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Hormonal function of adipose tissue – the importance of adipokines

Funkcja hormonalna tkanki tłuszczowej – znaczenie adipokin

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Abstract

Introduction. *Despite the historical perception of adipose tissue as primarily a store of excess accumulated energy, the intensive development of knowledge about the physiology of the human body has allowed a broader look at the impact of adipose tissue products on many metabolic processes. A number of adipokines, i.e. biologically active substances synthesized by adipose tissue cells, has been extended for over 20 years, which allows us to see the important role of this tissue in human metabolism, and thus facilitates further directions of development in the field of knowledge about the physiology of the adipose layer.* **Aim**. *This publication summarizes the knowledge about the importance of the most common adipokines. leptin, adiponectin, apelin, visfatin, interleukin-6 and TNF-alpha, which will allow a relatively broad look at the current, comprehensive knowledge in the field of hormonal functions of adipose tissue.* **Materials and methods**. *A review of publications from the years 1993-2021 regarding knowledge in the field of the aforementioned adipokines was made. Articles in selected Internet databases were included. Next, an attempt was made to summarize the overall endocrine functions of adipose tissue.* **Results**. *Adipokines affect a large number of physiological processes in the body. The earliest detected is leptin, which regulates the feeling of hunger, but is also important in the immune system and in carbohydrate and lipid metabolism. The influence of adiponectin, which regulates the influence of many organs, such as the liver, heart, pancreas or skeletal muscles, is well known. Apelin, in turn, is important in the development of cardiovascular diseases, regulates carbohydrate and lipid metabolism, and has an antioxidant effect. Visfatin has a similar effect. In turn, interleukin-6 is a pro-inflammatory and carcinogenic factor. Its higher values have been found in diseases associated with the development of chronic inflammation, such as coronary artery disease or rheumatoid arthritis, and its influence has also been described during the so-called "cytokine storm" during the development of COVID-19. Tumor necrosis factor a has a similar meaning, i.e. pro-inflammatory and carcinogenic.* **Conclusions**. *Over the last decades, a great progress has been made in the field of knowledge about the hormonal function of adipose tissue. Thanks to this, we know that it can affect many chronic diseases, as well as predispose to the development of cancer. Taking into account the increasing percentage of overweight and obese people and the promising results regarding the metabolic functioning of adipose tissue, this topic should be developed in further studies. (Gerontol Pol 2023; 31; 11-18) doi: 10.53139/GP.20233102*

Keywords: *adipose tissue, adipokines, leptin, adiponectin, visfatin, interleukin-6*

Streszczenie

Wstęp. *Pomimo historycznego postrzegania tkanki tłuszczowej jako przede wszystkim magazynu nadmiaru zgromadzonej energii, intensywny rozwój wiedzy o fizjologii organizmu człowieka pozwolił w sposób szerszy spojrzeć na wpływ produktów tkanki tłuszczowej na wiele procesów metabolicznych. Szereg odkrytych w ciągu ponad 20 lat adipokin, czyli substancji biologicznie czynnych, syntezowanych przez komórki tkanki tłuszczowej, pozwala dostrzec istotną rolę omawianej tkanki w metabolizmie człowieka, a tym samym ułatwia dalsze kierunki rozwoju w zakresie wiedzy o fizjologii warstwy tłuszczowej.* **Cel.** *W omawianej publikacji podsumowano wiedzę na temat znaczenia najpowszechniejszych adipokin. leptyny, adiponektyny, apeliny, wisfatyny, interleukiny-6 oraz TNF-alfa, co pozwoli spojrzeć w sposób stosunkowo szeroki na aktualną, całościową wiedzę z zakresu funkcji hormonalnych tkanki tłuszczowej.* **Materiały i metody.** *Dokonano przeglądu publikacji z lat 1993-2021 dotyczących wiedzy z zakresu wspomnianych adipokin. Uwzględniono artykuły wchodzące w skład wybranych baz internetowych. Następnie, podjęto próbę podsumowania ogólnych funkcji hormonalnych tkanki*

