

MODERN APPROACHES TO THE PROBLEM OF BODY WEIGHT REGULATION (REVIEW)

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The review is concerned with the systematization and description of new discoveries, as well as the analysis of experimental and clinical findings in the field of body weight control and methods of obesity control as the basic element of the pathogenesis of many cardiovascular and endocrine diseases. Protein-peptide hormones responsible for body weight control are presented in accordance with their production sites (adipose tissue hormones, neurohormones, gastrointestinal hormones) and the character of their regulatory effect (orexins, anorexins, adipocyte proliferation and differentiation regulators, decouplers of oxidative phosphorylation, etc). Recently, in addition to new hormones discovered, cell receptors have been isolated from them and thoroughly studied.

The review represents new data on synergism and antagonism of hormones, their binding to specific cell receptors of target tissues. The mechanism of regulatory signal transmission with some messengers (5'-AMP) or with tyrosine kinase phosphorylation of intracellular proteins has been shown experimentally for some of these hormones.

The review demonstrates the capabilities of activation and blocking of the expression of some genes as a prospective way of a directed impact on the regulatory systems of body weight control. We have suggested that there appeared new possibilities for revealing individual genetic causes of body weight disorders and the development of new principles of their correction by gene therapy.

Key words: body weight regulation; hormones that regulate body weight; proteins and peptides — factors of body weight control; obesity.

World civilization development results in an increased number of diseases, the basic element of the pathogenesis of which is an apparent increase in standard body weight. So, in the USA about 30% of population suffer from obesity, and approximately 35% have overweight (according to body mass index — BMI) [1]. The similar tendency is typical for nearly all European countries including Russia [2, 3].

In recent years, there have been a lot of discoveries in science worldwide, which dramatically change the common concept of body weight control as an elementary relationship of regulatory factors in accordance with the energy conservation law. There have been isolated and studied a variety of new hormones synthesized in various organs and tissues, which are not internal secretion glands, as well as there have been discovered a number of substances, which by some means or other have an effect on the relation of the utilized energy and

“unnecessary” energy consumption. However, up to the present there is no decisive answer to the question, why one and the same diet in two subjects of the same sex, age and similar energy consumption can result in significant differences in body weight. As a rule, in such cases, “to explain” these differences, the following phrases conveying nothing are used: “the differences are of genetic nature”, “congenital condition”, “body type peculiarities”, etc.

The present review aims at analyzing and systematizing the information collected by now and concerning different aspects of body weight regulation problem, and it is our opinion that it should contribute to better understanding of genetic and epigenetic mechanisms of body weight control and widening the range of applicability of the fundamental science discoveries in medical practice.

For a long time there has being formed the concept of

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obesity as the result of excess calorie intake compared to the necessary energy consumption for physical activity. However, in fact, the body can distribute the calories derived from food at least by three ways:

- 1) the change of excess metabolic fuel into fat, and fat preservation in adipose tissue;
- 2) excess metabolic fuel burning using additional physical activity;
- 3) “unnecessary” burning of metabolic fuel using heat production increase (thermogenesis) in separate mitochondria.

A human and an animal have a complicated system of hormonal and neuronal signal acts meant for maintaining the balance of metabolic fuel and energy consumption in order to keep adipose tissue weight at an optimal level. To describe the obesity mechanism it is essential to understand the role of various limiting factors and counterbalances to maintain body weight balance both under ordinary conditions, and also in their disorders resulting in obesity development [4]. Among these factors the hormones produced not only by “classical” internal secretion glands, but also by a number of other organs and tissues are of particular importance. In the present review we do not consider those regulatory factors, which have been well studied and described in medical literature, such as male and female sex hormones, glucocorticosteroids, thyroid hormones, insulin, glucagon, adrenalin, etc; in contrast, the attention is given to the characteristics of newly discovered substances produced by various organs of the body and participating in body weight control.

Hormones of adipose tissue

After D. Freedman discovered leptin (1994), the so called lipostatic theory of body weight regulation has gradually started to develop. According to the theory, a feedback signal occurring in adipose tissue has an effect on brain centers controlling eating behavior and activity (metabolic and motor).

