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Review

Secretory function of adipose tissue

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Abstract

There are two kinds of adipose tissue in mammals: white adipose tissue – WAT and brown adipose tissue – BAT. The main function of WAT is accumulation of triacylglycerols whereas the function of BAT is heat generation. At present, WAT is also considered to be an endocrine gland that produces bioactive adipokines, which take part in glucose and lipid metabolism. Considering its endocrine function, the adipose tissue is not a homogeneous gland but a group of a few glands which act differently. Studies on the secretory function of WAT began in 1994 after discovery of leptin known as the satiation hormone, which regulates body energy homeostasis and maintenance of body mass. Apart from leptin, the following belong to adipokines: adiponectin, resistin, apelin, visfatin and cytokines: TNF and IL 6. Adiponectin is a polypeptide hormone of antidiabetic, anti-inflammatory and anti-atherogenic activity. It plays a key role in carbohydrate and fat metabolism. Resistin exerts a counter effect compared to adiponectin and its physiological role is to maintain fasting glycaemia. Visfatin stimulates insulin secretion and increases insulin sensitivity and glucose uptake by muscle cells and adipocytes. Apelin probably increases the insulin sensitivity of tissues. TNF evokes insulin resistance by blocking insulin receptors and inhibits insulin secretion. Approximately 30% of circulating IL 6 comes from adipose tissue. It causes insulin resistance by decreasing the expression of insulin receptors, decreases adipogenesis and adiponectin and visfatin secretion, and stimulates hepatic gluconeogenesis. In 2004, Bays introduced the notion of adiposopathy, defined as dysfunction of the adipose tissue, whose main feature is insulin and leptin resistance as well as the production of inflammatory cytokines: TNF and IL 6 and monocyte chemoattractant protein. This means that excess of adipose tissue, especially visceral adipose tissue, leads to the development of a chronic subclinical inflammatory condition, which favours the development of insulin resistance and Type 2 diabetes. Obesity is a systemic illness caused by energy transformation homeostasis disorder which results in an increase in the amount of body fat mass. It affects approximately 40% of dogs and 20% of cats. Illnesses which accompany obesity result, to a great extent, from the secretory role of adipose tissue, which is still little known, which should be included when planning treatment of an obese animal.

Key words: adipose tissue, insulin resistance, adipokines

There are two kinds of adipose tissue in mammals: white adipose tissue (WAT) and brown adipose tissue (BAT). There are differences between WAT and BAT in their structure and functions regarding the way in which triacylglycerols are accumulated, the shape and number of mitochondria, the presence of adrenergic nerve endings, and vascularity. In general, it is assumed that the main function of WAT is accumulation of an energy substrate in the form of triacylglycerols whereas the function of BAT is heat generation (Wójcik and Górski 2011).

Nowadays, WAT is not perceived solely as an energy storage reservoir and source but is also considered to be an endocrine gland that produces hormones and bioactive substances called adipokines. Adipokines take part in glucose and lipid metabolism, body's immune response, and are often the cause of obesity-related diseases (Cancello et al. 2004). Considering its endocrine function, the adipose tissue is not a homogeneous gland but a group of a few glands which act differently. In the visceral adipose tissue, secretion of interleukin-6 (IL 6), Tumor Necrosis Factor (TNF), and resistin and visfatin higher than in the subcutaneous adipose tissue are observed, whereas in the subcutaneous adipose tissue, higher concentrations of leptin and adiponectin occur (Kershaw and Flier 2004). It is also important that the visceral adipose tissue secretes substances directly to the portal vein from where they directly reach the liver and have impact on it's function – cytokines released to the liver increase concentration of C Reactive Protein and contribute to hepatic steatosis. The subcutaneous adipose tissue releases leptin and adiponectin to the systemic circulation (Heilbrom et al. 2004, Nedergaad et al. 2005). The studies on the secretory function of the white adipose tissue began in 1994 as a result of discovery of leptin, a hormone produced by mature adipocytes (Zhang et al. 1994). Leptin is sometimes called the satiation hormone, which regulates body energy homeostasis and maintaining of body mass (in Greek leptos means thin, slim). It is protein with a mass of 16.7 kDa created in the mature white adipose tissue. Its biosynthesis and secretion depend on the mass of a body fat and reflect the content of energy resources of an organism. The main factors which have an impact on secretion of the hormone are sizes of adipocytes and mass of the adipose tissue. Concentration of leptin in blood serum in obese individuals is higher but leptin resistance occurs and even administration of exogenous leptin does not reduce body mass (Hukshorn and Saris 2004, Meier and Gressner 2004). Small amounts are also secreted by the placenta, brain, stomach, and mammary gland, and in the liver in birds (Masuzaki et al. 1997, Bado et al. 1998). Leptin biosynthesis is stimulated by insulin,