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tłuszczowej. **Wyniki.** *Adipokiny wpływają na dużą liczbę procesów fizjologicznych odbywających się w organizmie. Najwcześniej wykrytą jest leptyna, regulująca uczucie głodu, ale także mająca znaczenie w układzie immunologicznym oraz w gospodarce węglowodanowej i lipidowej. Dobrze poznany jest wpływ adiponektyny, regulującej wpływ wielu narządów, takich jak wątroba, serce, trzustka czy mięśnie szkieletowe. Apelina z kolei ma znaczenie w rozwoju chorób sercowo - naczyniowych, reguluje gospodarkę weglowodanową i lipidową, a także działa przeciwutleniająco. Podobny wpływ wywiera wisfatyna. Czynnikiem prozapalnym oraz kancerogennym jest z kolei interleukina - 6. Jej wyższe wartości stwierdzono w chorobach związanych z rozwojem przewlekłego stanu zapalnego, takim jak choroba wieńcowa czy reumatoidalne zapalenie stawów, opisano także jej wpływ w trakcie tzw. "burzy cytokinowej" w trakcie rozwoju COVID-19. Podobne znaczenie, czyli prozapalne i kancerogenne, wykazuje tumor necrosis factor a.* **Wnioski.** *W ciągu ostatnich dekad poczyniono duży progres w zakresie wiedzy o funkcji hormonalnej tkanki tłuszczowej. Dzięki temu wiemy, że może ona wpływać na wiele chorób przewlekłych, a także predysponować do rozwoju nowotworów. Biorąc pod uwagę wzrastający odsetek osób z nadwagą i otyłością oraz obiecujące wyniki dotyczące funkcjonowania metabolicznego tkanki tłuszczowej, temat ten powinien być nadal rozwijany w kolejnych badaniach. (Gerontol Pol 2023; 31; 11-18) doi: 10.53139/GP.20233102*

Słowa kluczowe: *tkanka tłuszczowa, adipokiny, leptyna, adiponektyna, wisfatyna, interleukina-6*

Introduction

Adipose tissue, which is a connective tissue found primarily in the subcutaneous layer and is characterized by excessive development in the case of a greater supply of energy with food than is required, has met with wide interest since prehistoric times. Before the development of scientific methodology allowed the discovery of its detailed metabolic functions, fat was primarily associated with the fact that it develops in people consuming larger amounts of food. For this reason, obese people were perceived as wealthy and of high social status, and the excess of adipose tissue was definitely positively associated [1]. At the same time, already in ancient times, the first indications appeared that the excessive development of adipose tissue may lead to the development of cardiovascular diseases or hinder the functioning of the respiratory system [2].

This trend changed in Western European countries with the development of the industrial revolution in the eighteenth century, which allowed the production of food in previously unknown quantities [1]. It was also then that the first scientific publications on the causes of excessive development of adipose tissue and its negative effects on the functioning of the body began to appear [3]. In the 19th century, the negative impact of being overweight and obesity became common knowledge in all social groups [4].

In recent decades, with the development of global prosperity, the phenomenon of being overweight and obesity has become an increasing medical, but also cultural, social and economic problem. For this reason, its metabolic function met with considerable interest from researchers who looked for it not only as a function of storing excess energy or as a tissue of thermoregulatory importance [5]. One of the milestones in understanding the role of adipose tissue was the discovery of leptin, a "satiety hormone" involved in the long-term control of food intake, produced by adipocytes [6]. Since then, adipose tissue has been the subject of in-depth research, which in turn contributed to the discovery that it is not only an "energy store", but also an active endocrine organ that synthesizes numerous biologically active substances called adipokines. Among them there are numerous cytokines, enzymes and peptide hormones that perform multidirectional biological functions. They participate, among others, in the regulation of appetite, maintaining energy homeostasis, metabolism of carbohydrates and fats, regulation of vascular hemostasis, blood pressure, inflammatory and immunological processes [7].

Currently, adipokines are the subject of constant research, and the family of these substances is constantly expanding with newly discovered compounds. Undoubtedly, knowledge about the functions of newly discovered adipokines becomes extremely important in the context of their future clinical applications, and therefore further research on them is justified [8].

