The role of leptin in eating disorders – current views

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Summary:

Eating disorders constitute a dynamically developing group of diseases, in which only some have well-established diagnostic criteria, e.g. anorexia nervosa or bulimia nervosa. Many symptoms of eating disorders are hard to be qualified to any known disorder from that group, and quantity and diversity of symptoms connected to eating grow systematically. It makes the work of clinicians and psychotherapists more difficult, as well as hampers communication between specialists. It is also a challenge for scientists to create new qualifications based on known and theoretical pathomechanisms connected to disruptions in food intake regulation.

Key words: eating disorders, leptin, satiety, hunger, anorexia nervosa, bulimia nervosa, obesity

Introduction

Centers located in hypothalamus involved in the regulation of food intake integrate peripheral signals transmitted to the central nervous system (CNS) via hormonal (from adipose tissue and gastrointestinal tract) and various neural pathways. Satiety and hunger centers are located in the arcuate (ARC), periventricular (PVN), lateral (LHA) and the ventromedial (VMH) hypothalamic nucleus [1]. In addition, a center regulating the hedonistic aspect of food intake, named appetite is localized in the lateral hypothalamus (cannabinoid and opioid systems) [2]. Also other neurotransmitter pathways, involved mainly in stabilizing the mood, participate in the perception of satiety and hunger. The increased activity of dopaminergic, α2-adrenergic and GABA-ergic neurotransmitters pathways, enhances perception of hunger and increases food intake. On the other hand, activation of serotonergic, β-adrenergic and cholinergic

systems increase the feeling of satiety and reduce food intake [1]. It seems that both these groups of signaling pathways as well as those related to the regulation of appetite are associated with psychological mechanisms that influence food intake (the system of reward and punishment).

The complexity of central mechanisms regulating food intake allows the possibility of numerous eating disorders development, as well as makes it difficult to develop effective methods of their pharmacotherapy.

One of the peripheral signals inhibiting signaling pathways of hunger sensation and stimulating the pathways of satiety perception in the hypothalamus is leptin, a hormone secreted by adipose tissue.

The aim of the study is to present current views on the role of leptin in the regulation of food intake in eating disorders and its potentially use in their pharmacotherapy.

The history of leptin research

In the 1950s a hypothesis was proposed that there is a hormone which regulates body mass by its effect on hypothalamus. It was also proved that mice with genetically determined obesity do not have the satiety hormone. During the same period, a lipostatic hypothesis was also formulated, according to which there is a negative feedback between the fat deposits accumulated in organism and the brain regulation of food intake. It was assumed that there is a peripheral „satiety signal" („anorexic factor") which would limit food intake when there is a adequate energetic reserve in the organism [3]. This factor was identified in 1994 by Zhang *et al.* [4] who observed that mice with the *ob* gene mutation develop obesity and infertility, while administration of leptin decreased food intake and body mass, and restored fertility. The name "leptin" derives from the Greek word *leptos* that means "thin". Leptin is a protein with the molecular mass of 16 kD, composed of 146 amino acids and is coded by the *ob* gene. In 1995, Tartagila *et al.* [5] isolated the leptin receptor gene and localized places of its expression in another species of mice with genetic obesity (db/ob). They also showed that obesity in this type of mice is determined by the mutation of leptin receptor gene and leptin resistance. These animals, despite an increased concentration of circulating leptin, manifested excessive food intake, decreased basal metabolic rate, as well as insulin resistance and hyperinsulinemia, accompanied by the type 2 diabetes development. Administration of synthetic leptin to the ob/ob mice and to the mice with normal body mass was reducing food intake, increasing energy expenditure, and decreasing body mass. However, administration of leptin to the db/db mice was neither decreasing food intake and nor reducing body mass [6].

