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BASIC ENDOCRINE PRODUCTS OF ADIPOSE
TISSUE – A REVIEW

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Summary


Thorough studies in the recent years have proved that white adipose tissue is not only a depot of triacylglycerols, but possesses to some extent the typical features of an endocrine organ secreting biologically active substances. Changes in size of adipocytes due to reduction or increase in the amount of accumulated fat, modulate and alter their endocrine functions, which is very often linked to various metabolic disorders. Adipose tissue is a source of the hormone leptin – one of the main regulators of energy balance in organism; adiponectin – a hormone reducing hepatic gluconeogenesis and increasing oxidation of lipids in striated muscles; resistin and resistin-like molecules, which are linked to insulin resistance. Adipose tissue cells in obese individuals produce greater amounts of proinflammatory cytokines, soluble adhesion molecules, chemotactic proteins, procoagulatory factors. The aim of this brief overview is to summarize the most important data concerning the main secretory products of adipose tissue, commonly named adipokines.

Key words: adipokines, adiponectin, adipose tissue, leptin, resistin

LEPTIN

The hormone leptin is one of the secretory products of adipose tissue. Its molecular weight is 16 kDa and its structure is encoded in the ob gene. Leptin is the main regulator of energy expenditure and
intake, thus regulating the overall systemic energy balance. Expression of leptin is proportional to size of adipocytes (Maffei et al., 1995; Considine et al., 1996) and to amount of adipose depot (Considine et al., 1996). Besides adipose tissue, synthesis of leptin has been proved in some other tissues and organs: placenta, ovaries, skeletal muscles and stomach (Hoggard et al., 1997a, b; Bado et al., 1998; Wang et al., 1998). Placental synthesis is probably linked to providing the foetus with energy (Hoggard et al., 1997a) and regulates the maternal organism-foetus transfer of energy. Brown adipose tissue also produces leptin (Moinat et al., 1995; Siegrist-Kaiser et al., 1997; Kutoh et al., 1998). Being a hormone, leptin possesses some specific characteristics – its secretion is pulsatile and circadian, with a night secretory peak and a daily decrease (Lofthus et al., 1997). Its main function is regulation of body mass (Pelleymounter et al., 1995). Effects of leptin are due to its influence on some structures of the hypothalamus (arcuate nucleus), which are responsible for appetite and thermogenesis regulation. Signalling pathways of leptin action have being intensively investigated. These include influence on melanocortin and inhibited synthesis of neuropeptide Y – a powerful stimulator of appetite (Adage et al., 2001; Harris et al., 2001). Leptin reaches the hypothalamus by means of specific transport systems that transfer it through the blood-brain barrier. Thus, disorders in transport systems lead to leptin resistance even during hyperleptinaemia (Frederich et al., 1995a).

Exposure to low temperature leads to a decrease of leptin in circulation, which indicates its role in thermoregulatory adaptive mechanisms. These mechanisms include alteration in sympathetic-adrenal activity and influence on β3-adrenoceptors in adipose tissue (MacDougald et al., 1995; Moinat et al., 1995; Peino et al., 2000).

Starvation is a factor leading to decreased expression of the ob gene and to reduced levels of circulating leptin (Har die et al., 1996; Leininger et al., 2000). This way, fasting regulates short-term energy stores (Frederich et al., 1995b; Boden et al., 1996) probably by means of β3-adrenoceptors.

Leptin increases energy expenditure, as shown in experiments with rodents, probably by enhancing thermogenesis through activation of the expression of uncoupling proteins (UCP) in adipose tissue (Scarpace & Matheny, 1998). It stimulates the growth of endothelial cells, angiogenesis (Bouloumie et al., 1998; Sierra-Honigmann et al., 1998) and wound healing (Ring et al., 2000). In obese individuals, leptin promotes aggregation of platelets (Nakata et al., 1999).

Several independent experiments have shown that correction of leptin deficiency in ob/ob mice by injecting recombinant leptin, activated the reproductive axis (sterility is a permanent sign in both genders having this mutation) and restored fertility in both genders (Barash et al., 1996; Mounzih et al., 1997). In both mice and humans (Chehab et al., 1997; Masuzaki et al., 1997) leptin levels are increased in pregnancy.

