Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 62; Numer/Number 3/2011
ISSN 0423–104X

The role of leptin in the regulation of carbohydrate metabolism

Leptyna i jej rola w regulacji metabolizmu węglowodanów

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Abstract

The hormone leptin is secreted from white adipocytes, and serum levels of leptin correlate with adipose tissue mass. Leptin was first described as acting on the satiety centre in the hypothalamus through specific receptors (ob-R) to restrict food intake and enhance energy expenditure.

Leptin plays a crucial role in the maintenance of body weight and glucose homeostasis hrough central and peripheral pathways, including regulation of insulin secretion by pancreatic β cells. Leptin may also directly affect the metabolism and function of peripheral tissues. Leptin has been implicated in causing peripheral insulin resistance by attenuating insulin action, and perhaps insulin signalling, in various insulin-responsive cell types.

Research has demonstrated a significant relationship between leptin and insulin, but the mechanisms underlying the changes of leptin induced by insulin, and vice versa, remain to be studied in more detail.

Recent data provides convincing evidence that leptin has beneficial effects on glucose homeostasis in mouse models of insulin-deficient type 1 diabetes mellitus.

Our study suggests that leptin could be used as an adjunct of insulin therapy in insulin-deficient diabetes, thereby providing an insight into the therapeutic properties of leptin as an anti-diabetic agent. Safety evaluation should include a careful assessment of the effects of this combination therapy on the counterregulatory response to hypoglycaemia. The role of leptin in alpha-cell function has not been studied in detail. Extensive studies will be needed to determine the long-term safety and efficacy of this therapy.

(Pol J Endocrinol 2011; 62 (3): 252–261)

Key words: *leptin, adipose tissue, leptin secretion, insulin secretion, insulin resistance, diabetes mellitus*

Streszczenie

Leptyna jest hormonem wydzielanym przez adipocyty, jej stężenie w surowicy koreluje z masą tkanki tłuszczowej. Pierwsze opisano działanie leptyny na ośrodek sytości w podwzgórzu poprzez jej specyficzne receptory (ob-R) dla hamowania przyjmowania pożywienia i zwiększania wydatkowania energii. Leptyna odgrywa zasadniczą rolę w utrzymaniu masy ciała i homeostazy glukozy. Odbywa się to na drodze jej działania ośrodkowego i obwodowego, włączając regulacje sekrecji insuliny przez komórki β. Leptyna także może bezpośrednio wpływać na metabolizm i funkcję tkanek obwodowych. Może być także włączona w powodowanie obwodowej oporności na działanie insuliny poprzez osłabianie działania insuliny i prawdopodobnie wrażliwości na jej działanie w różnych insulinowrażliwych typach komórek. Wiele danych przedstawia znamienne relacje pomiędzy leptyna i insuliną, lecz dla wyjaśnienia mechanizmów wpływu leptyny na insulinę i odwrotnie konieczne są dalsze badania.

Ostatnie dane dobitnie wskazują, że leptyna wywiera korzystne działanie na homeostazę glukozy w badaniach u myszy z deficytem insuliny (cukrzyca typu 1).

To sugeruje, że leptyna może być użyta jako lek wspomagający w terapii cukrzycy z niedoborem insuliny, tym samym rozważana do zastosowania w terapii jako lek przeciwcukrzycowy.

Konieczna jest ocena bezpieczeństwa stosowania takiej terapii na odpowiedź mechanizmów kontrregulacyjnych na hipoglikemię. Dotychczas ostatecznie nie wyjaśniono wpływu leptyny na funkcje komórek α. Konieczne są szczegółowe badania efektywności i długotrwałego bezpieczeństwa takiej terapii. **(Endokrynol Pol 2011; 62 (3): 258–261)**

Słowa kluczowe: *leptyna, tkanka tłuszczowa, sekrecja leptyny, sekrecja insuliny, insulinooporność, cukrzyca*

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Introduction

The results of experimental and clinical research by American scientists into the use of leptin in type 1 diabetes mellitus treatment have recently been published [1–4]. It would be useful to remind ourselves of the role of leptin in the maintenance of energy homeostasis in the body, as well as look back at previous assessments of its therapeutic use [5–9].

Leptin is one of the adipokines, and its synthesis is controlled by the *"ob"* gene located on the 7q31.3 chromosome [10]. Leptin plays a key role in body energy balance regulation. Its receptors 'ob-R' sites placement determines both central and peripheral leptin action [11–13]. Receptors are located mainly in the hypothalamus, but shorter isoforms are found peripherally in multiple organ tissues such as the liver, intestines, muscles, adipose tissue, pancreatic β cells, heart, lungs and kidneys.