Composition of the gene coding leptin

In humans leptin is coded by a gene homogenous with the mouse *ob* gene, located on the long arm of the 7q31.3 chromosome, that contains two introns, which divide the coding region among three exons. Mutations of *leptin* in humans are rare and were first described in

1997 in Pakistani siblings, where the mutation consisted in deletion of guanine in codon 133. Low serum leptin concentration in these children was accompanied by excessive hunger, obesity and puberty disturbances. However, the carbohydrate metabolism was not impaired [7]. Subcutaneous administration of the recombined human leptin to three children with *leptin* mutation led to the food intake decrease (by 45-84%) and body mass reduction, mainly by fat mass loss, there was also normalization of LH and FSH concentrations adequate to the age, however, the changes in the basic energy expenditure were not observed [8].

Sources of circulating leptin and factors influencing its serum concentration

The main source of the circulating leptin are adipocytes of the white adipose tissue. Lower amounts of leptin are secreted by the following: placenta, gastric mucosa, small intestine epithelium, liver, bone marrow cells, skeletal muscles, pituitary gland, and hypothalamus [9]. Leptin circulates in the blood in the free form and bound to plasma proteins. There are three fractions of leptin-binding proteins found in humans. Their molecular mass was estimated at app. 176, 240 and 450 kD. Leptin in peripheral blood also circulates in the form bound to the soluble isoform of leptin receptor, OB-Re [10]. Serum leptin concentration is directly proportional to fat mass. In women with the same BMI as in men, serum leptin concentration is 2-3-fold higher, as the consequence of different distribution of adipose tissue (leptin is secreted in greater amounts by the subcutaneous than visceral adipose tissue). Secretion of leptin by adipose tissue also depends on sex hormones - estrogens stimulate its synthesis, while androgens inhibit it. This is, among others, the reason why leptin concentration in procreative age is higher in women than in men, and decreased in perimenopausal and postmenopausal women [11]. The increase in serum leptin level is also observed during pregnancy, with its peak in the second trimester, and significant decline after the labor. The increase of leptin concentration during pregnancy is not only a result of body mass increase, but also stimulation of its secretion by insulin and estrogens and its production by placenta and developing fetus. It is suggested that the decrease in leptin level after delivery reduces fertility in the breastfeeding period [12].

Leptin is secreted in the circadian rhythm. Its highest serum concentrations are observed at night $(00.00 - 2.00$ a.m.$)$, and the lowest during the morning, between 8.00 and 9.00 a.m. [13]. Leptin is also an important factor participating in the reproduction. As it has already been mentioned, the lack of leptin in the ob/ob mice as well as the lack of receptor response to its activity in the db/db mice, in addition to hyperphagia and obesity, caused infertility. On the other hand, administration of exogenous leptin restored fertility only in the ob/ob mice [14,15]. The increase of circulating leptin levels in boys and girls during puberty participates in the activation of the hypothalamus-pituitary-gonad axis by stimulating gonadoliberin release [16]. As it has been shown leptin is the missing factor in the hypothesis formulated in the 1970s by Frish's and Revelle's that there is a critical body mass, which is necessary to achieve the next stage

of puberty [17]. Leptin regulates also function of the hypothalamus-pituitary-gonad axis in the reproduction age both by the influence on the release of gonadoliberin in hypothalamus, and by direct stimulation own receptors in pituitary gland and increase of FSH and LH secretion [18, 19]. In cachexia, e.g. in women with anorexia nervosa, with too low fat deposit and extremely low circulating leptin levels, develops secondary amenorrhea, and prevents pregnancy in conditions of prolonged starvation [20].