Scientific data show that hyperinsulinaemia increases plasma levels of leptin and gene expression in white adipose tissue in mice and humans (Saad et al., 1998; Bradley & Cheatham, 1999; Leonardt et al., 1999). Leptin inhibits insulin secretion in experiments with isolated islet cells in mice (Poitout et al., 1998) and in humans (Seufert et al., 1999). It impairs insulin-mediated glucose transport in adipose tissue (Zierath et al., 1998). Non-
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esterified fatty acids decrease the levels of leptin expressed by adipocytes (Shintani et al., 2000).

Leptin has marked immunomodulatory effects on non-specific defense mechanisms. It is evidenced that IL-1 and TNF-α directly increase expression of ob RNA and serum leptin levels in rodents (Grundfeld et al., 1996). On the other hand, the administration of exogenic leptin stimulates LPS-induced phagocytosis and the expression of proinflammatory cytokines (TNF-α, IL-6, IL-12) by mice macrophages. Leptin also promotes the haemotaxis of neutrophils and significantly intensifies the development of oxidative killing mechanisms (Faggioni et al., 1998).

ADIPONECTIN

Adiponectin is a protein with a molecular weight of 30 kDa that circulates mainly in hexameric, oligomeric and less in trimeric form (Innamorati et al., 2006; Ujiie et al., 2006). Full-length adiponectin has a fragment containing a globular domain, with marked metabolic effects on skeletal muscles (Ceddia et al., 2005). Various forms of adiponectin have different metabolic activity depending on the nature of tissue they are acting on (Tsao et al., 2002; 2003). Regulation of adiponectin action is complex and not well understood. It is realized on many levels including formation of different circulating forms, enzyme cleavage and existence of receptor isoforms.

Expression of adiponectin RNA is decreased in a genetically determined obesity model (db/db) as well as in diabetes in mice and people (Hu et al., 1996). Plasma levels of adiponectin are lower in obese diabetic mice and people (Hu et al., 1996; Mori et al., 2001), patients with cardiovascular diseases (Hotta et al., 2000), hypertension or metabolic syndrome (Trujillo & Scherer, 2005). These findings reveal that the decrease of adiponectin is typical of disorders linked to insulin resistance. It is still not known whether it is a reason or consequence of such disorders.

In skeletal muscles adiponectin increases the expression of molecules taking part in fatty acids transport (such as CD 36) and the expression of uncoupling protein 2, which is responsible for the predominant transformation of energy into heat. These effects lead to decrease in triacylglycerols in skeletal muscles, and subsequently to improved insulin action in muscle tissue (Yamauchi et al., 2002).

Adiponectin increases the in vivo expression of peroxisome proliferator-activated receptor-α (PPAR-α), thus promoting fatty acids oxidation, respectively energy expenditure, leading to decrease in triacylglycerols in liver and skeletal muscles and to improved insulin sensitivity (Yamauchi et al., 2003).

Some data state that adiponectin stimulates the glucose uptake in tissues and the production of lactate, but suppresses liver gluconeogenesis (Yamauchi et al., 2002). Adiponectin and some of leptin effects are mediated by the adenosine monophosphate-activated protein kinase, which is probably a common mechanism for the insulin sensitivity improving effect of adipokines (Minokoshi et al., 2002).

Several studies have proved the direct antisclerotic effect of adiponectin (Matsuzawa et al., 2004), due to inhibition of adhesion molecules expression, inhibition of monocyte adhesion to endothelial wall (Ouchi et al., 1999), inhibition of expression of scavenger receptors class A of macrophages thus suppressing the development of foam cells (Ouchi et al., 2001), inhibition of DNA synthesis indu-
Basic endocrine products of adipose tissue – a review

RESISTIN

Resistin is a product of white (Kim et al., 2001; Steppan et al., 2001; McTernan et al., 2002) and brown adipose tissue (Viengchareun et al., 2002; Nogueiras et al., 2003a) with a hormonal activity. It is found in many other tissues and organs – the hypothalamus, the pituitary gland (Morash et al., 2002), adrenal glands (Nogueiras et al., 2003a), pancreas (Minn et al., 2003), gastrointestinal tract (Nogueiras et al., 2003a), myocytes (McTernan et al., 2002), spleen (Milan et al., 2002), white blood cells and plasma (Lu et al., 2002). Resistin is a cysteine-rich peptide hormone. It is a homodimer that is easily transformed in monomeric form (Banerjee & Lazar, 2001). Resistin and resistin-like molecules (RELMs) – polypeptides consisting of 105–114 amino acids, can be classified as a new cytokine family (Rajala et al., 2002). RELMs are three types – α, β and γ, with a different structure in the C-terminus of their polypeptide chains (Steppan & Lazar, 2002).

