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Review Article

The Problem of Obesity and Asprosin

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Abstract

Background: Obesity is a chronic metabolic disease that causes an increase in the size and number of adipocytes, resulting in quantitative and qualitative changes in cytokine production, contributing to the development of metabolic disorders such as type 2 diabetes mellitus, cardiovascular and oncologic diseases. Asprosin is an adipokine mainly synthesized and released by white adipose tissue during fasting. The contribution of asprosin to the regulation of oxygen-binding properties of blood has implications for the formation of oxygen supply and adaptive reserves in individuals with metabolic disorders.

Keywords: Obesity; Asprosin; Oxygen

Obesity is an excessive accumulation of triglycerides by adipocytes due to increased energy expenditures of the organism. This pathology is considered as a chronic metabolic disease, which causes an increase in the size and number of adipocytes, resulting in quantitative and qualitative changes in the production of cytokines, contributing to the development of metabolic disorders such as type 2 diabetes mellitus, cardiovascular and oncologic diseases [1]. Neurohumoral mechanisms and environmental factors are involved in the formation of obesity, which contributes to the imbalance between incoming and expended energy.

In obesity, adipose tissue remodeling is observed, resulting in impaired adipogenesis, which leads to adipocyte hypertrophy, which stimulates increased production of proinflammatory cytokines. In combination with reduced angiogenesis, adipocyte hypertrophy leads to hypoxia, which promotes necrosis and apoptosis of adipocytes and infiltration of adipose tissue by macrophages. While increased concentrations of pro-inflammatory cytokines disrupt insulin signaling, as a consequence progenitor cells may alter the differentiation pathway from adipogenesis to fibrogenesis, resulting in fibrosis of the extracellular matrix leading to adipocyte size restriction and fat displacement into tissues.

Such factors as sedentary lifestyle, chronic stress, high-calorie diet, eating disorders contribute to obesity. An important factor in the development of this pathology is a violation of the metabolism of hormones: ghrelin, leptin, insulin and others. Insulin affects the absorption of glucose by the cell, in its excess there is an increase in lipogenesis, leading to an increase in adipose tissue.

The hormone ghrelin, consisting of amino acids, synthesized by cells of the gastrointestinal tract, affects homeostasis by increasing hunger and stimulating food intake. When ghrelin levels increase, obesity develops, as patients lack the feeling of satiety and, consequently, overeating occurs.

Opposite to ghrelin acts leptin, which suppresses appetite. A decrease in leptin levels leads to overeating and weight gain. While an increase in its level stimulates inulin secretion and increases lipogenesis [2].

Angiotensin 2 is produced in adipose tissue, which contributes to increased blood pressure and growth factor synthesis leading to myocardial hypertrophy and, consequently, heart failure. With increasing body weight, there is an increase in the concentration of insulin-like growth factor-1, which is synthesized in the liver, cardiomyocytes, connective tissue and stimulates the synthesis of nitric monoxide, which leads to vasodilation of blood vessels [3]. Insulin-like growth factor-1 increases the sensitivity of body cells to their own insulin, while increasing insulin levels decreases its concentration.

In obesity, there is a decrease in the synthesis of adiponectin by adipose tissue, which is responsible for the production of nitric monoxide, which ensures the survival of endothelial cells. These changes affect not only blood vessels but also lymphatic vessels, thereby causing a decrease in lymphoangiogenesis and enhancing the development of lymphedema, which contributes to the deterioration of the drainage and pumping function of the lymphatic system and the development of fatty infiltration around lymphatic vessels, stimulating the release of proinflammatory cytokines [4]. During prolonged inflammatory process, there is an accumulation of active oxidants that affect the vessel wall and destroy its endothelium, which ultimately leads to a decrease in the concentration of nitric monoxide and an increase in the synthesis of proinflammatory cytokines and chemokines, leading to an increase in blood pressure [5].

Obesity leads to fatty liver dystrophy. Adipose tissue releases free fatty acids, dietary lipids, adipocytokines, and inflammatory mediators that are deposited in the liver, pancreas, and connective tissue, resulting in lipotoxicity, which is the cause of IR. Deposition of lipids in the liver leads to the appearance of non-alcoholic fatty liver disease, which is accompanied by inflammatory infiltration, tissue necrosis and its replacement by connective tissue [6].