glucose, corticosteroids, large amounts of fat and carbohydrates in the diet, and regular meals. Secretion of the hormone is hampered by glucagon, catecholamines and low temperature (Konner et al. 2009). It is also known that leptin release is subject to day and night rhythm in humans – it is low during the day and increases at night, which is explained as an effect of not eating (Sinha et al. 1996).

Leptin regulates the metabolism of an organism via the central and peripheral nervous system (Fig. 1). Via the central nervous system, it takes part, as an anorexigenic protein factor, in the regulation of food intake by acting on the hypothalamus where it inhibits secretion of neuropeptide Y and Agouti-related protein, which stimulate appetite. Leptin in the hypothalamus also stimulates the POMC (proopiomelanocortin) system and CARD system (a protein whose transcription is stimulated by cocaine, amphetamine, and corticotropin-releasing hormones), which inhibit appetite, reduce the mass of the adipose tissue and increase the amount of energy expenditure which results in the loss of body mass (Wiesner et al. 1999, Hukshorn et al. 2004, Meier and Gressner 2004). Via the peripheral nervous system, leptin regulates the metabolism of an organism through inhibition of lipogenesis, stimulation of lipolysis, and an increase of oxidation of fatty acids (by stimulating their β -oxidation). The influence of leptin on glucose transformation is still not fully understood and it is now thought that leptin increases glycolysis and the insulin sensitivity of tissues and inhibits hepatic gluconeogenesis. Leptin also stimulates the growth of cancer cells (Horiguchi et al. 2006, Wiwanitkit 2007).

When discussing the biological role of leptin, its counterpart ghrelin should be mentioned. Ghrelin was discovered in 1999 and most of it i.e. approximately 70% is released from the parietal cells of the glands of the body and the fundus of the stomach (Date et al. 2000, Muccioli et al. 2002, Greenman et al. 2004); the rest of it is released in the intestines, the pituitary gland, and the hypothalamus. Leptin is also secreted by cancer cells (Date et al. 2000). Its most important function, however, is to stimulate secretion of the growth hormone but it is also the only hormone acting in the central nervous system which stimulates appetite and inhibits proliferation of breast and prostate cancer cells (Inui et al. 2004).

Apart from leptin, there are other adipokines whose role is still being studied such as: adiponectin, resistin, apelin, visfatin and the cytokines: TNF i.e. a tumour necrosis factor and interleukin-6 (IL 6) (Trayhurn and Wood 2004, Tilg and Moschen 2006).

Adiponectin is a polypeptide hormone with a mass of 33 kDa secreted by adipose cells and it has an anti-