Leptin is a relatively small (16 kDa) protein produced by adipocytes, stimulates the production of anorexigenic peptide hormones in hypothalamic arcuate nuclei, one of which is α -melanocyte-stimulating hormone (melanoliberin, α -MSH) producing neuronal signals, which suppress appetite and stimulate metabolic fuel consumption. On the other hand, leptin and insulin inhibit orexigenic neurosecretory cells resulting in reduced production of orexigenic hypothalamic hormones and the lower signal “eat!” sent by cortical neurons to the tissues [5, 6].

However, such an easy and graceful feedback loop frequently appears to be incompetent due to congenital or acquired leptin resistance [7]. Therefore, high expectations for leptin as a powerful obesity stopper have been fallen short.

In the following years a variety of hormones

produced by adipose tissues (adipokines) has been discovered, and, consequently, adipose tissue has been demonstrated to be the most important endocrine organ of the body. Next we are to present the most extensively studied representatives of these hormones.

Adiponectin is a glycoprotein hormone discovered in 1995–1996 independently in several laboratories worldwide, as the main targets they use myocytes and the liver. In these tissues it improves insulin sensitivity, and has an anti-atherogenic effect. Adiponectin acts through 5'AMP-protein kinase (AMPK). AMPK, which inhibits acetyl coenzyme-A-carboxylase and relieves suppression of β -oxidation by malonyl-coenzyme A, enhances the absorption of fatty acids by myocytes from blood, and β -oxidation rate in muscles, stimulates glucose consumption and its catabolism in muscles and the liver. Adiponectin gene knockout animals have metabolic syndrome with marked insulin resistance [8–10].

Adipolin is a new adipokine, which has an anti-inflammatory effect and reduces glucose, regulates carbohydrate and lipid metabolism in the liver and adipose tissue. The concentration of the hormone negatively correlates with BMI, waist/thigh ratio, and glucose concentration in blood [11]. An exact mechanism of adipolin regulatory effect has not been discovered yet, however, the expression of its gene is known to decrease in experimental rodents with induced obesity. Adipolin injected in such animals reduces the accumulation of macrophages and expression of proinflammatory genes of adipose tissue. Adipolin is a new and attractive target for the development of agents to treat insulin resistance, diabetes mellitus and obesity [10, 12].

Resistin is a peptide hormone produced in adipocytes as well, but it is an adiponectin antagonist. Resistin has both paracrine and telecrine effect, since it has receptors in adipose tissue itself, and also in the liver. Resistin level increases with body weight gain. There has been established the direct interaction between resistin level and low-density lipoprotein (LDLP) levels, triglycerides, fasting glucose, C-reactive protein (CRP), as well as with anthropometric data (BMI, waist and chest circumference), and indirect interaction — with high-density lipoprotein (HDLP) level. Resistin can serve as an indicator to determine the severity of insulin resistance, obesity, and atherosclerosis. Liver is the first target organ of resistin effect resulting in hepatic insulin resistance development [13]. Resistin is a promoter of adipose cell maturation, it acts as an autocrine regulator of the formation of prodiabetic factors in adipose tissue. Moreover, this adipocyte-specific hormone can be characterized as a proliferative, anti-apoptotic, proinflammatory and pro-angiogenic regulator [14, 15].

Visfatin is a protein hormone found in 2004. It is produced by visceral adipocytes and has an impact on those tissues, which have insulin receptors, though its receptors differ from insulin ones, and therefore, these hormones-synergists do not compete for binding sites

on membranes of target cells. Visfatin level grows proportionally with obesity degree. It has insulin mimetic activity, since it stimulates autophosphorylation of β -subunits of an insulin receptor, and thus, stimulates tyrosine-type phosphorylation of intracellular proteins, catalyzed by β -subunits, the active centers of which has tyrosine kinase activity [16–19].

Chemerin is one of newly found adipokines. It is secreted like 18-kDa nonactive precursor protein (prochemerin). Chemerin level in blood correlates with obesity and dyslipidemia, and can play a role in insulin resistance development. mRNA expression of both chemerin and chemerin receptor sharply increases during the differentiation of preadipocytes into adipocytes. Local production of chemerin activates adipogenesis, and through its receptor or, probably, through any other receptor, various functions of mature adipocytes are modeled. Chemerin is one of adipokines participating in the pathogenesis of obesity and inflammation, and included in congenital immune system [20, 21]. Chemerin and apelin levels positively correlate with inflammation in adipose tissue in obesity and type 2 diabetes melitus [22–24].

