The Importance of Leptin in Animal Science

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Abstract
There are two different neurons that control the energetic homeostasis in animals: appetite-stimulating and appetite-suppressing neurons. Leptin is a peptide hormone (also known as “satiety hormone”), released by adipose cells, being an anorexigenic compound which inhibit the hunger. Leptin function in animal organism is opposite by the action of ghrelin – a peptide hormone acting as an orexigenic compound that activate the hunger sensation. The quantity of leptin produced in organism is correlated by the size and the number of adipocytes, and of course by the lipid tissue mass. The action of leptin is in accordance with the neuropeptide Y that signaling the brain to increase the appetite and make the animal to eat. When the animals lose weight, the mass of adipose tissue is diminished, that has as consequence a decrease the leptin concentration in the blood. Blood leptin is correlated also with other characteristics, such as: fasting for a short term, stress, physical activity, sleep duration (prehibernation and hibernation), insulin concentration, obesity and diabetes.

Keywords: animals, leptin, energy homeostasis.

1. Introduction
Energy homeostasis is possible by the exogenic and endogenic nutrients, but also by some compounds that regulates the metabolic rate. For human and animal organism the energy expenditure is also correlated with the environmental conditions (or habitat), as well is depended by physical and psychical activity. Some of energy regulate compounds are secreted by different cells and are hormones – that acts directly on the appetite.

In the last time researchers came with two terminologies linked directly to the appetite: orexigenic neurons and anorexigenic neurons. The orexigenic neurons stimulate the production of some peptide hormones, such as neuropeptide Y (NPY) – that acts on the hypothalamus stimulating the appetite. NPY peptide depends by ghrelin produced in the stomach, by leptin and adiponectin produced in adipocytes, and by insulin produced in pancreas, being also in relation with anorexigenic neurons. On the other hand the anorexigenic neurons produce peptide hormones, such as α-melanocyte stimulating hormone (α-MSH) – that suppressing the appetite. As well, the anorexigenic activity is depended by leptin produced by the cells from adipose tissue, and by insulin produced by β-cells from the islets of Langerhans in pancreas [1-3].

Body weight for adults human and animal is maintain constant by the food or feed intake – that is also evaluated mainly as energy intake. There has to be a balance between energy intake (energy input) and energy expenditure (energy output).
Thus, taking in consideration the differences between these two processes, we can find three states: positive energy, negative energy and neutral energy balance [4].

Positive energy balance is found in case of a greater energy input compared to energy output, and energy from nutrients is stored as adipose tissue (when weight gain). Negative energy balance corresponds to a lower energy input compared to energy output, and the nutrients do not meet the demand, case when the adipose tissue and/or muscle tissue is used as energy supply (when weight loss). The body weight is in a perfect balance when the demand energy is satisfied by the input energy. But, how is this coordinated in the human or animal organism? Well, the organism has some special secreted compounds, as hormones, that stimulates or inhibits the appetite. Sometimes there are natural situations, both for human and animal organism, that modify the balance to a positive or negative state, such as pregnancy, lactation or hibernation. Thus, in the case of pregnancy or lactation the mother needs more energy for baby development or to produce the milk – and this energy can be taken from an increasing food intake or can be taken from the mother metabolic processes – when has as a result a weight loss. On the other hand, before hibernation the animals increase the energy intake (and make energy reserves as adipose tissue), while during the hibernation state they use the energy resulted by lipids’ (adipose tissue) catabolism [5, 6].

There is a “lipostat theory” that postulates the process by which the organism get signals that inhibit the long-term appetite and induce the organism to consume its own energy reserves (endogenous nutrients), whenever the body weight overcome some pre-set limits. Last years some researchers demonstrate that there are some hormones that increases metabolic rate and inhibit the appetite (such as leptin) by sending signals to the brain centres to control eating [1].

The opposite state is the “glucostat theory” that postulates the process by which the organism regulates the short-time appetite, being responsible by the frequency and the quantity of meal, preventing the excess of food or feed intake [2].

