Role of ghrelin and leptin in the regulation of carbohydrate metabolism. Part II. Leptin

Rola greliny i leptyny w regulacji metabolizmu węglowodanów. Część II. Leptyna

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Summary

Leptin is produced by mature adipocytes. Its amount correlates positively with the mass of the adipose tissue. Leptin plays a crucial role in maintaining body weight and glucose homeostasis. It is transported through the blood-brain barrier to the central nervous system, where it activates the autonomic nervous system, causing the feeling of satiety and inhibiting appetite. It also acts through central and peripheral pathways, including the regulation of insulin secretion by pancreatic β cells. Leptin may also directly affect the metabolism and function of peripheral tissues. It has been found to play a role in peripheral insulin resistance by attenuating insulin action, and perhaps also insulin signaling, in various insulin-responsive cell types.

Recent data provide convincing evidence that leptin has a beneficial influence on glucose homeostasis. Studies suggest that leptin could be used as an adjunct of insulin therapy in insulin-deficient diabetes, thereby providing an insight into the therapeutic implications of leptin as an anti-diabetic agent. Extensive research will be needed to determine long-term safety and efficacy of such a therapy.

Key words: leptin • adipose tissue • insulin secretion • insulin resistance • diabetes mellitus

Streszczenie

Leptyna jest wytwarzana przez dojrzałe adipocyty. Jej ilość dodatnio koreluje z ilością tkanki tłuszczowej. Leptyna odgrywa główną rolę w utrzymywaniu masy ciała oraz homeostazy glukozy. Jest transportowana poprzez barierę krew-mózg do ośrodkowego układu nerwowego, gdzie aktywuje autonomiczny układ nerwowy wywołując uczucie sytość a hamując apetyt. Ponadto leptyna działa poprzez szlaki ośrodkowe i obwodowe, regulując m.in. syntezę insuliny przez trzustkowe komórki β. Leptyna może także bezpośrednio wpływać na metabolizm i funkcję komórek obwodowych. Stwierdzono, że może zmieniać obwodową insulino oporność, a także szlak sygnałów insuliny w różnych rodzajach komórek wrażliwych na ten hormon.

Ostatnie dane dostarczają przekonywających dowodów na to, że leptyna korzystnie wpływa na homeostazę glukozy. Badania wskazują, że leptyna może być wykorzystana w terapii wspomagającej leczenie insuliną w cukrzycy zależnej od insuliny, co znaczy, że może ona mieć lecznicze zastosowanie jako lek „przeciwcukrzycowy". Potrzebne są jednak szeroko zakrojone badania, aby ocenić długofalowe bezpieczeństwo i skuteczność takiego leczenia.

Słowa kluczowe: leptyna • tkanka tłuszczowa • wydzielanie insuliny • insulino oporność • cukrzyca

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LEPTIN SYNTHESIS

Leptin is a hormone taking part in the energy homeostasis of the body. It is produced by mature adipocytes in an amount which correlates positively with the mass of the adipose tissue. Its production also takes place in other organs. Synthesis of leptin is regulated by the Ob gene which can be found on the chromosome 7q31.3. The localization of the ObR receptors is responsible for the fact that this hormone shows central as well as peripheral effects. These receptors are present mainly in the hypothalamus (long isoforms, l-ObR), although short isoforms (s-ObR) can be found peripherally, including in the liver, intestines, muscles, adipose tissue, pancreatic β cells, heart, lungs and kidneys. Free leptin or a form bound to a soluble isoform of the s-ObR receptor is found in the blood and other body fluids [6,9,15,19,22,41,45].

INFLUENCE OF LEPTIN ON THE ENERGY HOMEOSTASIS OF THE BODY

After being released from the adipocytes, leptin is transported through the blood-brain barrier to the central nervous system, where it acts through other peptides and activates the autonomic nervous system, causing the feeling of satiety and inhibiting appetite. Leptin regulates the energy balance of the body by inhibiting the secretion of neurotransmitters, mostly neuropeptide Y (NPY), which is one of the strongest stimulators of the hunger center (and belongs therefore to orexigenic substances). Leptin also stimulates the release of melanocyte stimulating hormone (MSH), which again inhibits the appetite. Another factor that suppresses the need to eat, influenced by leptin, is the hypothalamic neuropeptide whose transcription is regulated by cocaine and amphetamine (CART – cocaine amphetamine regulated transcript). Additionally, glucagon like peptide 1 (GLP-1) seems to play a role in the regulation of the metabolic effects of leptin.

The most active is the free form of leptin, because only this one can pass through the blood-brain barrier. The soluble form of its receptor determines leptin's tissue bioavailability by inhibiting binding with membrane receptors [20].