Leptin receptors and intracellular signaling

The leptin receptor in humans is coded by the *Ob-R* gene, which is located on the 1p31 chromosome [10]. The leptin receptor exists in numerous isoforms: Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, OB-Rf and the soluble Ob-Re [21]. According to Frühbeck's [9] the criterion for isoform division into the long one (Ob-Rb) and the short ones (Ob-Ra, Ob-Rc, Ob-Rd, Ob-Rf) is divers length of the intracellular domain, which contains proline-rich 'box1' motif that is required for Janus kinase 1 (JAK1) interaction and activation. JAK 1 activation is the first step of leptin signal transduction in a cell. Apart from the intracellular domain, all the leptin receptor isoforms, except for Ob-Re, contain an extracellular and transmembrane domain [9]. The long Ob-Rb isoform, within the intracellular domain, contains three conservative tyrosine residues (Tyr 985, Tyr 1077 and Tyr 1138), which cause different ability of activating signal transduction in a cell and define pleiotropic nature of leptin receptors. Ob-Rb receptors on the cell surface dimerise in response to leptin binding, activated of JAK2 by transphosphorylation, which, in turn leads to phosphorylation of tyrosine residues within the intracellular domain of Ob-Rb [22]. Myers's et al study [21] revealed that the Tyr 985 and Tyr 1138 residues undergo phosphorylation during intracellular signal activation in the cell by stimulation of Ob-Rb, while the Tyr 1077 does not undergo phosphorylation and does not participate in signal transduction. The phosphorylated Ob-Rb tyrosine residues is binding sites for signaling proteins. Through the tyrosine residue Tyr 958, a signal transduction pathway ERK1/2 is activated in the cell – a pathway of extracellular signal-regulated kinases, as well as signal transduction by a cascade of mitogen activated protein kinases – MAPK [21]. MAPK moving into nucleus, triggering phosphorylation and activation of transcription factors, such as c-jun, c-phos, c-myc, erg-1 and, in consequence, inducing of genes expression regulating cell proliferation and differentiation [9]. According to Myers et al. [21], the phosphorylated Tyr 985 residue is also a binding site for the protein inhibiting signal transduction, i.e. the SOCS3 protein (suppressor of cytokine signaling 3). The SOCS3 binding to Tyr 985 terminates the signal transduction by Ob-Rb preventing JAK2 connecting to the receptor. Moreover, it was observed in cell cultures that leptin binding to Ob-Rb mediates in autophosphorylation of tyrosine residues of the insulin receptor substrates and activation of the PI3-K pathway. This process is independent on the phosphorylation of tyrosine residues within Ob-Rb [21].

Ob-Rb are present also in hypothalamus nuclei, where the satiety and hunger centers are located: in arcuate, ventromedial, lateral, paraventricular, and in the supraoptic

nucleus. On the other hand, the short Ob-Rb isoform (with 34-amino acids residues), a leptin transporter, is mainly located in the brain choroid plexus, hypothalamus, lungs, kidneys and adipose tissue. This receptor plays a key role in leptin passing through the blood-brain barrier. Another short Ob-Rc isoform with a 32-amino acids intracellular domain can be found mainly in endothelium of cerebral vessels and brain choroid plexus, but also in cerebral cortex, cerebellum, liver and lungs. It has also transporting role for leptin through the blood-brain barrier [23].

The role of leptin in the central regulation of food intake

It is currently known that the key pathways of satiety and hunger centers are located in ARC. Neuropeptide Y (NPY) and melanocortin receptor antagonist – Agouti-related peptide (AgRP), the main neurotransmitters responsible for the feeling of hunger are produced in a single type of neurons. While, second type of neurons synthesized with proopiomelanocortin (POMC) melanotropic hormone (α-MSH) and cocaine and amphetamine regulated transcript (CART), neurotransmitters stimulating the feeling of satiety [24]. ACR neurons create anatomically-functional connection with other hyperthalamus areas, such as paraventricular nucleus (PVN), lateral hypothalamic nucleus (LHA) and ventromedial nucleus (VMH). The melatocortin 4 receptors (MC4R) located in VMH are activated by POMC and CART, which leads to the feeling of satiety. Whereas, NPY and AgRP stimulate the release of orexin A and B and melanin-concentrating hormone (MCH) in LHA, and, in turn the intensification of hunger feeling [25].