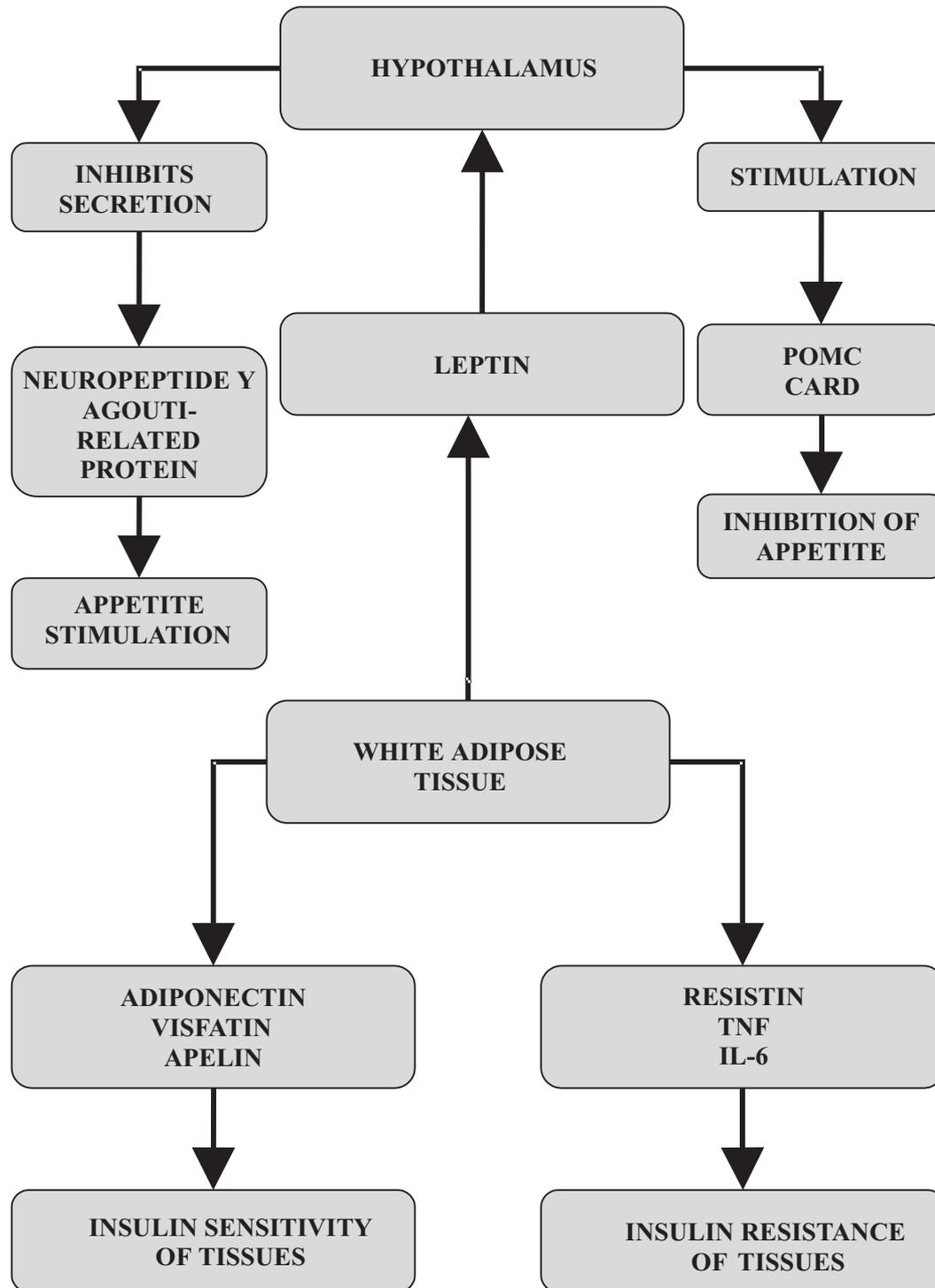


Fig. 1. Schematic of leptin activity.

diabetic, anti-inflammatory and anti-atherogenic function (Cummings and Schwartz 2003, Haluzik et al. 2004). It plays a key role in carbohydrate and fat metabolism. Its secretion is stimulated by insulin and inhibited by TNF and IL-6. Secretion of the hormone increases with reduction of body mass and decreases in the case of obesity (Żurawska and Drzeworski

2004, Kadowski and Yamauchi 2005). Adiponectin increases insulin sensitivity of tissues, stimulates muscle glucose uptake and inhibits hepatic gluconeogenesis, and decreases the concentration of free fatty acids by increasing oxidation. It is anti-atherogenic and anti-inflammatory to the capillary endothelium. It is an antagonist of receptor IL 1 and it stimulates

secretion of IL 10 (Kadowski and Yamauchi 2005, Kozłowska and Kowalska 2006). It is known that adiponectin acts in the same way in humans and cats, which indicates why, as in humans, insulin resistance and Type 2 diabetes occur in cats (yet it occurs very rarely in dogs) (Prostek et al. 2014).

Resistin is a peptide with a mass of 12 kDa produced by adipocytes and macrophages which exerts a counter effect compared to adiponectin (Banerjee and Lazar 2003). Its physiological role is to maintain fasting glycaemia and the effect of its action is formation of an excess amount of white adipose tissue (Steppan et al. 2001). Resistin activates gluconeogenesis, increases glycogenolysis and insulin resistance, and acts as a proinflammatory factor by increasing production of TNF, IL 1, IL 6, and IL 12 (Skowrońska and al. 2005).

Visfatin stimulates insulin secretion and increases insulin sensitivity and glucose uptake by muscle cells and adipocytes. It also has a strong proinflammatory function and activates leukocytes and cytokines and increases adiposeness (Fukuhara et al. 2005).

Apelin probably increases the insulin sensitivity of tissues. Hunger is a factor that inhibits secretion of apelin and, as like in the case of insulin, its concentration increases after a meal (Boucher et al. 2005).