Leptin, discovered only a dozen or so years ago, has provoked great interest from the very start, as witnessed by numerous publications looking at the mechanisms of its action and its influence on metabolic processes [14–17]. Leptin is secreted in pulses in daily rhythm, its secretion peak taking place at night, when its concentration is 30–100% higher than in the morning.

Leptin levels reflect not only the amount of accumulated fat, but also an individual's energy balance. Changes in leptin secretion have a significant influence on many metabolic and hormonal human body processes [14, 18, 19].

Insulin plays an important role in leptin secretion regulation. Indeed animal experimental studies suggest a direct insulin influence on leptin secretion.

After release from adipocytes, leptin is transported though the blood-brain barrier to the central nervous system, where via other peptides and the sympathetic system it causes hunger inhibition and a sensation of satiety. Leptin controls the body energy balance by inhibiting the secretion of neurotransmitters, including neuropeptide Y (NPY), which is the strongest hunger stimulator included in orexigenic compounds. Stimulation of MSH (melanocyte-stimulating hormone) release, caused by leptin, also inhibits hunger. Another leptin-dependent anorectic factor is CART (cocaine amphetamine-regulated transcript), a neuropeptide found in the hypothalamus. Glucagon-like peptide 1 (GLP-1) also probably takes place in the metabolic action of leptin.

Besides central action, many peripheral leptin effects have been described, including its influence on insulin secretion and action, the metabolism of adipocytes and skeletal muscles. Leptin is considered to be one of the peripheral glucose homeostasis regulators. It is also considered a metabolic signal regulating reproductive functions, haematopoesis, etc.

Leptin secretion differs in different stages of life [17, 20–23].

An insufficiency of leptin action may be caused by secretion disorders, disturbances of its transport from adipose tissue to the hypothalamus, or incorrect ob-R hypothalamic receptors function.

Role of leptin in maintaining glucose homeostasis

Leptin may act through receptors located in the CNS, but it may also have a direct action on different tissues. There is a direct relationship between leptin and insulin. The presence of leptin receptors in β cells indicates leptin's involvement in endocrine pancreas function [24, 25].

It is assumed that insulin increases leptin production by adipose tissue, whereas leptin inhibits insulin secretion and insulin gene expression. The suppressive action of leptin on insulin production is regulated both by the autonomous nervous system and directly by influence on leptin receptors in β cells. It can inhibit both basal and glucose-stimulated insulin secretion.

The mechanisms of the actions are varied: insulin secretion inhibition may be caused by leptin influence on ATP-dependent potassium channels. It is also believed that leptin antagonises cAMP signalling, and diminishes increases of cellular cAMP levels in response to β cells stimulation, for example by GLP-1.

It appears that leptin may antagonise insulin secretion from β cells both through cAMP-dependent protein kinase A (PKA), and protein kinase C (PKC) [26].

Leptin may play a role in preventing insulin hypersecretion. The mechanism of this regulation is yet to be fully explained [24].

It is clear that leptin's role in metabolic processes is not limited only to hunger regulation. It takes part in multiple processes, for example accelerating glucose utilisation and taking part in fat metabolism [15]. It has been proved that leptin or leptin receptors deficiency, both in *ob/ob* mice and in humans, leads not only to obesity development, but also increases insulin resistance and glucose intolerance, which are risk factors for diabetes development [24, 27, 28]. Experimental studies have shown that prolonged intravenous leptin infusion causes an increase of glucose use by an increase of tissues' insulin sensitivity. Moreover, an increase of insulin inhibiting influence on liver glucose production has been found [2, 29].

There are disagreements concerning leptin's influence on insulin secretion, and the results of studies into its influence on insulin resistance are also not clearcut [2, 30, 31]. It seems that part of these differences might be caused by the fact that experimental studies are partly

carried out *in vitro* on isolated cells, which excludes central leptin action. This also partly explains the differences between the results of experimental studies and clinical observations in humans.

An important role in maintaining glucose homeostasis is also played by leptin's influence on pancreas α cells. Experimental studies have found leptin to have an inhibitory action on these cells [19].

Leptin in diabetes mellitus and the outlook for its future use in therapy

Leptin secretion and leptin receptors disturbances have been found in diabetes patients [17, 32].

