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Is irisin really a neuroendocrine (f)actor?

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Abstract

Irisin was identified as a peptide hormone in 2012. The most important known physiological effect of irisin is that it activates uncoupling protein 1 and converts white adipose tissue to brown adipose tissue. Due to this effect of irisin on adipose tissue, it was thought that it may be closely related to obesity, feeding behavior and energy expenditure, and interest in research in this direction has increased. Later studies revealed that irisin, beyond its known effects, also influences the reproductive, nervous, cardiovascular, and excretory systems. Recent studies have determined that irisin has anti-oxidant, anti-inflammatory and anti-apoptotic properties, and it has been reported that pathologies such as obesity, endocrine and metabolic diseases, Alzheimer's disease, chronic kidney disease, cardiovascular diseases, atherosclerosis and cancer may be associated with changes irisin levels. The fact that irisin is expressed in different tissues other than muscle and fat tissue and exhibits autocrine and endocrine functions, as well as being expressed in different regions of the brain and participating in neuroendocrine processes in these regions, brings to mind that irisin may be a new neuroendocrine factor. In this review, we present information that will constitute evidence that irisin is a real neuroendocrine factor.

Introduction

In 2012, Boström and colleagues identified a new peptide, called irisin, that is released from skeletal muscle. They showed that irisin is a peptidergic hormone formed by the loss of 94 amino acids of fibronectin type III domain containing 5 (FNDC5), which has 206 amino acids and is released from muscle tissue during exercise [1]. Irisin is secreted by muscle tissue, in addition, it has also been reported as a new adipokine with important autocrine and endocrine functions [2]. It has also been shown that irisin is widely found in various other tissues, such as the heart, brain, liver, kidney, lung, spleen, skin, glands, adipose tissue and nervus system, in addition to muscle tissue [3,4]. There is no specific receptor identified for irisin, however, recent studies have demonstrated that irisin exerts its effect on fat cells and osteocytes by binding with the highest affinity to $\alpha v/\beta 5$, a member of the αv integrin family [5]. It is also known that irisin exerts its effects by activating AMPK-mTOR, PI3K/Akt [6], protein kinase p38, MAP kinase and ERK-MAP kinase [7] and ERK signaling pathways [8] in different cell types. Irisin have some well-known effects including increasing thermogenesis and energy expenditure by mediating the browning of white adipose tissue (WAT), thereby protecting against diet-induced obesity [1]. In addition to effects of irisin on fat metabolism and energy expenditure [9], it may also have effects on feeding behavior [10], the reproductive system [11] and other physiological functions [12,13].

Effects of irisin

Energy balance and expenditure

One of the known important effects of irisin is that it promotes transformation of WAT into brown adipose tissue (BAT), causing an increase in heat production and energy use in the fat tissue [1]. Exercise is known to cause an increase in irisin levels. In addition, irisin levels increase in obese individuals when they spend resting energy [14]. Depending on the effect of irisin on energy consumption; it contributes to reduction of body weight and thus has a positive effect on insulin sensitivity [15]. Slightly elevated irisin levels due to exercise lead to increased energy expenditure without any change in physical activity or food intake. As a result, body weight is controlled and blood glucose levels are balanced [16]. Irisin enables the activation of a specific protein called mitochondrial uncoupling

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protein-1 (UCP1) or thermogenin, in BAT [17]. This role of irisin on UCP1 levels in both WAT and BAT, affecting food consumption and weight gain, is important in obesogenic processes [9,10].

Feeding and obesity

Obesity is a multifactorial pathology that occurs when the energy intake into the body exceeds the amount of energy expenditure and results in excessive weight gain [18-21]. Excessive accumulation of WAT in the body and high body mass index (BMI) are known to be among the most important indicators of obesity. In fact, in healthy individuals, WAT plays a significant role in metabolism and energy homeostasis, but an excess of WAT can lead to disruption of energy balance, altered adipocyte homeostasis, excessive lipid storage, and changes in metabolic setpoints [22]. While some studies reported a positive correlation between serum irisin levels and BMI and body fat mass [23], others could not find this positive association [24]. Furthermore, a recent study has reported a decrease in this process [25]. One of the most important effects of irisin is that it causes browning of WAT [1]. The browning mechanism is carried out through peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1alpha (PGC-1α)/fibronectin type III domain-containing protein 5 (FNDC5, precursor to irisin) [26]. Irisin exerts this effect by increasing the level of UCP1 [1]. It shows that the distribution of UCPs in tissues has effects on functions such as mitochondrial function [27] neuronal cell survival [28], hormone secretion [29] and oxidative phosphorylation [30]. Previous findings from our laboratory have shown that different UCPs may display different functions depending on their distribution in different regions of the brain [31,32]. Current evidence in the literature suggests that although irisin increases food intake, it may be an important factor in preventing obesity because it promotes energy use and stimulates the browning of WAT.