Expression and secretion of leptin is increased by insulin, corticosteroids, TNF-α and estrogens, and is decreased by androgens, growth hormone, catecholamines, free fatty acids and PPAR-gamma agonists [4]. These hormones as well as the concentration of ObRa and ObRe receptors' isoforms implicate leptin resistance and sensitivity [31].

LEPTIN *VS.* INSULIN SECRETION AND RESISTANCE

Besides its central activity, many peripheral effects of leptin have been reported, including the influence on insulin secretion and activity as well as adipocyte and muscle metabolism [1,10,12,23]. Experimental studies on the effect of leptin on peripheral tissues often use pancreatic β cells as a model. The presence of receptors for this hormone on these cells implicates that leptin also has an impact on the endocrine activity of the pancreas. Mechanisms of these actions are diverse. Suppression of insulin secretion may result from the effect of leptin on the ATP-susceptible potassium channels. It is also suggested that the hormone antagonizes cAMP signaling, in this way decreasing the increments of cellular cAMP which develop as a response to β cell stimulation (i.e. by GLP-1). Moreover, leptin appears to antagonize insulin secretion by β cells through cAMP-dependant protein kinase A (PKA) as well as protein kinase C (PKC). These pathways might play a role in preventing insulin hypersecretion, although they have not been fully explained yet [11,13,43].

Leptin is believed to suppress basal and glucose stimulated insulin release as well as to decrease the second phase of insulin secretion. It activates the transcription of STST-3. The whole process of receptor activation is controlled by proteins that are dependent on suppressor of cytokine signaling (SCOS) activity [32,44,47].

Additionally, leptin was shown to increase insulin sensitivity and glucose tolerance through stimulation of glucose transport and metabolism in many different tissues. The deficit of its activity may result from secretion disturbances, adipose tissue – hypothalamus transport defects or disorders in the functioning of the Ob-R receptors located in the hypothalamus [17].

There is still much controversy over the influence of leptin on insulin secretion. Results of studies concerning its impact on insulin resistance are also not unequivocal. Some of the discrepancies may be a consequence of the fact that experimental studies are partially conducted *in vitro* on isolated cells, which excludes the central effects of leptin. This is also a potential cause of the differences between the results of studies and clinical observations in humans [27,30].

Leptin's metabolic activity depends on its influence on the lipid and carbohydrate turnover. However, the impact on lipids is opposite to that on the carbohydrate metabolism and similar to the action of insulin. Leptin decreases the antioxidative, lipogenic effects of insulin on the turnover of free fatty acids and decreases the activity of some antioxidative enzymes. In the skeletal muscles it stimulates glucose uptake and in the liver it shows an action similar to that of insulin on glycogenolysis and to that of glucagon on gluconeogenesis.

Furthermore, it was shown that the deficit of leptin or leptin receptors – in Ob/Ob mice as well as in humans – leads

not only to obesity, but also to insulin resistance and glucose tolerance impairment, which are both diabetes risk factors [35].

Experimental studies also revealed that prolonged intravenous leptin infusion causes increased glucose uptake through the increase of tissue insulin sensitivity. An increment of the suppressive insulin activity on hepatic glucose production was also discovered [37]. German and coauthors recently investigated hyperglycemia regulation by the central nervous system, which inhibits hepatic glucose production in insulin deficiency states [7].

Leptin enhances hepatic and muscle insulin sensitivity by decreasing the concentration of triacylglycerols in them, and decreases the amount of insulin which is secreted by the β cells [32,43]. The influence of leptin on the α cells of the pancreas is also significant for maintaining glucose homeostasis. Experiments proved this hormone to inhibit the function of these cells [46].

THE ROLE OF LEPTIN IN GLUCOSE HOMEOSTASIS IN DIABETES

In patients with diabetes leptin resistance on a cellular level as well as decreased leptin penetration to the central nervous system is observed [16,38]. Additionally, in the course of the disease, disorders in its secretion and leptin receptor function occur. As mentioned above, leptin enhances hepatic gluconeogenesis, inhibits insulin secretion from β cells, and probably leads to the degradation of insulin receptors. Defining the relation between the presence of active leptin receptors in the pancreas and growth of β cells seems to be important for diabetes treatment perspectives.

According to Yuan, leptin concentration correlates with the level of insulin resistance [50]. Sun and coauthors concluded that the concentration of soluble leptin receptors (s--ObR) may be significant for the assessment of the risk of type 2 diabetes [40]. Increased leptin levels (in comparison to healthy pregnant women) were also found in patients with gestational diabetes (GDM), glucose intolerance and diabetes diagnosed during pregnancy [39]. In addition, higher concentrations were described in newborns of mothers with type 1 diabetes [48].