Leptin induces liver gluconeogenesis, inhibits insulin release from pancreatic β cells, and probably also causes break-down of insulin receptors. Finding a link between the presence of active leptin receptors and an increased number of β cells would appear to be important for the prospects of diabetes treatment [3, 4, 25, 27, 33].

There are many disagreements concerning leptin's concentration in patients with diabetes. This is because the leptin level depends on many factors.

An increased leptin level compared to that found in healthy pregnant women has been found in women with gestational diabetes mellitus (GDM) or glucose intolerance freshly diagnosed during pregnancy [23]. An increased leptin cencentration has also been found in newborn babies of mothers with type 1 diabetes [34].

Studies performed in children and adolescents with type 1 diabetes mellitus indicate marked differences depending on the subjects' age, diabetes duration time and degree of metabolic control [17]. In adolescents with type 1 diabetes in the pubertal period, leptin concentration was higher than in a control group, while in girls there was a correlation with adipose tissue mass increase, although not all authors have confirmed these observations [21, 31]. As Kratzsch et al. has demonstrated [35], dramatic changes take place at fresh diabetes onset during metabolic decompensation: the number of soluble leptin receptors (sOB-R) increases, while leptin concentration drops. The pathophysiologic mechanisms of these changes are not yet fully understood, but they are probably connected to leptin resistance.

A marked decrease of leptin concentration has been found in patients during diabetes ketoacidosis (DKA) [36, 37]. Initial leptin concentrations were significantly lower compared to a control group. Introducing insulin treatment increased the leptin level. The main cause of leptin decrease during DKA is probably insulin deficiency. Introducing insulin therapy increases leptin concentration.

Serum leptin concentration in type 2 diabetes patients varies, and seems to have a connection to duration of diabetes. Low leptin concentrations have been found in obese patients with poorly controlled type 2 diabetes who show insulin deficiency. This is similar to what is found in DKA during type 1 diabetes. It confirms the assumption that one of the mechanisms leading to decreased leptin concentration may be insulin deficiency.

Concerning leptin concentration changes in patients with diabetes, it has been suggested that leptin could be used as an anti-diabetic drug, or as an addition to insulin therapy in insulin-dependent diabetes [1, 3, 9, 38, 39].

Studies of animals without obesity, and with experimentally induced diabetes, have shown that the destruction of β cells is accompanied by a decrease of leptin mRNA expression and serum leptin concentration [40].

Treating rats with recombinant leptin was found to restore euglycemia and normalise peripheral insulin sensitivity, which was found using a hyperinsulinemic euglycemic clamp [41].

An interesting study by Kojima et al. showed that leptin gene therapy regulates glucose concentration and energy homeostasis in diabetic rats [42]. The beneficial influence of leptin on glucose and lipids control in diabetic rats has also been demonstrated by Kusakabe et al. [43].

Recently, an extensive description of leptin's role in glucose homeostasis maintenance in both laboratory animals and humans has been put forward by Kraus et al. [3]. The mechanism of its function varies according to endogenous leptin level. The authors suggest further clinical studies are needed for a final assessment of its therapeutic safety.

Despite multiple reports published in recent years, many aspects of leptin secretion, action and mechanisms of its influence on carbohydrates and fats metabolism still await explanation. Data, as mentioned before, seems to indicate an adipo-insular axis. Both experimental results and clinical observations indicate a relationship between leptin and insulin secretion.

These observations may help in guiding therapy [2, 44]. It has been suggested that leptin might be used as an anti-diabetic drug or as an addition to insulin therapy in insulin-dependent diabetes patients [1, 3, 9, 38, 39].

The study by Yildiz et al. showed that leptin might be used for diabetes or glucose intolerance treatment in non-obese patients with decreased leptin level [39].

In some cases, the use of recombined leptin is the only effective means of treatment of the severe metabolic disorders that accompany lipoatrophy. Leptin's usefulness in patients with type 1 diabetes mellitus with generalised lipodystrophy has also been described [45].

Conclusion

At the present, leptin is known to be involved in multiple metabolic processes and in glucose metabolism. There have been many attempts to use these actions in diabetes treatment of obese type 2 patients, as well as in type 1 diabetes.

The results of experimental studies are encouraging. However, assessing the use of such therapy n humans demands further clinical studies. It is especially important to assess the risk of hypoglycaemia, considering leptin's suppressive effect on α cells.

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