It is proved that in case of excessive accumulation of fat, there is an accumulation of fatty tissue in the oropharyngeal space, causing compression of the pharynx from the outside and narrowing of the lumen of the upper respiratory tract, leading to hypoventilation of the body, and in some cases to obstructive sleep apnea syndrome and obesity-hypoventilation syndrome [7].

A number of studies have shown that in obesity the concentration of prothrombic and, consequently, antithrombic factors increases, although the concentration of the latter is higher, their activity decreases. IR occurring in obesity is characterized by the opposite effect of insulin on blood coagulation: insulin inhibits platelet adhesion and aggregation and inhibits plasminogen activation, but in obese individuals it loses this ability, which together with the above factors leads to the development of thrombosis.

A significant problem is the occurrence of oxidative stress [8], as its occurrence is stimulated by the lack of antioxidants of natural origin and a decrease in the activity of antioxidant enzymes.

With increasing body mass index, the level of sex hormones such as estrogen, estrone, testosterone increases, increasing the risk of breast cancer [9]. The development of obesity is influenced by thyroid dysfunction, with decreased levels of thyroid hormone there is a decrease in energy expenditure and basal metabolism, which leads to sedentary lifestyle and obesity [10].

Obese patients have progression of knee osteoarthritis, synovitis and varicose veins. It has been observed that as body weight increases, the severity of the course of osteoarthritis increases [11]. Despite the fact that adipose tissue secretes a large amount of estrogens, which increase bone mineralization, fractures in overweight individuals are more common, because these individuals have a higher chance of mechanical damage and have metabolic disorders [12].

Thus, the above indicates that the problem of obesity is urgent and its solution is important for improving public health, as well as preventing the development of various metabolic disorders and cardiovascular diseases.

Asprosin is a novel glucogenic adipokine mainly synthesized and released by white adipose tissue during fasting. This hormone is encoded by two exons (exon 65 and exon 66) of the fibrillin 1 (FBN1) gene. asprosin mRNA is produced independently of the internal promoter at the 3'-end of the FBN1 gene, allowing regulation independent of fibrillin synthesis and more economical with respect to cellular resources [13]. Fibrillin is a major component of extracellular microfibrils that are distributed throughout connective tissues. This hormone is synthesized from the C-terminal region of the FBN1 gene, which encodes profibrillin, which is cleaved by the protein furin. In response to fasting with a low glucose diet, asprosin is released as a secreted factor from white adipose tissue and transported to the liver to mediate the release of glucose into the bloodstream. By binding to OLFR734, an olfactory G-protein-

coupled receptor in liver cells, this hormone induces a glucogenic effect that regulates glucose homeostasis. The FBN1 gene has been shown to be abundantly expressed in human skeletal muscle mesoangioblasts, osteoblast-like cells and mesenchymal stem cells [14].

Asprosin plays an important role in the regulation of the functioning of the central nervous system, peripheral tissues and organs. It is involved in appetite formation, glucose metabolism, insulin resistance, and cell apoptosis. As a glucogenic peptide, asprosin enhances glucose release from liver cells by binding to the OLFR734 receptor and leading to activation of the G-protein-cAMP-PKA pathway as it enters the blood-brain barrier, and also acts as an orexigenic peptide that enhances food intake through activation of AgRP neurons in the hypothalamus [15]. Asprosin is thus involved in maintaining the body's energy homeostasis. Its concentration is elevated in obesity and related diseases. However, administration of antibodies to asprosin normalizes its levels and reduces food intake in obese mice, making it a significant factor in obesity and related diseases.

Asprosin acts on the olfactory G-protein-coupled receptor and potentially on other receptors, on hepatocytes and expressing agouti-related peptides, stimulating glucose and appetite secretion, respectively. Studies of the growing body have shown that this hormone has a number of effects on various metabolic tissues. Asprosin can attenuate insulin signaling and promote insulin resistance in skeletal muscle by increasing endoplasmic reticulum inflammation and stress. Importantly, this hormone may also play a protective role in cardiomyocytes exposed to hypoxia. In clinical studies, it has been reported that an increase in asprosin concentration was observed in obesity, type 2 diabetes mellitus and some other cardiovascular diseases associated with obesity [16].