2. Leptin structure and function

Leptin was first studied in 1994 and it is a peptide hormone that sends signals from adipose tissue to the hypothalamus, informing the metabolic biochemistry to decrease food or feed intake [7, 8]. It is form from 167 amino acids rest – known also with LEP, LEPD, OB, or OBS symbols. Leptin molecular mass is 16 kDa and the leptin receptors are very similar with glycoprotein gp130. Different leptin receptors presented high affinity for 125I-leptin membrane binding. Liu and his collaborators in 1997 expressed and characterized a human soluble leptin receptor, which acted as antagonist of binding the 125I-leptin to membrane receptor, and proposed to study further the possibility to use the leptin receptor in elucidation of the endogenous leptin function [8].

Because leptin is a peptide hormone we have to have in view the form of circulating leptin in the organism, and also to see if there is a bioactive form of leptin. Thus, human leptin can circulate in the organism in two forms: bounded by other proteins or free [9].

Leptin can be as well secreted in the gastric mucosa, transported to the intestinal lumen, and finally is bind to the leptin-receptors from the apical membrane in erythrocytes. This physiological process can influence the intestinal absorption of some amino acids, fact that was experimental demonstrated recently (2015) on rats [10]. Fanjul and his team generated physiological condition to evaluate in vivo the effect of leptin on some amino acids absorption (glutamine, proline, and β-alanine), administrated in single-pass perfusion. The presence of leptin inhibits the amino acids absorption (45%) for short time (80 minutes) after administration, but was completely reversed after leptin was eliminated from perfusion. As well, leptin presence influenced the galactose and glutamine absorption. Thus, their scientifically work brought new information that luminal leptin directly influence the nutrient absorption, and may indicate that leptin – as a hormone – may influence some transporters involved in nutrients uptake.

Researcher started to study the structure, function, role and activity of leptin in organism and thus it was introduced a new terminology: “leptinomania” [11]. As well, Bray in 1996 presented a research that explains that the leptin...
resistance can be linked to a slow signal of the leptin to hypothalamus, due to an increasing binding of the peripheral side of the brain [11].

3. Leptin and adipose tissue regulation

It is a hormone secreted and produced by adipose tissue (adipocytes) and is also known as “satiety hormone” or “stop eating hormone”, being part of anorexigenic factors. Thus, leptin regulates the body weight, having dual action by increasing energy consumption and decreasing appetite. This polypeptide hormone – leptin, is produced mainly by white adipose tissue, more precisely by adipocytes. White adipocytes are less represented in mammals during hibernation compared to brown adipocytes – that contain more mitochondrial stores storing iron, being also very well vascularized. But, the leptin can be produced by other cells like brown adipose tissue, by syncytiotrophoblasts from placenta, by placenta or ovaries cells, and by epithelial cells of mammary and gastric epithelium [11]. Thereby, the brown adipose tissue is well represented in newborn mammals and also before hibernation.

The biological importance of leptin is now related not only to adipose tissue and obesity, but also to hematopoiesis and blood pressure, immune and lymphoid homeostasis, bone structure and development, and angiogenesis [7].

Experimental research studies demonstrated that there are cases of leptin deficiency or leptin resistance, both metabolic processes being involved in unbalanced energy homeostasis, by increasing the appetite and decreases the energy expenditure in mice [13].

Likewise, the leptin plasma concentration, physical activity, and weight gain were evaluated by a researchers group in 2002, on weanling rats, in case of deficiency of zinc and reduce food intake. The results of this study presented that zinc deficiency decreased leptin plasma concentration (but not significantly and statistically different) compared to control, but significant reduced the food intake and body weight. Thus, the low metabolic activity and low leptin concentration in plasma was directly associated by feed intake and not by zinc deficiency. However, the study demonstrated that in weanling rats, zinc deficiency influences the leptin concentration in plasma, the metabolic rate and certainly the physical activity [14].

STAT3 mechanism is a signal transducer and also a transcription-3 activator (noted STAT3) which induce the gene transcription that control differentiation [15].