As was mentioned above, the expression of Ob-Rb was found in ARC, VHM, LHA, PVN and supraoptic nucleus. Physiologically, the stimulation of Ob-Rb in ARC by leptin and initiation of the intracellular cascade of signal transduction with JAK kinases and STAT protein (signal transducer and activator of transcription) inhibits the synthesis and release of neurotransmitters, such as NPY and AgRP. Additionally, leptin and insulin lead to hyperpolarization of neurons releasing NPY and AgRP by activation of the ATP-dependent potassium channels and also in this mechanisms reduce their production [26, 27]. By these mechanisms, leptin inhibits the pathways responsible for the feeling of hunger (reduced production of MCH and orexins in LHA). However, in obese these mechanisms are disturbed, probably as a result of leptin resistance development. As was mentioned above, the hormones of the long axis that regulates food intake are not the only factors influencing secretion of these neurotransmitters. Also, the alimentary tract hormones (the short, gut-brain axis of food intake regulation) have effect on NPY and AgRP secretion. Hormones responsible for the feeling of satiety, such as GLP-1, PYY, PP, CCK and OXM inhibit their secretion, while ghrelin, which regulates the feeling of hunger, stimulates them [28-31].

As mentioned before, also the cannabinoid system plays a role in food intake regulation. The activation of this system is mainly connected with searching and eating tasty meals and with the feeling of pleasure related to eating. This type of behavior associated with food intake is referred to as the appetite. Orexinogenic activity of the cannabinoid system is synergistic with the function of the opioid system. Leptin inhibits

the cannabinoid system activity regardless of the effect on NPY and AgRP secretion, by activation Ob-Rb in LHA [32].

An additional mechanism of leptin effects on the central regulation of food intake is the inhibition of the hypothalamic synthesis and secretion of ghrelin. Moreover, the central ghrelin synthesis is reduced by PYY and CCK [33].

As was described above, leptin constitutes only one of the peripheral links influencing the activity of central pathways regulating food intake, while the feeling of satiety and hunger is regulated by complex interactions of hormones and neurotransmitters.

Leptin and obesity

Leptin, as an adipose tissue hormone, is a key negative food intake regulator. Impairment of leptin secretion (ob/ob mice) as well as the lack of active leptin receptors (db/db mice) leads to hyperphagia and obesity development in animals [34]. Central leptin administration to mice with ob/ob mutation reduces food intake by stimulation of receptors localized in hypothalamus, increases energy expenditure and leads to body mass reduction [35, 36]. Such effects of the exogenous leptin were not observed in the db/db mice.

In another experimental model, peripherally-administered leptin reduced food intake only in the case of its initially low serum leptin concentration, but not in the case of animals with diet-induced obesity (DIO) with high circulating leptin levels [37]. Therefore, we should rather talk about a food intake stimulation by low circulating leptin concentration (absolute deficit) as about a signal informing the brain about the lack of energy reserves, which has developed in the course of evolution to protect organism from cachexia. However, the results of the recently published studies revealed that a decrease of serum leptin concentration observed after a significant body mass reduction (the relative deficit) also constitutes a food intake stimulating factor . It may be one of the mechanisms that explains a feeling of increased hunger in subjects undertaking attempts to reduce body mass and contributes to the recurrent body mass gain (the yo-yo effect) [38].

The results of experimental studies as well as the increased circulating leptin concentrations observed in 90-95% of obese subjects led to the hypothesis about "leptin resistance" [39]. According to various hypotheses, the mechanism "leptin resistance" is connected with impaired passing by the blood-brain barrier [39] and the impairment activation of intracellular pathways. This hypotheses was not definitely confirmed.

Leptin in anorexia nervosa (AN) and bulimia nervosa (BN)

The first study performed in patients with AN and BN have shown that leptin levels in these groups of patients are decreased proportionally to the reduced fat reserves, indicating the absence of disturbances of the physiological mechanisms regulating its secretion [41, 42, 43]. In these patients low leptin level participates in the development of secondary amenorrhea by disturbance in the activity of hypothalamic-pituitary-

ovarian axis. Nutritional therapy increases serum leptin levels and is followed by resumption of menses [44].

