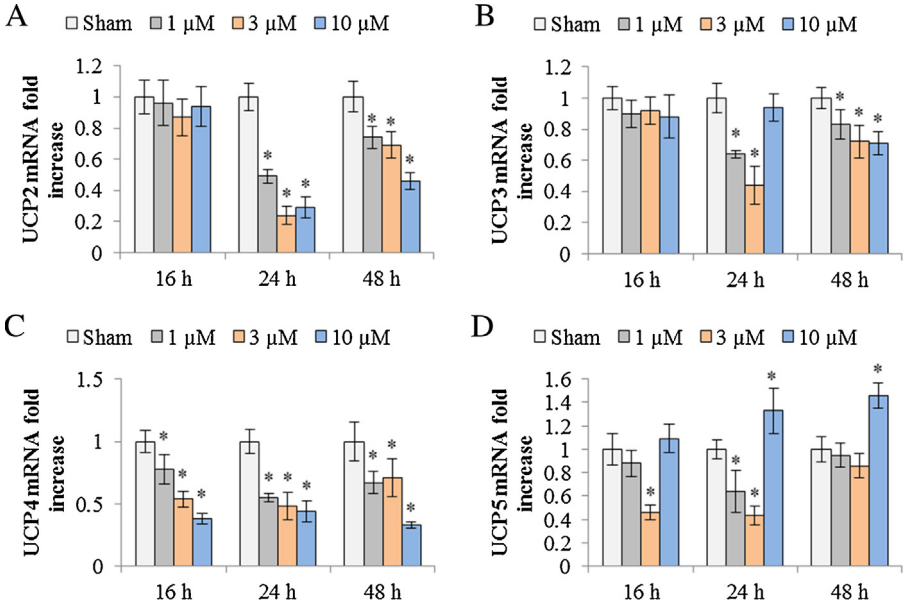

Fig. 2. UCP2 (A), UCP3 (B), UCP4 (C) and UCP5 (D) mRNA levels in hypothalamus after treatment with 1, 3 and 10 μM concentrations of irisin. The graph show normalized mRNA levels for indicated genes. Statistical analysis were performed using one-way ANOVA and bar graphs are mean ± SD. *$p < 0.05$ compared to the sham group.

in mitochondrial biogenesis, endocrine functions, neuroprotection, synaptic message and cell differentiation [24].

Irisin is a newly-defined myosin and is produced by the proteolytic disintegration of the Fibronectin type III domain-containing protein 5 (FNDC5), which is a membrane protein that response to the exercise [11]. The peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) level that increases during exercise stimulates the FNDC5 transcription from the muscle tissue and increases the irisin level in circulation [11,43]. Clinical studies have reported that increased circulating levels of irisin after acute or chronic exercise [2,31,61]. It is assumed that the irisin mediates some of the useful effects of the exercise. The most important role of the irisin is triggering the brown adipose tissue development [6]. Zhang et al. [71] suggest that irisin can probably prevent obesity and related type 2 diabetes by stimulating expression of white adipose tissue browning-specific genes (especially UCP1) via the p38 MAPK and ERK pathways.

Irisin is mainly synthesized in the muscle tissue; however, it has been shown that it also exists in cerebrospinal fluid cerebellum purkinje cells, intercellular nerve endings and neuron and neuroglia [7,11,22,46]. Zhang et al. [70] reported that central irisin administration significantly increases the locomotion and metabolic activity. Brailoiu et al. showed that after the irisin treatment, cytosolic Ca^{2+} concentration and neuronal depolarization increased in nucleus ambiguus neurons [12]. It has been shown that the *in vitro* neuron cell differentiation of the FNDC5/irisin is active in neurogenesis and hippocampal cell proliferation [28,39] but its role in CNS is not clear yet. When the effects of the irisin on different areas in the CNS and the UCP1 are considered, it is assumed probable that it has an effect on the UCP expression in