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Irisin and its physiological effects on metabolic processes in the human body

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ABSTRACT

Irisin is a newly discovered hormone. It is released from skeletal muscles during an exercise, which primarily increases peroxisome proliferator–activated receptor gamma co-activator (PGC-1α) expression in cardiac and skeletal muscles. In addition, it enhances several metabolic parameters, such as insulin sensitivity and signaling, initiates AMP-activated protein kinase, phosphorylates PGC-1α, and produces fibronectin type III domain–containing protein 5, which in turn produces irisin. It is distributed throughout the body and has a physiological effect on several tissues and organs, performing several functions. Moreover, It plays roles in the browning of white adipose tissues, which release energy stored as heat and thus maintain the body's balance, and in insulin resistance, maintaining body mass and thus reducing obesity. Therefore, studying the expression and physiological function of irisin may provide insights into its use as a treatment for many diseases, such as type II diabetes, obesity, and heart diseases. This article reviews progress in research on the role of irisin on the physiological state of humans.

Introduction

Discovery

The function and mechanism of action of irisin during a physical exercise has attracted considerable interest since it has been discovered as a myokine with clinical implications related to energy balance [1].

Structural Feature

Increase in the expression of fibronectin type III domain–containing protein 5 (FNDC5) and its cleavage induce irisin secretion [2]. Exercise-induced muscle contraction is the primary trigger of irisin release, enhancing the transcription of peroxisome proliferator–activated receptor gamma co-activator (PGC-1α), which stimulates the expression of FNDC5, which in turn promotes the release of irisin from the extracellular domain of FNDC5 [3].

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Biological Functions

Irisin has many functions, such as regulating energy metabolism [4], improving muscle–bone connections, and reducing insulin resistance (IR) [5]. In adipose tissues, irisin is considered not only a myokine but also an adipokine. It may stimulate white adipose tissues, demonstrating its potential role in protection from various diseases, such as obesity [6]. Irisin may play an important role in many physical process in the human body and is an essential therapeutic target for many diseases [1].

Chemical Structure

Chemically, irisin is a component of the cellular membrane protein FNDC5, which comprises a fibronectin III domain and C-terminal domain. Irisin/FNDC5 consists of 209 aa residues with 29 aa N-terminal end; 94 aa residue of fibronectin type III domain; a linking peptide containing 28 aa residues; a 19 aa residue trans membrane domain; and a

cytoplasmic domain consisting of 39 amino acid residues [7]. The structure of irisin is crystallographic and comprises a fold similar to the folds in fibronectin type III domain proteins. The crystal figure of irisin shows a homologous structure with fibronectin III domains because it consists of an N-terminal domain residues (30–123 aa) with C-terminal tails consisting of 124–140 residues [8]. Compared with other forms of fibronectin type III domain, irisin constitutes a continuous β-sheet dimer, which is involved in the activation and signaling to receptors. The irisin dimer core is formed by the interactions of β-sheets, and 10 backbone hydrogen bonds mediate two interacting four-stranded β-sheets. Irisin consists of (112) amino acid composed of (94) amino acid residue extracellular fibronectin type III domain and is cleaved from the C-terminal end of FNDC5[8], having a molecular weight of approximately 12 kDa [9].

Regulation of Production and Release

Irisin synthesis and secretion are induced by exercise, during which PGC-1α, which can control various genes in response to nutriment and physiological activity, is overexpressed in skeletal muscles, brown tissues, and cardiac and liver tissues [10] (Figure 1). Exercise increases the expression of PGC-1α chiefly in cardiac and skeletal muscles and enhances several metabolic parameters, such as insulin sensitivity and signaling and induces AMP-activated protein kinase (AMPK) activation, PGC-1α phosphorylation, and FNDC5 production, resulting in the cleaving of FNDC5 and subsequent production of irisin [7]. Irisin raises the rate of uncoupling protein-1 and browning of white adipose tissues, thereby improving thermogenesis and the energy consumption of adipose tissues [11].

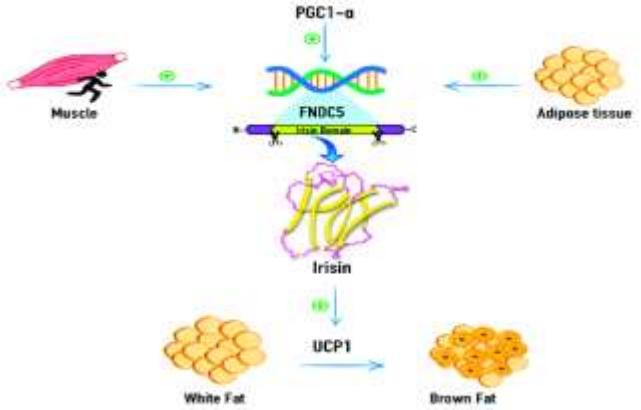

Figure (1): Regulation of Irisin Synthesis and Release **[12]**.