Materials and methods

The article is a review of the latest knowledge on selected, particularly important adipokines: leptin, adiponectin, apelin, visfatin, interleukin-6 and TNF-alpha. Their characteristics summarize the basic knowledge about the hormonal function of adipose tissue. The following internet databases were searched: Cochrane, Pubmed, Science Direct, Scopus, Web of Science and Google Scholar using keywords: adipose tissue, hormones, adipokines, cytokines, inflammation. The work is a summary of original articles, systematic reviews and meta-analyses from 1993-2021.

Leptin

The gene encoding leptin, called OB or LEP, was identified in 1994 and the initial studies in mice proved the participation of the described protein in the regulation of body weight, energy metabolism and food demand. The above-mentioned gene in humans is located on chromosome 7q31.3 and shows the highest expression in adipose tissue [9]. Leptin secretion depends on food intake, total body fat and is proportional to body weight and nutritional status, and on the concentration of hormones that regulate its production: insulin and other pancreatic peptide hormones, corticosteroids and tumor necrosis factor alpha (TNF-alpha) stimulate it, while catecholamines and possibly thyroid hormones reduce it [10].

Leptin is secreted mainly by the white adipose tissue. Its deficiency promotes food intake by increasing the concentration of AgRP and neuropeptide Y in the arcuate nucleus, as well as orexin and melanin-concentrating hormone in the lateral hypothalamus. This leads to the activation of food intake by affecting the decrease in the concentration of pro-opiomelanocortin-regulated transcript as well as cocaine and amphetamine in the arcuate nucleus in the hypothalamus. Leptin also affects the reward and motivation systems for feeding, and acts in the brainstem causing the feeling of satiety. It is secreted pulsatilely and is characterized by a clear circadian rhythm – the concentration of the described hormone increases in the evening and early morning, with a clear increase in secretion at night. In order to maintain its proper concentration and function, regular sleep is necessary, the deprivation of which may reduce its level, and consequently lead to obesity. However, the exact mechanisms of this phenomenon are not known and more research is needed to prove the dependence of leptin secretion on sleep time and its impact on the development of obesity [11].

As a result of many studies, various functions have been assigned to leptin in the human body. This cytokine regulates the hunger center in the hypothalamus, affects angiogenesis by activating the STAT3 signaling pathway dependent on the Janus JAK2/STAT3 kinase, affects the activity of the immune system, and also stimulates the beta islets of the pancreas and sensitizes cells to insulin, regulates glycemia, has a protective effect on tissue and affects fertility, menstruation and pregnancy. However, its best known function is the effect on the metabolism of adipose tissue – it inhibits the synthesis of triglycerides and stimulates lipolysis. Leptin deficiency can be the cause of many metabolic disorders, including those associated with lipodystrophy. It has been shown that the administration of recombinant leptin – metreleptin to patients can bring good therapeutic effects in the case of diseases with a deficiency of the described hormone. In patients suffering from lipodystrophy, after administration of the drug, normalization of glycaemia, triglycerides and HDL cholesterol levels was observed. Administration of metreleptin also reduced appetite and decreased BMI of patients. The described medicinal substance is approved in the treatment of certain diseases associated with lipodystrophy. However, more data is needed to prove its effectiveness in treating other metabolic disorders [12].

Leptin belongs to the group of long-chain type I helical cytokines, and its action is enabled by specific leptin receptors present on cells. In addition to the effect of leptin on energy homeostasis, the presence of the described receptors on all types of leukocytes suggests its participation in the modulation of the activity, proliferation and viability of cells of the immune system. It has been proven that leukocytes themselves are also able to produce leptin. With the participation of exponents of inflammation present in the body, such as IL-1, IL-6 or TNF-alpha, leptin enhances the inflammatory response, increasing the chemotaxis of granulocytes, macrophages, increasing the amount of free oxygen radicals and increasing the proliferation of Th and B lymphocytes. Chronic inflammation associated with metabolic, infectious and autoimmune diseases, on the other hand, may lead to the development of leptin resistance, which may result in obesity and a compensatory increase in leptin concentration, which, as mentioned earlier, enhances the inflammatory response. This leads to the occurrence of a "vicious circle". These facts may be helpful in the future for the use of leptin as a marker and predictor in inflammatory diseases, as well as for the development of therapy related to the action of leptin [13].