Apelin is a recently identified ligand for APJ-receptors of the small bowel and hypothalamus, a pro-peptide containing 77 amino acid residues cleaving into several shorter peptides, which are the ligands for apelin receptors. It is synthesized not only in adipocytes, but also in the stomach, heart, small intestine and hypothalamus. When injected in brain ventricles, apelin causes the reduction of food intake both in well-fed, and in hungry rats. The data confirm a possible role of apelin in eating behavior control [25–27].

β -Arrestin is a protein repressing adipogenesis and inflammatory processes in adipose tissue in obesity. The mechanism of its regulatory action is not understood yet, however, β -arrestin is known to interact with some signal molecules; this mechanism, in particular, includes regulatory events associated with peroxisome proliferator-activated receptor gamma (PPAR- γ), protein kinase-activated AMP (AMPK), protease-activated-receptor-2 (PAR2), cannabinoid receptors, etc [28, 29]. β -arrestin gene knock-out mice had high predisposition to diet-induced obesity [30]. All the above mentioned characteristics of the protein give grounds to consider it to be a potential remedy for obesity and metabolic disorders resulted from obesity [31].

Neurohormones

Agouti-peptide (AgRP) is a neuropeptide (more precisely, it is a protein, since it contains 132 amino acid residues) produced in hypothalamic arcuate nuclei, namely, in AgRP/NPY-neurons. It increases appetite reducing metabolism level and energy consumption. It is one of the most powerful and sustained appetite stimulator. It is a paracrine stimulator of cortical neurons

responsible for esuriency. Agouti-peptide was identified independently by two research groups based on amino acid-like sequence, which was known for agouti-signal peptide — a protein synthesized in skin and responsible for skin color control. AgRP appetite-stimulating effects are inhibited by leptin and activated by ghrelin [32].

Neuropeptide Y is a peptide (36 amino acids) produced in hypothalamic arcuate and dorsomedial nuclei. It controls central and peripheral functions by binding to receptors associated with G-proteins Y_xR ($x=1, 2, 4, 5$) [33]. Hypothalamic orexigenic (appetite-stimulating) neurons activate eating behavior by producing neuropeptide Y, which passed to the following neurons in the chain to send a signal “eat!” to brain. Neuropeptide Y level in blood increases with hunger and decreases with the sense of fullness [34–36].

Orexin A and B are hypothalamic neuropeptides discovered in the late 1990-es and formed in hypothalamic nuclei from crude preprotein — pre-orexin. Posttranslational hydrolysis of the protein results in two peptides: the longer one — orexin A containing 33 amino acids, and the shorter one — orexin B with 28 amino acid residues. These peptides have not only appetite-stimulating effect, but also activate thermogenesis in brown adipocytes. They regulate sleep and wake circadian cycles, spontaneous physical activity, perception of pain, odor, sexual and cognitive functions [37]. In orexin-knock out animals obesity developed, total energy consumption level lowered, mainly, due to decreased physical activity [38]. The recent studies have shown orexin A to have neuroprotective properties as well raising nervous tissue resistance to ischemic damaging effect due to lipid peroxidation inhibition and a decreased level of caspase-induced apoptosis [39].

Proopiomelanocortin derivatives are the family of peptides referring to melanotropin group (melanocortins, melanocyte-stimulating peptides (α -MSH, β -MSH, γ -MSH)) resulted from posttranslational proteolysis of proopiomelanocortin protein (POMC) synthesized in hypothalamic arcuate nuclei in response to leptin regulatory stimulus. Proopiomelanocortin is also a precursor of ACTH, lipoprotein and endorphin. As it turned out recently, in addition to a regulatory effect on melanin synthesis in skin melanocytes, hair follicles and iris, melanocortins directly participate in body weight regulation through appetite control function. They are typical anorexins, i.e. appetite-suppressing hormones [40, 41]. Melanocortin underproduction or impaired expression of their receptors result in obesity development. Melanocortin receptor mutations were revealed in about 1–5% subjects with BMI over 40, these mutations being typical for early severe obesity [2]. Experiments on animals succeeded in delivery and build in normal MSH genes using virus vectors (Lentivirus) [42].