Leptin resistance and elevated endocannabinoid tone are characteristic for obesity disease. In 2008, Buettner and his collaborators studied the correlation between leptin concentration and STAT3-independent mechanism in Sprague Dawley rats. This experimental research showed that leptin administrated to rats into mediobasal hypothalamus inhibited the lipogenesis of white adipose tissue (WAT), independently of STAT3 signaling. However, the suppressing of WAT lipogenesis by hypothalamic leptin action is lost if the signal of phosphoinositide-3-phosphokinase secreted in hypothalamus is prevented or if the sympathetic denervation of adipose tissue takes place [16].

4. Interaction of leptin with various metabolites and hormones

Some adipocytes release different hormones which influences the metabolic processes by different mechanisms. Thus, some hormones originating from adipocytes, such as leptin and adiponectin, together with ghrelin – are influenced by the thyroid function. In the same time adiponectin, leptin and ghrelin influence the insulin response and glucose homeostasis in human and animal organism [17].

Ghrelin is a peptide hormone, also known as orexigenic hormone, hunger hormone, or lenomorelin. This hormone acts directly to energy homeostasis, transducing different signals to the nuclei of hypothalamus, stimulating the hunger sensation. Biochemically, ghrelin or lenomorelin structure has 28 amino acids (12 different amino acids), where the third serine from end is octanoylated – this being necessary for biological activity [18].

Ghrelin decreases the glycaemia and lipid oxidation, stimulating the appetite and consequently increasing energy, promoting a positive energy balance. So, ghrelin is acting as an antagonic compound compared to leptin – which is elevated in obesity.

Also, new researches demonstrated that leptin – associated with obesity – is considered important factor in cardiac risk. As well, in hyperthyroidism
the leptin concentration decreases generating an associated low-leptin, low-ghrelin state [17]. Physiological leptin concentration from plasma varies between 1 and 10ng/ml (approximately 0.06÷0.6nM). Though, most of the researches presented the results of leptin correlated with insulin after in vivo experiments using concentration of leptin over physiological limits. Muller and his researcher collaborators showed that leptin concentration clearly affected the relation between insulin and glucose transport, glycogen, lipidic and protein anabolism, but the influence was direct dose-dependent [19]. As well, there is an influence of plasma leptin concentration on insulin pathways which also affect the skeletal muscle, being related with phosphatidylinositol-3-kinase activity that binds the insulin receptors – being considered substrate. Leptin suppresses the increasing free fatty acids oxidation in muscles. But, different experimental studies present synergic and antagonist effects of leptin action. Thus some researches present synergic effects between an increasing uptake of free fatty acids and glucose uptake, mediated by insulin; and another studies present antagonic effects on repressing the fatty acids oxidation and insulin. Insulin appears to increase the energy and amino acids storage, although leptin stimulates the catabolism of triacylglycerol and utilization of fatty acids in energetic purpose [13, 20-22]. Leptin signal is a complex process somehow similar with the mechanism of interferon receptors and growth factors, also known as JAK-STAT system. When leptin binds to two monomers from extracellular part, the leptin receptor dimerizes. Janus–kinase (JAK) phosphorylates the both monomers on a tyrosine rest from intracellular domain, and thus the phosphorylated tyrosine is prepared to bind three proteins used for signaling transduction and used for transcription activators (usually noted as STAT, STATs or fat-STATs) [23]. The STATs dimerize after phosphorylation and migrate to the nucleus, binding to the specific DNA-sequences and stimulating target genes expression, including the gene that produce the α-melanocyte-stimulating hormone [23]. On the other hand, leptin is involved in insulin homeostasis and reproduction function, and thus – leptin and insulin behaving as a non-competitive antagonism. As well, physiological concentrations of leptin inhibit the insulin homeostasis, having as direct effect the oestradiol formation in granulosa cells from bovine follicles [12]. Lindheim and his research team demonstrated that ovarian hyperstimulation increases significantly the serum leptin concentration in humans. This conclusion may be linked to the idea that leptin is involved in follicular growth and/or maturation [24]. Leptin is involved in growth hormone activity. These reports were conducted on in vivo studies, using growth hormone deficient animal models, such as humans, rodents, sheep and swine [25-29]. Some results were contradictory. Thus, Houseknecht and his research team incubate bovine adipocytes with growth hormone alone and in combination with insulin, dexamethasone and with insulin-like growth factor-1 (IGF-1). After incubation for 24 hours, the growth hormone alone did not present any effect on leptin expression from bovine adipose tissue, but in combination with other components, the growth hormone diluted the effect of insulin or dexamethasone stimulation on leptin expression [30]. Other experimental in vivo studies presented an inhibitory effect of growth hormone on leptin expression [31-33]. Leptin is also involved in catabolism of different nutrients and thermogenesis. Leptin induces an increase of norepinephrine release which stimulate the gene transcription for uncoupling protein, resulting a transfer of electron from oxidative phosphorylation that consume lipids, having a thermogenic effect [23]. The concentration of blood leptin is mostly higher in obese persons and animals compared with individuals with normal body weight. Of course, there is an exception for ob/ob animals, which cannot produce leptin. But studies conducted on highly obese humans with a defective leptine gene, the administration of leptin injection resulting in dramatic weight loss [23]. There were researches of leptin involving in hibernation and starvation of mammals. He and his collaborators, in 2010, studied the leptin proteins in hibernating greater horseshoe bats (Rhinolophus ferrumequinum) and non-hibernating fruit bats (Rousettus leschenaultii). The results presented a random loop for non-hibernating bats leptin protein, and had a helical structure of leptin protein for hibernating bats. These findings explain that the structure of leptin
peptidic hormone change its function in animal organism [34].