Expression of resistin is promoted by many factors: growth hormone (Holdaway et al., 2004), dexamethasone (Shojima et al., 2002), androgens (Nogueiras et al., 2003b), hyperglycaemia (Rajala et al., 2002; Shojima et al., 2002), neuropeptide Y. Levels of resistin in circulation increase with age probably because of higher body fat percentage (Oliver et al., 2003).

Inhibitors of resistin expression include insulin (Shojima et al., 2002; Kawashima et al., 2003), thyroid hormones (Nogueiras et al., 2003b), adrenaline (Shojima et al., 2002), starvation (Banerjee et al., 2004), peroxisome proliferator-activated receptor γ (PPAR-γ) (Walczak & Tontonoz, 2002). PPAR-γ is a nuclear receptor essential for adipocyte differentiation and lipid metabolism (Walczak & Tontonoz, 2002). It is a transcription factor regulating the production of proteins, involved in lipid and glucose metabolism and endocrine function of adipose tissue (Walczak & Tontonoz, 2002). Overexpression of PPAR-γ reduces the expression of resistin. This effect is promoted by drugs playing the role of PPAR-γ agonists. They are called thiazolidinediones and are used to reduce insulin resistance (Arner, 2003). Resistin counteracts the effects of insulin and impairs glucose metabolism (Steppan et al., 2001; Banerjee & Lazar, 2001). It inhibits glucose uptake by L6 myocytes via decreasing the activity of cell surface glucose transporters. Injectable application of resistin in mice leads to impaired glucose tolerance (Moon et al., 2003). Application of antiresistin antibodies in mice with diet-induced obesity, insulin resistance and hyperglycaemia leads to decreased blood glucose levels and improved insulin sensitivity (Vernon et al., 2001).

Data about links between resistin, obesity and insulin resistance are controversial. Some studies reveal that obesity positively correlates with the levels of resistin in rodents (Steppan et al., 2001) and humans (Mooreadian, 2001; Degawa-Yamauchi et al., 2003). A correlation between resistin, insulin resistance and hypertension has also been reported (Silha et al., 2003). In castration-induced visceral obesity in rabbit models, the lipid profile and insulin sensitivity were negatively affected (Georgiev et al., 2010). In obese canine models insulin sensitivity and glucose tolerance were impaired (Slavov et al., 2010). In experimental obesity models (ob/ob mice), the expression of resistin in white adipose tissue was...

CYTOKINES

A number of low molecular signal peptides, commonly known as cytokines, are secreted by activated leukocytes and other cells, including adipose tissue cells. In obese individuals, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are produced in great amounts by the white adipose tissue.

Tumor necrosis factor-α

TNF-α is produced mainly by phagocytizing cells of immune system and cells of adipose tissue, especially in abdominal obesity. Synthesis of small amounts of TNF-α has been proved in skeletal and heart muscle (Hamann et al., 1995). TNF-α possesses a wide range of effects. It affects osteoclasts, chondrocytes and fibroblasts, increasing synthesis of prostaglandins and enzymes. Activation of T- and B-lymphocytes, in the course of immune response, is one of its main effects. TNF-α increases the expression of major histocompatibility complex molecules and thus plays the role of an essential link between components of innate and acquired immunity. It activates eosinophils and NK-cells, promotes macrophages to produce interleukin-1 (IL-1) and TNF-α (autocrine stimulation) and neutrophils to produce platelet-activating factor (PAF) (Mohamed-Ali et al., 1997).

In rodents with genetically determined obesity and insulin resistance, adipose tissue levels of TNF-α increase twofold, which proves the link between obesity, diabetes and TNF-α.