Adiponectin

Adiponectin was first described in 1995, attracting considerable attention due to its significant role in the metabolism of many organs. Organs regulated to a greater or lesser extent by adiponectin include: liver, heart, pancreatic β cells, kidneys and skeletal muscles. Adiponectin strongly inhibits hepatic gluconeogenesis by inhibiting genes involved in glucose production. By acting locally in key metabolic tissues, it promotes insulin sensitization. In addition, adiponectin protects against many pathological events in various cells by inhibiting cell death, inhibiting inflammation or increasing cell survival [14].

Adiponectin is the most abundant adipokine in the blood, with levels ranging from 5 to 30 µl/ml [15]. It is secreted mainly by white adipose tissue [16], and its main functions include intensifying the biosynthesis of fatty acids and inhibiting gluconeogenesis in the liver [17]. In addition, it increases glucose uptake in skeletal muscles through signaling pathways, which leads to improved insulin resistance [18].

Obesity reduces adiponectin secretion, and when people lose weight, adiponectin levels increase, which is positively related to a reduction in BMI (body mass index) [19]. For this reason, obesity and obesity-related diseases such as type 2 diabetes are closely related to serum adiponectin levels, and its deficiency is associated with insulin resistance and cardiovascular and inflammation-related diseases [20], as well as increasing risk of atherosclerosis [21].

Abnormal values of adiponectin are found in numerous diseases associated with the development of chronic inflammation. It has been established that patients with rheumatoid arthritis have higher levels of adiponectin compared to healthy individuals [22]. Moreover, on the basis of studies in patients with RA, characterized by the presence of a systemic inflammatory reaction, it was suggested that a significantly elevated level of adiponectin may act not so much as anti-inflammatory, but even pro-inflammatory [23]. This is confirmed by observations on patients with chronic kidney disease, inflammatory nephritis, type 1 diabetes, cystic fibrosis or systemic lupus erythematosus (SLE), where systemic inflammation also develops, and where high levels of adiponectin have also been observed [19].

Apelin

In 1998 Tatemoto and his partners used bovine gastric glandular epithelium cells to identify a 36-amino acid endogenous peptide and ligand of the previously examined G-protein APJ receptor known as apelin. Identical cDNAs were later found in different human tissues – its expression has been confirmed in adipose tissue as one of the adipokins, but also in heart, lungs, stomach, liver, pancreas, uterus, ovaries and the central nervous system [24]. It holds a major role in physiological processes in organism through various pathways and therefore is also a valid part of pathological reactions. It is formed from the inactive 77-amino acid preproapelin, which is then cut by endopeptidases into smaller polypeptide chains, where the most active form is apelin 13, and the most common form is first described apelin 36. Biologically active forms are later broken down by ACE2 - an enzyme that converts angiotensin type II into inactive metabolites [25].

Apelin is a significant factor in cardiovascular diseases development as it can regulate blood pressure by taking part in the water and electrolyte management, the neuroendocrine modulation, the immunological processes, angiogenesis, lipid metabolism and possibly more which makes it a source of interest for many scientists. It holds a special role in organism homeostasis as it protects the tissues by activating its signaling pathways.

Visfatin

Visfatin is a cytokine first isolated in 1994 that has been shown to be produced by activated lymphocytes, neutrophils, monocytes, macrophages, hepatocytes, am-

Table I. Apelin /APJ receptor/G-protein protecting mechanisms on cardiovascular system [26]

Factors participating in signaling pathways	Effect obtained	Long-term consequence
PI3K,pAkt, mTOR, NO	⇩ Vasoconstriction, vascular smooth muscle cell proliferation	⇩ PAH, hypertension
pERK1/2, Ca2+	⇩ Vascular smooth muscle cell proliferation	⇩ Myocardial contractility
TGFβ, PDGFβ	⇩ Myocardial fibrosis, liver fibrosis	⇩ Myocardial dysfuncton, liver dysfunction
AMPK	⇩ Glucose uptake, betaoxidation, lipolysis	⇩ Diabetes, hypertension