Galanin is a hypothalamic neuropeptide (be more precise, the family of peptides of similar structure),

able to increase food intake, reduce glucose tolerance, raise the risk of obesity and dyslipidemia that promotes insulin resistance development and the rise of blood pressure. Galanin also decreases metabolism level inhibiting tissue oxygen consumption and producing carbon dioxide [43, 44]. It is produced in paraventricular nuclei and in amygdaloid nucleus [45]. Its regulatory effect is closely related to the effect of other pituitary-hypothalamic hormones. So, anorexigenic effect of growth hormone is mediated by decreased galanin production [46]. Adrenalin, the level of which increases in fasting along with orexigenic hormones including galanin, inhibits galanin secretion (by 100% in well-fed rats, and by 50% — in hungry rats) [47].

Endogenic opioids (endocannabinoids) is a group of neuropeptides synthesized in paraventricular nuclei and lateral hypothalamic nuclei. Their functions significantly differ from those of peptides formed in arcuate nuclei [48]. Opioids are well known as very intensive central analgesics. Recently, some researchers have demonstrated a key role of opioids in pathophysiology of different diseases including obesity. Endogenic ligands for opioid receptors originate from three independent genes, and their processing result in the formation of such primary opioid peptides as β -endorphin, met- and leu-enkephalin and dynorphin. These peptides and their derivatives reveal different affinity and selectiveness degree as related to μ -, δ - and κ -receptors localized in the membranes of central and peripheral neurons, neuroendocrine, immune and mucous cells, as well as in the cells of many other organs and systems [49]. Lipid-rich diet-induced obesity reveals positive correlation with the number of μ -opioid receptors [50]. On the other hand, dynorphin, endogenic agonist of κ -receptors, is directly related to food intake control [51]. Dynorphin, as well as galanin, neuropeptide Y and melanocortins, stimulates appetite and increases food intake [52].

Nociceptin (orphanin, FQ), a 17-amino acid peptide, first isolated in 1995, is produced in different brain parts including cortical neurons, pons varoli, hippocampus, the cells of olfactory nuclei, substantia nigra, brain stem, and some other areas [53]. It increases food intake in experimental animals when infused intracerebroventricularly. Nociceptin is a ligand (agonist) of opioid receptors (ORL1) involved in the regulation of a number of other central functions, such as pain, psycho-emotional stress, locomotor activity and memory. Some researchers believe nociceptin to have an effect on body weight not only by food intake stimulation but through energy consumption decrease [54]. Orexigenic effect of nociceptin is accompanied by its inhibiting effect in relation to anorexigenic melanocortin (α -MSH) receptors [55, 56].

Cocaine- and amphetamine-regulated transcript (CART) is a multifunctional protein functioning as a regulator of satisfaction, sense of fullness, and stress

excitement. It is secreted by the cells of hypothalamus, hypophysis, adrenals, digestive tract, and pancreas, and has evident antioxidant properties [57]. Animals and humans with a defective CART gene were characterized by Langerhans islet dysfunction, impaired insulin secretion and body weight increase [58]. So, Leu34Phe missense mutation of pro-CART gene found in the members of one of American families was accompanied by decreased number of bioactive CART, with the gene of this protein having poor expression and handling that resulted in the development of the above mentioned symptoms [59]. This regulator decreases food intake in animals, however, it is still unclear how the effect correlates with obesity, and likewise the mechanism of the effect remains unclear [60].

Ciliary neurotrophic factor (CNTF) is a neurotrophic cytokine, peptide belonging to interleukin-6 (IL-6) family. Initially it was characterized as neuron survival factor, which is a powerful neuroprotector in multiple retinopathy [61]. However, later CNTF has been found to be a unique remedy to reduce food consumption and body weight in rodents with induced obesity and leptin resistance [62]. It improves metabolic indices in obese insulin resistant animals [63]. The mechanism of CNTF regulatory effect is still unclear, however, recently, CNTF with its receptor subunits have been demonstrated to be able to transfer to anorexigenic nuclei of POMC-neurons of hypothalamic arcuate nuclei. Further, the stimulation of hypothalamic nuclear fraction using CNTF has been shown to induce phosphorylation of several signal proteins including serine/threonine protein kinase Akt, as well as POMC gene transcription. Based on the findings the researchers suggested that CNTF regulatory effect is mediated by melanocortins [64].