Effect of Irisin as a Metabolic Regulator

Irisin as an adipokine

Two types of adipose tissues (white and brown) can be found in the human body and have distinct functions. White adipose tissues consist of triglycine, which is considered the main component, contributes to the protection of the human body, and maintains temperature. By contrast, brown adipose tissues promote and dissipate energy in the form of heat, thus maintaining balance in body temperature [13]. Bright cells are thermogenic (brownish white) or beige adipocytes derived from white adipose tissues [14].

White adipose tissue cells can transform from energy-storing cells to energy-dissipating cells, maintaining balance in the entire body's energy expenditure. Thus, these cells play a role in the treatment of many diseases, including metabolic disorders and obesity [1]. Exercise promotes the proteolytic cleavage of FNDC5 and subsequent irisin production by inducing the expression of PGC-1α. Irisin circulates to fat tissues and induces the transition of white adipose tissues to brown adipose tissues [15]. In vitro experiments revealed that irisin is produced in human preadipocytes and 3T3-L1 adipocytes [16]. The levels of the irisin precursor PGC-1α found in fat tissues are higher than those found in muscles after exercise and are associated with the irisin secretion [17].

1- Irisin as a myokine

The skeletal muscle is considered the largest organ in the body and is well-known for its mechanical functions in movement and posture. In addition, it plays an active role in the secretion of physiological factors. Skeletal muscles are produced, expressed, and secreted in the form of peptide and act as myokines [18], which are interrelated in osteogenesis and fat browning [19] and in endothelial function, fat oxidation, and myogenesis [1]. They are secreted by stimulation from muscle contraction [18].

Additionally, information on the metabolic functions of skeletal muscles remains incomprehensive. Irisin stimulates the uptake of glucose by skeletal muscles, promotes AMPK phosphorylation, and inhibits AMPK-blocked glucose uptake [20]. Muscle mass is the principal predictor of high levels of circulating irisin in humans [16], and decrease in age-related muscle mass may result in low levels of circulating irisin in adults [21].

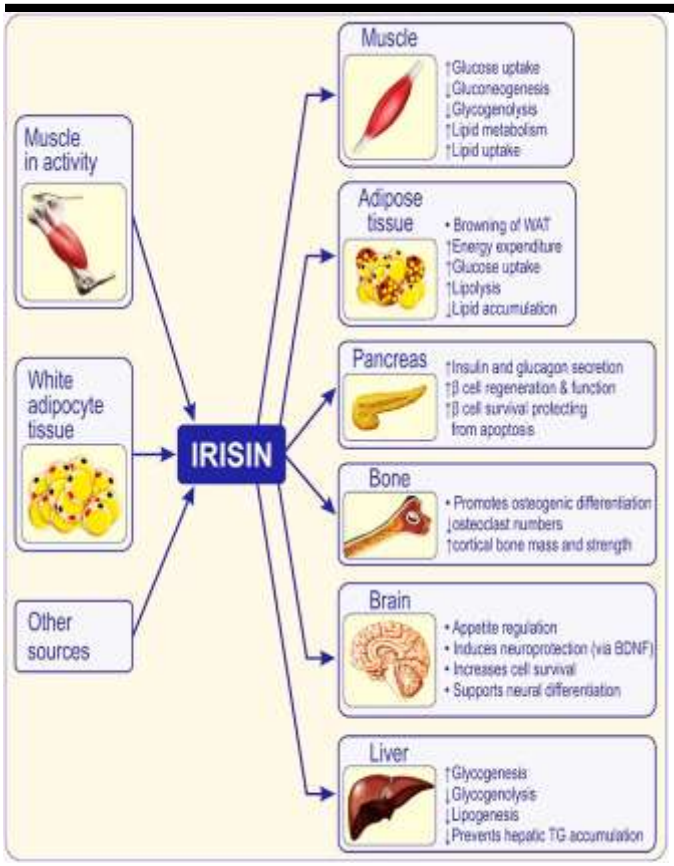

Figure (2): Effect of irisin released from muscle and adipose tissues on metabolic processes in the body [22].

2- Effects of irisin on bones

Physical exercise has a beneficial effects on bone metabolism [23], and intense exercise can stimulate the release of irisin [24].

Within 30 min after an intense exercise, young healthy adults' circulatory irisin concentrations increases considerably [25].