Nowadays, it is also thought that active brown adipose tissue may prevent obesity and insulin resistance (Cinti 2011, Wójcik and Górski 2011).

In 2004, Bays (2004) introduced the notion of adiposopathy defined as dysfunction of the adipose tissue, whose main feature is insulin and leptin resistance as well as the production of the inflammatory cytokines TNF and IL 6, and monocyte chemoattractant protein (Bays 2004). This means that excess of adipose tissue, especially visceral adipose tissue, leads to the development of a chronic subclinical inflammatory condition, which favours the development of insulin resistance and Type 2 diabetes (Siemińska 2007). There is a theory which assumes that the inflammatory reaction in obesity is a mechanism which protects the organism from reaching the point at which excess accumulation of fat impairs the possibility of movement. Accumulation of lipids and adipose tissue is a typical anabolic process stimulated by insulin, whereas release of cytokines is said to start an inflammatory process which initiates catabolic processes resulting in release of lipids and an attempt to inhibit further increase in body mass (Xu et al. 2002). It is still not known for certain what initiates the inflammatory reaction and it is now assumed that there are three most likely causes:

1) the inflammatory reaction is in the adipose tissue in response to adipocyte hypoxia – an increasing fat cell moves away from blood vessels and hypoxia

causes the release of IL 6 (Trayhurn et al. 2008).

2) oxidative stress caused by an increased supply of glucose to the fat cells. Sugar is taken up by endothelium cells of the stroma vessels and increases the production of free radicals in them which damages the cells by triggering an inflammatory reaction (Lin et al. 2005)

3) cell stress theory, which assumes that adipocyte hypertrophy contributes to the impairment of the functions of the endoplasmic reticulum and the activation of stress-sensitive proteins which occur in it (Persegin et al 2003).

TNF within the adipose tissue is secreted by adipocytes and stromal cells and is responsible for causing insulin resistance by blocking the receptors for this hormone, and has an impact on pancreatic beta cells inhibiting insulin secretion (Liu 1998). In a fat cell, TNF inhibits its ability to esterify fatty acids, decreases secretion of adiponectin, and inhibits the transport of glucose to the liver cells and fatty acid oxidation. Approximately 30% of the circulating IL-6 comes from the adipose tissue, and synthesis in the visceral adipose tissue is about three times higher than in the subcutaneous adipose tissue. High concentrations of this cytokine cause insulin resistance – IL-6 decreases expression of insulin receptors, decreases adipogenesis and secretion of adiponectin and visfatin, and stimulates liver gluconeogenesis. It is not yet known exactly how the above-mentioned cytokines block insulin receptors and insulin signal transmission (Kern et al 2001, Ruan and Lodish 2003).

Obesity is a systemic illness caused by energy transformation homeostasis disorder, which results in an increase in the amount of body fat mass above the accepted norm. It occurs as a result of excess filling in of already existing adipose cells with triacylglycerols (hypertrophy) or formation of new ones (hyperplasia) or both phenomena at the same time. Obesity results from a positive energy balance and affects more and more pet animals. According to different authors, dogs and cats with excess body mass constitute approximately 40% and 20%, respectively, of the population in highly-developed countries. The reasons for this phenomenon is, as usual, identical with humans i.e. too high amount of energy supplied, too little physical activity, and nutrition factors related to frequent consumption of snacks. Of course, there are also reasons typical for animals only, such as castration or breed predispositions. Obesity therapy consists in achieving a negative energy balance as a result of a complex dietary treatment combined with physical activity. A study on the possibility of transdifferentiation of adipocytes and a clinical use of this phenomenon is now in progress. It is thought that detailed

knowledge of mechanisms and the working out of a technique for increasing the number of BAT cells at the cost of WAT cells would be an unusually effective weapon for fighting obesity and insulin resistance. It is also worth mentioning that removal of subcutaneous adipose tissue (liposuction), which is a recent trend among people, causes growth of the visceral adipose tissue, a build-up of fat in the liver, and an increase of insulin resistance as the production of cytokines does not change (Perseghin et al. 2003).

Excess accumulation of adipose tissue causes illnesses associated with insulin resistance, especially diabetes in cats and osteoarthritis. Illnesses which accompany obesity result from the secretive role of adipose tissue, which is still little known, and which should be included in the planning of treatment for an obese animal (Prostek et al 2014).

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