The feeling of satiety is chronically stimulated despite low levels of leptin, both in the restricting (AN-R), and bingeing-purging (AN-BP) type of AN [45]. Also gut -brain axis, e.g. secretion of ghrelin, obestatin, neuropeptide YY, GLP-1 in patients with AN and BN does not seem to be significantly affected, however some differences were described [46-48]. Therefore, control of eating behaviour in AN and BN has been pathophysiologically linked to dysfunctions of reward and punishment mechanisms. It is suggested that observed changes in circulating leptin levels in AN and BN may represent homeostatic adaptations to malnutrition, and not contribute to the development and the maintenance of aberrant non-homeostatic behaviors, such as self-starvation and binge eating [49].

In summary, the mechanism of food intake regulation is extremely complex and leptin, as well as the activity of leptin-dependent central pathways, constitute only one of the links. The increased of leptin secretion in obese subjects does not prevent a further body mass gain, because simultaneously with the increase of circulating leptin concentration develops leptin resistance. The knowledge about the mechanism of leptin resistance development is still limited. Yet, both the absolute and relative leptin deficiency (caused by body mass decrease) stimulates food intake. This mechanism may hamper the long term maintenance of reduced body mass in obese and be partially responsible for the yo-yo effect. Furthermore, in AN and BN patients, low leptin concentration does not stimulate food intake. Therefore, changes in leptin secretion in these disorders reflect only fat deposits. The issue of food intake regulation still constitutes an open research area, and new findings are expected to change the perspective of viewing the problem of eating disorders.

Роль лептина в нарушениях питания – современные взгляды

Содержание

Нарушения питания являются динамически развивающуюся группу болезней, в которой только немногие причислены к обще обязывающим критериям диагностики, нп. психическая анорексия и булимия. Много симптомов в спектре нарушений питания нельзя причислить до никакой медицинской единицы, а число и разнообразность симптомов, связанных с нарушением питания систематически ворастает. Это затрудняет работу клиницистов и психотерапевтов и создает проблмы коммуникации между специалистами. Также и для научных работников является полем исследований новых классификаций явления, опирающихся на известных и предполагаемых патомехализмов принимающих участие в регуляции приема и периваривания пищевых продуктов.

Ключевые слова: нарушения питания, лептин, насыщение, голод, псыцхическая анорексия, булимия, ожирение

Rolle von Leptin in Essstörungen – zeitgenössische Einsichten

Zusammenfassung

Die Essstörungen bilden eine dynamisch variierende Gruppe von Krankheiten, in der nur für wenige die allgemein geltenden diagnostischen Kriterien festgesetzt wurden, z.B. Anorexia nervosa oder Bulimie. Viele Symptome aus dem Bereich der Essstörungen kann man zu keiner der bekannten

Krankheitseinheiten in dieser Gruppe der Störungen einordnen, und die Zahl und Unterschiedlichkeit der Symptome von Essstörungen steigt systematisch. Es macht die Arbeit der klinischen Ärzte und Psychotherapeuten schwer, es entstehen Probleme bei der Kommunikation zwischen den Fachärzten. Es bildet such eine Herausforderung für die Wissenschaftler zur Bildung neuer Teilungen, die sich auf bekannten und angenommenen Pathomechanismen stützen, die an den Störungen der Regulation der Nahrungseinnahme teilnehmen.

Schlüsselwörter: Essstörungen, Leptin, Sattheit, Hunger, Anorexia nervosa, Bulimie, Adipositas

Le rôle de leptine dans les troubles des conduites alimentaires – conceptions contemporaines

Résumé

Les troubles des conduites alimentaires forment un groupe de troubles changeant dynamiquement dont seulement certains ont les critères diagnostiques établis par ex. anorexie nerveuse ou boulimie. On ne peut pas qualifier plusieurs symptômes des troubles des conduites alimentaires comme typiques à ces maladies et la quantité et la diversité de ces symptômes augmentent toujours. Tout cela rend plus difficile le travail des spécialistes –cliniciens et thérapeutes en incitant à la fois les chercheurs à créer les nouvelles qualifications basant sur les pathomécanismes connus ou supposés liés avec les troubles des conduites alimentaires.

Mots clés : trouble des conduites alimentaires, leptine, satiété, faim, anorexie nerveuse, boulimie nerveuse, obésité

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