Another research article conducted also on hibernation little brown bats (Myotis lucifugus), studied the leptin quantum as a satiety hormone during prehibernation. Thus, in prehibernation phase the body weight and adipose tissues mass of bats increased to a maximum level in the 12th day. But leptin secretion from adipocytes and plasma increased before adiposity increasing, and then significantly decreased after the adiposity started to increase, especially represented by brown adipose tissue. This can explain how some mammals can achieve the hibernation phase, when the leptin metabolic signals are removed during fattening stage in prehibernation phase [35].

5. Conclusions

Body weight is controlled by anorexigenic and orexigenic factors, more often by different peptidic hormones, such as; leptin, ghrelin, adiponectin, α-melanostimulating hormone, and insulin.

Leptin, adiponectin and α-melanostimulating hormone are anorexigenic hormones, suppressing the appetite and inhibit the hunger sensation. Signals of leptin secretion are transported to hypothalamus, from where the organism gets signals that influence the energy homeostasis. Ghrelin is an orexigenic hormone, stimulating the appetite, and is strongly correlated with the insulin resistance.

Leptin is secreted in gastric mucosa from stomach, is transported to intestinal lumen, being finally bounded to leptin receptors in erithrocites. Structurally, leptin is a peptide hormone form from 167 amino acids rests, with 16kDa molecular mass, and the structure of leptin receptors are similar with glycoprotein gp130. Leptin circulates in organism bounded by other proteins and as free leptin, unbounced by other compounds.

Leptin regulates the body weight, by increasing energy consumption and decreasing appetite. It is produced mainly by white adipose tissue (adipocytes), and also by brown adipose tissue, syncytiotrophoblasts from placenta, placenta or ovaries cells, and epithelial cells of mammary and gastric epithelium.

The peptidic hormone, leptin, influences the carbohydrates, lipidic and proteins metabolic processes by various mechanisms, controlling the body weight. Leptin function is correlated with different compounds (insulin, ghrelin, adiponectin, α-melanostimulating hormone), and influence the muscle activity, energy homeostasis, the metabolic rate, growth and development, thyroid function, cardiac activity, reproduction, prehibernation and hibernation phase, being also correlated with some diseases, such as obesity and diabetes.

References