An association between adipokines and neuropathic pain has been demonstrated, and it was found that administration of asprosin significantly reduced both mechanical and thermal hypersensitivity, reflecting an antihypersensitivity effect, while the most effective time of asprosin effect on pain threshold was observed 60 min after its administration [17]. This hormone inhibits lipid accumulation in macrophages and reduces atherosclerotic burden in mice [18].

White adipose tissue is the dominant source of this multifunctional adipokine, but other tissues can also produce asprosin, such as salivary glands, pancreatic B cells, and cartilage. This factor plays an important role in the metabolic process, induces glucose production in the liver, and affects appetite. Clinical and preclinical studies have shown dysregulation of circulating asprosin levels in several metabolic diseases, including obesity, type 2 diabetes mellitus, polycystic ovary syndrome, nonalcoholic fatty liver dystrophy, and some types of tumors.

It has been found that decreased asprosin concentration in patients with SOVID-19 leads to decreased metabolic activity and consequently inhibits energy production, which increases oxidative stress in patients [19]. Other studies have found that asprosin in increased concentrations affects the life span of cardiomyocytes by preventing their hypoxia-induced death by enhancing mitochondrial respiration and proton leakage [20].

Asprosin levels have been found to be elevated in individuals with coronary heart disease, which is associated with the effect of this hormone on the development of insulin resistance and dyslipidemia [21]. In addition, it was found that the concentration of this peptide in plasma increases with increasing coronary lesions [22]. It should be noted that in patients with non-alcoholic fatty liver disease, an increase in the concentration of asprosin has been observed [23].

Asprosin causes and even exacerbates vascular endothelial dysfunction, suggesting that it is an early marker of blood vessel dysfunction [24]. In a study, Chinese researchers [25] found a correlation between asprosin levels and obstructive sleep apnea syndrome and found that there was a positive correlation between this hormone and the severity of this disease: there was a positive correlation between asprosin and body mass index, fasting glucose and triacylglyceride levels, and IR; a negative correlation was observed between this hormone and cholesterol and high-density lipoproteins.

In a study of patients with coronovirus infection (when oxygen saturation decreased below the critical value of 70-74%), increased release of asprosin was observed [26]. These changes in coronovirus and diabetic patients as a function of their oxygen saturation suggest that this hormone functions as a “metabolic oxygen sensor”.

We have previously shown that an increase in asprosin concentration is accompanied by changes in hemoglobin affinity for oxygen and synthesis of the gas transmitters nitrogen monoxide and hydrogen sulfide in individuals with different body weights [27]. According to our study [28], plasma concentration of asprosin in

insulin-resistant individuals with normal body mass index (20.95 (18.87; 25.11) p < 0. 05, pmol/l) was significantly higher than in healthy subjects (8.6(8.0; 9.2) pmol/l), and in overweight and obesity I degree this parameter had even higher value 40.26 (37.36; 41.26), p < 0.05, and 66.81 (62.33; 69.6), p < 0.05, pmol/l. In insulin-resistant subjects with obesity of the first degree with increased content of asprosin, there was a decrease in the degree of oxygen saturation of venous blood and its partial pressure in comparison with subjects with normal and excessive body weight. An increase in the index of hemoglobin affinity to oxygen p50real was revealed in insulin-resistant subjects with normal body weight in comparison with healthy subjects, which is characterized by a shift of the oxyhemoglobin-oxygen dissociation curve to the right, and a decrease in p50real was revealed in subjects with excess body weight and obesity of the I degree. The occurring shift of oxyhemoglobin dissociation curve to the left reduces oxygen mass transfer to tissues, which reflects decompensation of oxygen homeostasis mechanisms. Asprosin affects the processes of energy exchange of the organism and, accordingly, its oxygen supply. In these individuals, asprosin, determining the energy-dependent processes of the cell, affects the intracellular oxygen content and, accordingly, the mechanisms of blood oxygen transport, in particular, its oxygen-binding properties. Participation of the hormone asprosin in the regulation of the gas-transmitter system and in the formation of blood oxygen transport mechanisms is important for the formation of oxygen supply, for increasing the adaptive potential in persons with metabolic disorders.

Thus, changes in the activity of the gas-transmitter system (nitrogen monoxide and hydrogen sulfide) in IR with different concentrations of asprosin are important for the formation of blood oxygen transport mechanisms. The contribution of asprosin to the regulation of oxygen-binding properties of blood is important for the formation of oxygen supply and adaptation reserves in individuals with metabolic disorders.

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