Reproduction

In mammals, although the relationship between metabolism and reproductive function is well known [33,34], an association between irisin and reproduction is not clear. Irisin is an adipo-myokine that has recently attracted great attention due to its relationship with reproductive functions. However, there is still no correlation between the findings regarding the effect of irisin on the secretion of pituitary-hypothalamic-gonadal axis hormones and reproductive functions. One study showed that irisin can play a role in the central regulation of reproductive behavior and also reduces testosterone levels by suppressing LH and FSH secretion [11]. Another study was reported that infusion of irisin improved sexual behavior, sperm morphology, sperm motility, and decreased fat-induced testicular damage in HFD-fed rats, but no significant changes in FSH, LH, and testosterone levels were found [35]. In another study in a similar experiment model, it was revealed irisin administered intraperitoneally increased the LH and FSH levels in the blood plasma [36]. Poretsky and colleagues determined that irisin significantly upregulated CYP19A1 mRNA levels and they put forward that this may directly affect the expression of the genes important for ovarian steroidogenesis and female reproduction [37]. It has been shown that irisin reverses paroxetine-induced hyperprolactinemia and improves decreasing testosterone levels [38]. It has been reported that irisin plays a role in the timing of puberty onset in female mice via a centrally mediated mechanism [39] and it acts as a trigger for the activation of the hypothalamic neuronal network monitoring the onset of puberty [40]. Irisin levels in girls with central precocious puberty (CPP). These findings were taken to suggest that increase irisin levels may be used as a marker of CPP [41]. As can be seen from the current literature, although there are several studies investigating the relationship of irisin with reproductive functions, there is still no consensus on the effects of irisin on various points. Despite this, it is obvious that irisin has positive/negative effects on both puberty and the hormones in the hypothalamic-pituitary-gonadal axis and is/will be involved in this process as a neuroendocrine factor.

Other effects

Bone loss

Bone turnover is a dynamic process and affected by physical activity, nutrition status and various hormones [42]. Recently, irisin is thought to prevent obesity-related bone loss [43]. In obesity, adipocytes inhibit osteogenic differentiation balance of bone marrow mesenchymal stem cells (BMSCs) [44]. Irisin reduced obesity-induced bone loss by blocking production of interleukin secretion from adipocytes [45]. Inhibition of adipocyte IL6 secretion by irisin is also mediated by downregulation of the TLR4/MyD88/NF-κB pathway. By inhibition the activation of the TLR4/MyD88/NF-κB pathway, irisin reduces IL-6 secretion in adipocytes to increase the osteogenesis of BMSCs [46].

Cardiac injury

Irisin binds to the receptor integrin αV/β5 to alleviate cardiac injury and prevents cardiac damage by maintaining musculoskeletal homeostasis via integrin αVβ5 [47]. This adipo-myokine has a protective role against cardiac damage caused by diabetes-related cardiomyopathy and mitochondrial damage in cardiomyocytes. This protective effect is mediated through cGAS/STING [48], which is involved in the pathophysiology of cardiovascular diseases in the presence of innate cellular immunity, and through the activation of mitochondrial ubiquitin ligase. Inhibition of inflammatory aging is another mechanism of its protective effect in cardiovascular disease [49]. Irisin increases the proliferation and migration of cardiac myocytes and endothelial cells by inducing the ERK1/2 pathway [50]. Via the ERK1/2 pathway, irisin improves cardiac microcirculation and reduces oxidative stress. It induces relaxation responses in the aortic blood vessel [51].

Cognition

It has been suggested that irisin has effects on the nervous system and improves cognitive functions, particularly learning and memory [52]. It has been observed

that irisin expression is reduced in individual with brain damage, and irisin supplementation significantly improves brain functions and memory [53]. A strong link has been found between irisin levels and episodic memory and general cognition in individuals at risk of dementia [54]. A positive relationship has been observed between irisin levels and neurocognitive performance in obese patients with Alzheimer's Disease [55]. There is an important association between blood irisin levels and cognitive disorders [54]. In addition, irisin prevents neuronal damage by supporting neurogenesis, reducing the level of some proinflammatory cytokines, and reducing oxidative stress. It appears that irisin has positive effects on the nervous system [56].

Cancer

Irisin reduces cancer cell division and prevents cell proliferation [57]. Huang et al. suggested that irisin causes cell cycle arrest in the G(2)/M phase, thus preventing glioblastoma cell proliferation and invasion [58]. Irisin receptors inhibit the growth of cancer cells by activating AMPK and inhibiting mTOR expression [6]. Therefore, the irisin shows antitumor properties by affecting tumor tissues.

Blood pressure and vascular calcification

There is a negative relationship between circulating irisin level and blood pressure. For example, it has been observed that irisin levels decrease as blood pressure increases in preeclampsia, dialysis patients, hypertensive diabetics [59]. Irisin affects the morphology and growth factors of the thoracic aortic walls and activates the smooth muscle cells in the thoracic aortic layers. Irisin strengthens the thoracic aortic wall by increasing the elasticity of its wall. Once it was revealed that irisin could be a determinant for vascular calcification, it was thought that irisin could provide protection against risk factors for vascular calcification such as kidney diseases, diabetes and hypertension. Irisin improves phenotypic transformation of vascular smooth muscle cells and vascular endothelial dysfunction. This finding shows that irisin has both protective and predictive role in vascular calcification [60].

Conclusion

Data in the literature show that irisin, secreted from muscle tissue during exercise, participates in many more physiological functions in the body than just mediating energy balance and browning of WAT. Additionally, in clinical studies, changes in irisin levels have been associated with many pathologies, especially metabolic diseases such as obesity. These data indicate that irisin will be a very remarkable agent for researchers in the future. Taken together, the evidence in the literature would not be wrong to say that irisin may be a real neuroendocrine (f)actor, as it has active roles both peripherally and at central levels such as the hypothalamus.

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