Nesfatin has been relatively recently identified as the product of posttranslational processing of nucleobindin 2 protein (NUCB2) widely expressing in different brain parts [65]. Despite the fact that nesfatin was first found in hypothalamus as one of factors of the sense of fullness, in recent years nesfatin has been proved to be also abundant in X/A-like gastric endocrine cells, which produce orexigenic hormone — ghrelin (See below). The last mentioned indicates that it is gastric mucosa that can be the principal place for the synthesis of this hormone [66]. Nesfatin regulates glucose metabolism and energy metabolism in many tissues. It potentiates both insulin release from β -cells of pancreas, and also insulin effect on the liver, where energy is stored up. Moreover, nesfatin regulates the differentiation of adipocytes in adipose tissue. NUCB2 gene expression has been proved to correlate positively with obesity development. Thus, this hormone plays a key role in the integration of food intake level, glucose metabolic rate, and energy stores and energy consumption balance. Nesfatin expression, secretion and/or regulatory effect dysfunction can be involved in the pathogenesis of type 2 diabetes mellitus, obesity, and metabolic syndrome [67, 68].

Digestive hormones

Ghrelin is a peptide consisting of 28 amino acids, derived from pre-proghrelin — a protein produced in endocrine X/A-like cells of stomach [69, 70]. Hypothalamus, hypophysis, pancreas, kidneys, myocardium, blood vessels, adipose tissue, ovaries, placenta are the targets of ghrelin regulatory effect. Affecting hypothalamic nuclear cells associated with cortical neurons ghrelin activates orexigenic neuropeptide Y secretion that causes esuriency, and thus, increases food intake. On other targets ghrelin inhibits a proinflammatory cascade, has antinociceptive and anti-inflammatory activity [71].

Peptide YY (PYY) is a peptide hormone synthesized in L-cells of ileum and the large intestine. Peptide YY molecule includes 36 amino acids, and has the sequences similar to pancreatic polypeptide and neuropeptide Y. Peptide YY synthesis is stimulated by fats, carbohydrates and bile acids of chymus, as well as by gastrin-releasing peptide of the stomach. Peptide YY is an inhibitor of gastric, bile and pancreatic secretion, decreasing gastrointestinal motility. It is a typical anorexin. It targets hypothalamic nuclei producing hormones of satiety. Simultaneously it inhibits neurons, appetite depending on them. Peptide YY content in blood significantly increases resulting from regular aerobic physical exercises (swimming, running, aerobics, etc.) that in the long run decreases appetite, food consumption, and therefore, body weight [72, 73].

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) refer to incretin class. GIP — a peptide hormone containing 42 amino acids — is an intestinal hormone produced in enterosecretory K-cells of the small intestine in response to food in digestive tract.

Glucagon-like peptide is produced in L-cells located in the distal part of the small intestine and the proximal part of the large intestine. It has hypophagic effect on the receptors of area postrema cells, as pancreatic hormone amylin, which has the same effect [74].

These incretins are produced within a very short period of time (minutes), and during this time they stimulate insulin secretion by β -cells of Langerhans islets. The effect of these hormones is mediated by specific receptors of one and the same family (GIPR, GLP-1R), which situated in β -cells and other organs and tissues (stomach, jejunum, heart, kidneys, lungs, pancreas, central nervous system). These hormones have a direct relationship to obesity and insulin resistance, as their deficiency result in the development of the mentioned conditions, and their administration can be used as preventive and treatment measures [75, 76].

Enterostatin is a pentapeptide, one of anorectic enterohormones originating from partial proteolysis of procolipase — a protein synthesized by exocrine cells

of the pancreas. There are enterostatin receptors in many tissues including cortical neurons. Enterostatin having an effect on cortical neurons causes the sense of fullness [77]. This peptide has been shown to reduce food intake in rodents if administered peripherally or centrally [78, 79], to suppress insulin secretion [80], to inhibit the expression of agouti-peptide receptor [81], to reduce cholesterol level in blood serum [82].