However, the results of studies concerning leptin and its s-ObR levels in type 1 diabetes, especially in children, are not unequivocal. An investigation by Kratzsch and coauthors conducted in children with recently diagnosed type 1 diabetes showed dramatic changes during periods of metabolic decompensation: the number of sOb-R grew, accompanied by a decrease in leptin level. The pathophysiology of these phenomena has not been fully explained yet, although it might be related to leptin resistance [24].

A pronounced leptin level decrease occurs in patients with diabetes during ketoacidosis (DKA). The initial concentrations were found to be significantly higher in comparison to the control group. Introducing insulin therapy increased the leptin level. It is probable that the main cause of these phenomena is the insulin deficiency during DKA.

The results of Szalecki and coworkers revealed that leptin levels are higher in children with type 1 diabetes, depend on the kind of insulin therapy, and relate to anthropometric parameters, age and age at diabetes onset [42]. S-ObR levels are also significantly higher in children with type 1 diabetes, and correlate with the above-mentioned factors and additionally with diabetes duration. Experimental studies showed that leptin insufficiency plays an important role in the pathogenesis of insulin resistance [8].

The leptin levels in patients with type 2 diabetes are diverse and seem to be related to the duration of the disease [29]. In obese people with poorly controlled type 2 diabetes who present insulin deficiency, the leptin levels are low – as in the course of DKA in type 1 diabetes. This fact confirms the hypothesis that one of the mechanisms leading to hypoleptinemia may be an insufficient amount of insulin. A relation between insulin secretion, insulin resistance and leptin concentration was described in healthy individuals as well as people with type 2 diabetes. Measurement of the leptin-adiponectin ratio (L/A) might be useful for assessing insulin resistance.

Despite the wide research that was conducted in the past years, many aspects concerning the secretion and action of leptin as well as its influence on carbohydrate and lipid metabolism need to be further explained. Present data, as mentioned before, suggest that an adipo-insular axis may exist [2]. It is assumed that insulin increases the production of leptin by the adipose tissue, and leptin – in a counter-regulatory mechanism – inhibits the secretion and gene expression of insulin. The suppressive activity of leptin is regulated not only by the autonomic nervous system, but also directly, by the leptin receptors that are present on β cells.

Sun and coworkers suggest that the concentration of s-ObR, independently from the leptin level, is the best parameter describing the risk of type 2 diabetes development [40]. The relation between leptin concentration and susceptibility to insulin has been confirmed by the observations of many authors [3,28,43,50]. These findings not only have scientific importance, but might also be useful for future therapeutic possibilities [18].

Experimental studies conducted in non-obese animals with artificially induced diabetes showed that β cell destruction is accompanied by lower leptin mRNA expression and decreased serum leptin levels. Interesting data were published by Kojima and coauthors, who found that leptin gene therapy regulates glycemia and energy homeostasis in diabetic rats [21]. A positive effect of leptin on glucose and lipid levels in a rat diabetes model was also described by Kusakabe and coworkers [26]. Additionally, Natio and coauthors recently presented the results of a study on the influence of leptin on glucose metabolism, complications and duration of life in mice with diabetes [34]. These researchers showed that leptin was useful in the treatment of insulin-dependent diabetes in mice.

LEPTIN IN TYPE 1 DIABETES – PERSPECTIVES FOR TREATMENT

A profound description of the role of leptin in glucose homeostasis, in laboratory animal models as well as in humans, was provided by Kraus and coauthors [25]. Lately the results of experimental and clinical studies on the use

of leptin in type 1 diabetes treatment have been published [5,14,25,33,36,49]. Wang and coworkers showed that in uncontrolled diabetes in non-obese mice, leptin used in monotherapy or combined with a low dose of insulin reverses the catabolic state by inhibiting hyperglucagonemia [49]. Such a mechanism is also suggested by other authors [46]. In addition, a positive effect of leptin-insulin treatment on glucose homeostasis in diabetic mice was presented by Kraus et al. [25].

In some cases the use of recombinant leptin is the only effective method of treating severe metabolic disorders that accompany lipoatrophy. Positive outcomes of leptin used in the treatment of patients with type 1 diabetes and concomitant generalized lipodystrophy were also described [36]. However, for the assessment of such therapy in humans further clinical investigations are needed. In particular it is necessary to determine the risk of possible hypoglycemia which may occur due to the influence of leptin on α cells [46]. It has to be remembered that substantial differences in the course of type 1 diabetes in humans and mice exist. Therefore in the future efforts should be made to conduct studies on the efficacy and safety of such treatment in humans.

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