In 1993, the direct link between TNF-α and insulin resistance was proved in experimental rodent obesity model by neutralizing TNF-α, which led to improved insulin sensitivity and improved signalling function of insulin receptors (Hotamisligil et al., 1995). It was also shown that different adipose depots produce various amounts of TNF-α. Intraabdominal fat appears to be the main source of this cytokine, while subcutaneous fat produces less TNF-α (Mohamed-Ali et al., 1997).

Interleukin-6

Adipose tissue produces another multifunctional cytokine – IL-6 (Fried et al., 1998). IL-6 is expressed by various types of cells – immune cells, fibroblasts, endothelial cells, myocytes and some endocrine cells (Dimitris et al., 1998) and differs from other cytokines because it acts at a distance from the site of its production. That is why IL-6 is called “endocrine cytokine” (Papanicolau & Vgontzas, 2000). Being pleiotropic and involved in inflammation and the regulation of endocrine and metabolic functions, IL-6 has become a cytokine of great interest. One third of circulating IL-6 is produced by adipose tissue (Mohamed-Ali et al., 1997). Production by visceral adipose tissue is threefold higher than production by subcutaneous adipose tissue. Local and circulating levels of IL-6 increase together with other pro-inflammatory cytokines (TNF-α, IL-1, IFN-γ) in cancer, cachexia and most infections, which are accompanied by insulin resistance (Nielson et al., 1994). IL-6 is the pro-inflammatory cytokine that is most closely linked to insulin resistance and diabetes type 2 (Keru et al., 2003). According to Yudkin et al. (2000), IL-6 is the key factor in interactions between obesity,
inflammation, stress and coronary heart disease.

It was found that Kupffer cells act as mediators in liver acute-phase reaction (Kanemaki et al., 1998). After stimulation with pro-inflammatory cytokine (TNF-α, IL-1), Kupffer cells produce IL-6, which activates hepatocytes. Suppression of hepatic acute-phase reaction is easily reached through elimination of cytokines from circulation (Cheng et al., 1998) or release of IL-10 from Kupffer cells, which altogether reduces local IL-6 production by means of gene suppression (Cheng et al., 2000). Besides, part of IL-6 mediated production of acute-phase proteins is decreased by IL-1 and IL-4, and some of acute-phase proteins can modulate cytokine production of macrophages and monocytes by negative feedback inhibition loop (Soszynski et al., 1996).

Nervous and immune systems are closely linked and act synergistically, that is largely due to the direct innervation of immune organs (spleen, thymus, bone marrow, lymph nodes) by nerves of autonomic nervous system (Vizi et al., 1995). Data show that IL-6 is produced in stress, probably through a β-adrenoceptor mechanism, and plays an active role in stress response. IL-6 is one of most potent activators of the hypothalamic-pituitary-adrenal axis (Mastorakos et al., 1993). It acts mainly by affecting cells synthesizing adrenocorticotropic hormone in the anterior pituitary. The effects of IL-6 on stress system are seen when inflammatory and to lesser extent non-inflammatory stressors act upon the organism (Donald et al., 1994). Glucocorticoids inhibit IL-6 production in vivo and in vitro (Breuninger et al., 1993), which proves the existence of a negative feedback and the central role of this cytokine in interactions between immune and neuroendocrine regulation. So, IL-6 produced by adipose tissue is the link between energy exchange, endocrine, immune and nervous systems.

To sum up, adipokines and cytokines, produced by adipose tissue, affect various physiological systemic functions, which are related to metabolism and energy accumulation and expenditure, and directly influence innate immune mechanisms. The imbalance and increased levels of these signalling molecules in obesity, appear to be the leading pathogenic factors involved in development of many disorders – insulin resistance, atherosclerosis, hypertension, metabolic syndrome and others. Insufficient data in this field of science raise the necessity of further detailed research to clarify many aspects of adipose tissue physiology and pathology, including its endocrine properties and the effects of its secretory products.

REFERENCES


Kanemaki, T., H. Kitade, M. Kaibori, K. Sakitani, Y. Hiramatsu, Y. Kamiyama, S. Ito & T. Okumura, 1998. Interleukin 1beta and interleukin 6, but not tumor necrosis factor-alpha, inhibit insulin stimulated glyco-


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