niotic epithelial cells, vascular endothelial cells, synovial cells, pancreatic beta cells, and visceral adipose tissue cells. The gene encoding this protein is located on chromosome 7q22. It exists in two isoforms: intracellular and extracellular [27]. Visfatin, depending on the site of action, can play the role of a cytokine, enzyme or hormone. It has been proven that high BMI increases its concentration. Based on studies conducted on mice, it is suggested that it may be important in the regulation of insulin secretion, phosphorylation of the insulin receptor, and also affect the expression of many genes related to the work of pancreatic beta cells. Current knowledge leads to the conclusion that visfatin is extremely important in the process of glycemic regulation by affecting the secretion and action of insulin, but its relationship with the compensatory or pathophysiological mechanism of diabetes has not been thoroughly understood [28].

Conflicting data also result from studies examining the effect of visfatin on the metabolism of cholesterol and triglycerides. Most researchers show a positive correlation between the level of the described adipokine and the concentration of HDL and triglycerides. Some authors, however, suggest that the effect of visfatin on the lipid profile is not related to insulin resistance or the content of adipose tissue in the body of patients, but to the participation of the described protein in the synthesis of NAD involved in metabolism [29].

Interleukin-6

Interleukin-6 (IL-6) is another cytokine and adipokine with comprehensive effect regulating homeostasis and metabolism. Through excessive lipolysis and triglyceride release, and a decrease in insulin sensitivity it causes a negative effect on organism and is the object of interest in treatment of many disorders [30]. Higher levels of Il-6 were observed in coronary artery disease, abdominal aortic neurotysm, rheumatoid arthritis, atrial fibrillation and stroke so it can be seen as bad prognostic marker. Genetically inherited reduced signaling of IL-6 protects from cardiovascular diseases and extends lifetime [31].

IL-6/STAT3 signaling notably plays an important role in cancer development. Its oncogenic effect has been confirmed for example in hepatocellular cancer where cancer-assiociated fibroblasts supress the immune system and influence tumor environment using inflammatory factors and neutrophils [32]. Another research shows IL-6/STAT3 participation in breasts cancer. It promotes tumor proliferation, invasion and metastasis in ER+ breast cancer by hijacking estrogen receptor. This pathway is a promising anchor point in further studies for oncological therapies [33]. As it is known, adipose tissue and its produced adipokines are highly associated with cancer. Its inflammatory and pathological effects are one of the causes of greater risk in obese patients.

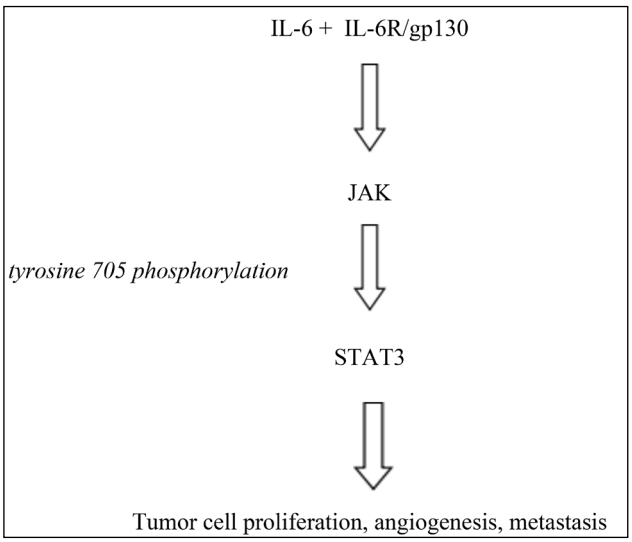

Figure 1. IL-6/STAT3 pathway effect [34,35]

TNF α

Tumor necrosis factor α is a known cytokine connected to inflammatory pathways. It leads to an increase in the intracellular concentration of free radicals and consequently apoptosis, stimulates the liver to produce acute phase proteins, including CRP, increases insulin resistance in peripheral tissues, attracts neutrophils and stimulates phagocytosis. TNF α is also one of the adipokines produced by adipocytes. What is interesting, its overactivity in adipose tissue has been confirmed in obesity, that started to be seen more as inflammatory disease. It affects NADPH oxidase what implies reactive oxygen species (ROS) stimulation. In consequence, NO concentration is reduced and so is the relaxation of vascular smooth muscle cells (VSMC) [36]. TNF α can also inhibit insulin's receptors expression, what leads to hiperinsulinemia and diabetes. Its effect is diverse as one of the most common pathophysiological factor [36,37].