Apolipoprotein IV is an amphiphilic protein synthesized in the small intestine, along with apolipoprotein B48 participates in the formation of chylomicrons. Its gene also expresses in the hypothalamus. This protein is able to emulsify lipids, and it is attributed the role of a protector in relation to obesity and cardiovascular diseases [83, 84]. Among other anorexins such as peptide YY, cholecystokinin, and neuropeptide Y, it can have an effect on food behavior and reduce food intake [85]. Apo-A-IV knock-out mice have the lower level of triglycerides and cholesterol in blood plasma, hypolipidemia persisting against fat rich diet [86].

These animals are not revealed any anomalies in the system of lipid digestion and absorption, tolerance to nutritive lipids, just like fecal fat [87]. Apolipoprotein IV expression in hypothalamic neurons is regulated by leptin [88].

Xenin is a recently discovered 25-amino acid peptide produced by the family of K-cells of upper gastrointestinal tract in response to GIP regulatory signal [89]. The mechanism of its regulatory effect in relation to body weight regulation is still unclear, though the fact of its participation in the regulation is undeniable. Xenin has been proved to take part in glucose homeostasis regulation and potentiate GIP insulinotropic effects [90]. It can influence at the level of hypothalamic nuclei reducing food consumption using leptin- and melanocortin-independent mechanisms [91]. Xenin concentration in blood of subjects increases after food intake, therefore this peptide is considered to be one of the markers of the sense of fullness [92].

Uncoupling proteins

Uncoupling proteins (UCP) are able to damage the coupling of oxidative phosphorylation either as classical protonophores, or as channel-forming anion transporters, but all of them anyhow reduce proton membrane potential of mitochondrial inner membrane, and therefore, disturb ATP-synthetase catalytic function. The energy of electron transport in a respiratory chain is released in the form of heat [93]. The first protein found in brown adipose tissue and responsible for thermoregulation, in particular, in hibernation animals and infants, was thermogenin (UCP1) [94]. A great while brown adipocytes in adults were supposed to be completely reduced, however, recently, they have been proved to be still preserved as part of white fat, e.g. in inguinal and retroperitoneal region, around gonads, in

epicardium [95, 96]. In recent years, in different tissues, there was discovered a family consisting of about 35 mitochondrial proteins, which are anion transporters. Among them UCP2 and UCP3 are likely to participate in reactive oxygen species binding and/or metabolism of fatty acids; their uncoupling effect can be secondary. There is little information on proteins UCP4 and UCP5 (BMCP1), however, phylogenetic analysis shows that to a greater extent they are the development of protein UCP1 form and have certain specific functions [97]. This data indicate the availability of mitochondrial uncoupling proteins as new therapeutic agents to prevent acute damage of central nervous system cells [98].

The discovery of irisin by Swedish scientists with the lead of Boström in 2012 became a breakthrough. Irisin is a new peptide hormone secreted in muscular tissue, able to turn white adipocytes into brown ones [99] that opens up fresh opportunities for developing new methods to prevent and treat obesity, diabetes mellitus and metabolic syndrome [100].

Conclusion. The analysis of present knowledge concerning body weight regulation problem has shown that not only hormones of “classical” endocrine glands such as hypophysis, adrenals, pancreas, thyroid, gonads, and others take part in body weight control, but also a great number of hormones and hormone-like substances secreted in different tissue of the body (brain, adipose tissue, gastrointestinal tract, etc). There is no escaping the impression that science eventually starts “pulling out” a huge monster whose name is obesity mechanism. However, there is no cause for pessimism, since it becomes clearer and clearer why this pathology is so multifaceted, its causes being so various. The recent achievements of laboratory diagnostics, clinical biochemistry and molecular biology enable even today to find out what individual genetic and epigenetic factors result in obesity development in a certain patient. There are no theoretical and methodological prohibitions to reveal these factors, as human genome is decoded, and most protein-peptide body weight regulators can be quantified or characterized by their expression level. The prospects for obesity treatment and obesity related diseases are based primarily on the advances in gene therapy predicted by scientific futurology. Gene therapy is much more likely to be the basic treatment technique of such diseases in XXI c. [101, 102, 103].

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