Furthermore, running for 40 min can increase serum irisin concentration in cold (−5–5 °C) or hot (21–25 °C) environments [26]. Physical fitness is an important factor in determining irisin level [24]. Irisin concentration in athletes is positively associated with bone strength and mineral content in the bones. In former athletes with low physical activity, irisin leads to gradual bone loss [27]. Some studies have indicated the role of irisin in improving metabolic processes in the bones, such as enhancing bone mass and stimulating and improving osteoblasts, in addition to its role in determining bone mineral density [28]. The presence of receptors (integrin αV/β5) for the hormone irisin on bone cells confirms the effect of irisin on bone health [29]. The effect of irisin is either direct by increasing the differentiation of osteoblasts from their primitive form to their mature form through the Wnt/beta-catenin pathway, which is essential to humans, insects, and some species. This pathway regulates basic physiological and pathological processes, such as cell differentiation, programmed cell death, and cell proliferation.

[30]. Wnt/beta-catenin pathway downstream of the bone morphogenetic protein receptor signal is a direct or indirect pathway stimulating brown adipocytes [31].

4- Improving Insulin resistance (IR)

The role of irisin in reduced insulin resistance, glucose homeostasis, and type 2 diabetes mellitus (T2DM) development and whether it can be used as a therapeutic drug for diabetics remain unclear.

In humans, two pathways regulate glucose balance through hormones, directly regulating glucose levels by modulating the uptake, storage, and release of glucose or indirectly regulating glucose levels through interactions among hormones, such as glucagon and insulin. An unhealthy diet rich in calories and physical inactivity promote obesity and cause tissue infections due to imbalance that changes IR and glucose metabolism, promoting the development of T2DM (Gregor, M. F & Hotamisligil.,2011). In several studies conducted on rats when injecting them with irisin, a decrease in IR was observed after being induced by a high-fat diet [1]. Some studies have indicated that compared to healthy individuals, individuals with T2DM have reduced levels of irisin. Possibly due to a lack of PGC-1α expression in the muscles [32]. Choi et al (2013) represented that irisin level decrease low in the blood of patients with T2DM, compared to normal people. This indicates that irisin has an important role in regulating IR it may be an excellent option for use in the treatment of diabetes. Choi et al(2013) studied on the serum irisin level in individuals with new-onset T2DM compared with normal controls of glucose tolerance and revealed that a significant reduce in irisin levels was detected in patientsT2DM group.

5-Irisin and obesity

Obesity is considered one of the problems of the times and a source of concern for most people worldwide because it can lead to several diseases, including diabetes, heart disease, and osteoporosis [33]. Irisin concentration in obese people depends on calorie-restricted diets. This relationship may be accompanied by a clear drop in glucose level in the blood, and irisin can cause large energy loss. To compensate for the lost energy, triglycerides begin to provide energy. Increase in irisin level during abnormal metabolic processes lead to weight loss, improving metabolism [34].

Although exercise and diet control may be considered primitive solutions to reduce weight, they require additional interventions because of their limited effectiveness for many people. Therefore, to reduce obesity and its negative effects on lifestyle, treatment strategies with sustainable effects should be used. Many studies have been conducted on the relationship between obesity and irisin level [35].

Some studies have shown positive results in this relationship, while others have shown negative associations [36].

Most of the studies conducted on irisin agreed that this hormone has a positive role in BMI in men and women, with a higher percentage in men. One of the proposed reasons is the presence of the so-called resistance to irisin, as occurs in leptin, where the latter is secreted by adipose tissue in a low percentage, or it may be a myokine secretion to overcome the damage of metabolic processes that cause weight gain [35].

Obesity and IR depend on the whole body, in addition to muscle and oxidative stress. Irisin may be an indicator of chronic oxidative stress after muscle excretion and injury. Irisin level closely correlates with IR index in obese patients. The role of irisin is considerable after weight loss because it affects body composition, fasting glucose, glucose regulation, and IR. Moreover, weight loss and exercise influence the effectiveness of irisin, which may have a therapeutic role in the treatment of obesity [17].

Bostrom et al. (2012) suggested that the high irisin levels in obese people alleviate obesity and maintain glucose balance in the blood and irisin is a potential therapeutic agent for people suffering from metabolic disorders and other diseases.

Additionally, favorable correlations among body mass, fat percentage, and irisin level have been found. In healthy individuals, muscle cells produce most of the irisin content in the blood. However, in obese individuals, the level of irisin secreted from adipose tissues is higher than in that in the lean state because of increase in total body fat [29].

Irisin as a therapeutic agent

Obesity and diabetes affect millions of people globally and similar to other diseases, such as osteoporosis, metabolic disorders, polycystic ovaries, and heart diseases, lack completely effective treatments. Irisin exert positive effects on organs and tissues [17].

Irisin regulates metabolic processes and reduces metabolic syndrome (MetS) [37], serving as a promising indication for these diseases. MetS is defined as a group of metabolic disorders related to obesity and includes high blood pressure and blood glucose, hyperlipidemia, and abdominal obesity. These disorders lead to many problems, including cardiovascular diseases [38].