TNF α is also produced in peritumoral adipose tissue what makes it a factor involved in cancer pathogenesis. Adipokines are engaged in non-specific crosstalk with the tumor. Studies show that in oncological patients with cachexia the concentrations of proinflammatory factors in peritumoral adipose tissue, including TNF α, were substantially higher than in patients with weight-stable cancer. TNF α activates ubiquitin proteasome pathway and protein degradation causing the reduction of skeletal muscle mass. It also has an impact on increased lipolysis

and reduction of PPARy activity and whole adipose tissue. Moreover, it can make tumor more malignant through its inflammatory effects, leading to general weight loss and progressive organism weakness [38].

Discussion

Leptin deficiency can be the cause of many metabolic disorders, including those associated with lipodystrophy. Based on research by Y Brown et al., it can be concluded that low leptin levels in patients with lipodystrophy play an important role in mediating severe insulin resistance and metabolic complications. It has been proven that the administration of leptin to patients or mice with lipodystrophy improves insulin sensitivity and reduces the concentration of triglycerides in the body [39].

Adiponectin plays a significant role in the metabolism of many organs, such as the heart, liver, pancreas, kidneys or skeletal muscles, which has been described in many works and studies. At the same time, it shows anti-hyperglycemic, anti-atherosclerotic and anti-inflammatory effects, which aroused great interest and the desire to use this compound in the fight against obesity or insulin resistance [15]. However, the development of therapies based on the function of this compound has been hampered by its complicated regulation, as confirmed by H. Ruan et al. [40]. Both too high and too low levels of adiponectin can have a negative impact on a number of mechanisms in the body and adversely affect tissues, such as muscle tissue, as highlighted by M.P. Krause et al. and R. Ito et al. [19]. In turn, other studies have also confirmed that its incorrect values may lead to an increased risk of insulin resistance, atherosclerosis or chronic inflammation [21,22,24], which is why it is so important to maintain its proper concentration.

TNF-α is a known cytokine associated with inflammatory pathways and at the same time one of the important adipokines produced by adipocytes. It is primarily being studied in obese patients to assess its impact and link to various diseases. It was undertaken, among others, to attempt it as a marker of type 2 diabetes in the RESISTIN study, but adiponectin and resistin were found to be more predictive. However, this does not exclude the undeniable influence of TNF-α on this disease and further research is needed to confirm a more specific role of this adipokine. Moreover, Hotamisligil et al. observed that neutralization of TNF-α increased glucose uptake in peripheral tissues in obese diabetic rats [41]. As a result, targeting TNF-α to reduce hyperglycemia in patients has been considered, however, studies conducted so far have mostly failed to show a beneficial effect of TNF-α antagonism on insulin sensitivity [42].

Conclusions

Over the past decades, there have been great strides in understanding and elucidating new functions of adipose tissue. Thanks to the groundbreaking discoveries of leptin and adiponectin, adipose tissue was recognized as an endocrine organ and its importance in maintaining the metabolic homeostasis of the body began to be sought. It has been proven that in addition to the thermoregulatory and energy storage function, it also secretes many substances of a hormonal nature. Since then, many signaling mediators, called adipokines, have been identified and play an important role in regulatory processes. It is in the change in the level of adipokines that researchers look for a possible cause of chronic inflammation in obesity. This is related to the consequences of this global disease, such as metabolic syndromes, insulin resistance or an increased risk of cancer. Thus, due to the progressing epidemic of obesity and its relationship with the increased amount of adipose tissue in the body, there is an increasingly strong need to get to know this tissue as best as possible. The adipokines secreted by it turn out to be potential tools for the development of specific biomarkers of many diseases, and are also of great importance for the development of new therapeutic strategies. New information about their properties is still being discovered, thus their importance in the context of future clinical applications is constantly increasing. The large number of these compounds and the diversity of their functions should be taken into account, which requires further research, especially in a group of people, and encourages the dissemination of interest in adipokines and the discovery of their properties.

Conflict of interest
None

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