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BASIC ENDOCRINE PRODUCTS OF ADIPOSE TISSUE – A REVIEW

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Summary

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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

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. Adipocytes and their secretory products play active role in many physiological processes. They are highly active endocrine cells taking part in energy balance and some aspects of immune response. Adipocytes regulate not only the lipid metabolism, but also produce and modify a variety of endocrine factors, cytokines and extracellular matrix components. Adipose tissue is a source of leptin, adiponectin, resistin, resistin-like molecules, proinflammatory cytokines – tumour necrosis factor-α (TNF-α), interleukin-1, interleukin-6 (IL-1, IL-6), inducible nitric oxide synthase (iNOS, NOS2), transforming growth factor β1 (TGF-β1) etc.

This brief overview aims to summarize the most important data concerning the main secretory products of adipose tissue, commonly named adipokines.

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 depots (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 (Loffus *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-adrenoreceptors 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 (Hardie *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-adrenoreceptors.

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; Leonhardt *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-

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-

ced by different growth factors in cultured smooth muscle cells (Arita *et al*., 2002).

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), adrenalin (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. Injective 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 (Mooradian, 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

reduced. Janke *et al*. (2002) did not find any correlation between body weight, insulin sensitivity and gene expression of resistin in humans.

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 phagocyting 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.

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