Studies have conflicting results on the relationship between irisin and MetS. Some studies have shown that irisin level in children with MetS is low; thus, irisin is a marker of MetS in prepubertal children [37]. However, some studies have indicated that obese people have low irisin levels, which are linked to increase in fasting blood glucose and MetS [39]. One study [40] hypothesized that serum irisin level is a biomarker for MetS development because of the positive link between irisin concentration and some diseases. In addition, irisin concentration is a factor positively associated with total cholesterol. The association of irisin with BMI and fat percentage renders irisan an important therapeutic factor for controlling obesity [41].

In some cases of polycystic ovary syndrome, irisin may be a treatment option despite the contradictory results about body mass and fat percentage. It may be used as a treatment for thyroid problems, osteoporosis, and heart diseases caused by obesity [28], because it is an important factor for controlling weight.

Table (1): Effect of irisin on metabolism and related mechanism

Site of effect	Mechanism
Nervous system	Irisin has an important role in preserving neurons from damage, as well as reducing the effectiveness of some cytokines that cause inflammation in some neurons, in addition to maintaining neurogenesis[42]. Irisin signal generated in the cerebellum is transmitted by a neural pathway to adipocytes via synapses between the medulla and spinal cord[43].
Female reproductive system	Female fertility is presumably influenced by irisin/FNDC5, as total deletion of Fndc5 causes irregular estrous cycles, altered ovarian morphology in mice, decreased plasma levels of estradiol, follicle-stimulating hormone, and luteinizing hormone (LH) [44]**.** In pregnant women, there was increase concentrations of irisin in plasma then lower after birth, and are reduced in preeclampsia and gestational diabetes [45].
Pancreas	The irisin effect through maintaining and regenerating the functions of beta cells in the pancreas, as well as its effect in maintaining glucose balance through its work to increase the secretion of some hormones, the most important of which are insulin and glucagon [22].
Heart	The activation of paraventricular neurons leads to a rise in blood pressure and its development, so the irisin effect in lowering blood pressure and preventing heart disease by reducing the downregulation of para-ventricular nuclei activity [46].
Thyroid gland	Irisin affects thyroid hormones it turns out that irisin has a positive effect on the Thyroid-stimulating hormone (TSH) .while negatively affect with free thyroxin (fT4) and its synthesis is affected in cases of hypothyroidism and hyperthyroidism, so it is considered a metabolic indicator [47]. the FNDC5 gene is may be expressed in thyroid gland cells or the cells have irisin receptors on these membrane cells, which discloses a relation between irisin levels and hypometabolism [48].

Conclusion

Irisin is a promising target for therapeutic interventions and has important implications for the future of metabolic medicine. Continued efforts to elucidate its roles and mechanisms of action are warranted to fully harness its therapeutic potential and pave the way for novel treatment strategies for metabolic disorders

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الإيريسين والتأثيرات الفسيولوجية على عمليات التمثيل الغذائي البشري

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الخلاصة:

الإيريسين هو هرمون تم اكتشافه حديثًا ويتم إطلاقه من العضلات الهيكلية عند ممارسة التمارين الرياضية. وراثيًا، تزيد التمارين الرياضية في المقام الأول من تعبير PGC-1α في عضلات القلب والهيكل العظمي. كما أنه يطور العديد من المؤشرات الأيضية، مثل حساسية الأنسولين والإشارات، ويبدأ بعملية تنشيط البروتين كيناز المنشط AMP (AMPK)، وفسفرة PGC-1α، وإنتاج FNDC5، الذي يقسم FNDC5 وينتج الإيريسين. ويتم توزيعه في جميع أنحاء الجسم. وله تأثير فسيولوجي على العديد من أنسجة وأعضاء الجسم، إذ يقوم بعدة وظائف. وله دور في تسمير الأنسجة الدهنية البيضاء وإطلاق الطاقة المخزنة على شكل حرارة وبالتالي الحفاظ على توازن الجسم. وله دور في مقاومة الأنسولين، فهو يحافظ على كتلة الجسم وبالتالي يقلل من السمنة. ولذلك فإن دراسة تعبير ووظيفة الإيريسين الفسيولوجي قد تفتح آفاقا عديدة في استخدامه كعلاج للعديد من الأمراض مثل مرض السكري من النوع الثاني والسمنة وأمراض القلب والعديد من الأمراض الأخرى. يستعرض هذا المقال التقدم البحثي حول دور الإيريسين في الحالة الفسيولوجية للإنسان.

الكلمات المفتاحية: هرمون الايريسين، مايوكين، مقاومة الانسولين، الجهاز العصبي، السمنة.