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Gratis

Review Article

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Nonspecific Energy Expenditure of the Body and Body Mass Regulation

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Abstract

The principal possibility of nonspecific energy expenditure at all stages of the transformation of nutrients in the body is demonstrated. These stages include the processing of food in the mouth, digestion, absorption, interaction with the intestinal micro biome, and interstitial metabolic processes. Particular attention is paid to the role of nonspecific energy expenditure of the body in the regulation of body mass. The data on the pivotal role of reducing nonspecific energy expenditure in the development of obesity and associated pathological conditions are presented. The prospects for using uncouples of oxidative phosphorylation, fatty acids, carnitine, bile acids, sarcolipin and a number of other substances as regulators of the nonspecific energy expenditure and potential means of preventing and treating obesity are analyzed.

Keywords: Nutrients, Nonspecific energy expenditure, Obesity, Uncouples, Fatty acids, Sarcolipin, Browning

Abbreviations: ANT: Adenine Nucleotide Translocase; ROS: Reactive Oxygen Species; DNP: 2,4- Dinitrophenol; BMI: Body Mass Index; LCFA: Long Chain Fatty Acids**;** SCFA: Short Chain Fatty Acids**;** MCFA: Medium Chain Fatty Acids; PUFA: Polyunsaturated Fatty Acids; CDCA: Chenodeoxycholic Acid; $\Delta\mu H^+$: proton membrane potential; $\Delta\psi$: electric potential of the inner mitochondrial membrane; ΔpH: pH difference on both sides of the inner mitochondrial membrane; C_{12}TPP: dodecyltriphenylphosphonium; FABP(s): Fatty Acid Binding Protein(s); FCCP: carbonyl cyanide *p* (trifluoromethoxy) phenylhydrazone; FNDC5: fibronectin gene type III encoding iris in; HFD: High-fat diet; Sln: sarcolipin; UCP(s): uncoupling protein(s)

Introduction

Body mass and health obesity as a risk factor of cardiovascular and endocrine disorders

Objective of the article: Despite the undoubted progress in modern medicine, cardiovascular diseases continue to be the leading causes of death worldwide. To a large extent, this pattern is a consequence of the increasing prevalence of obesity in all civilized countries. Overweight is well-known to be directly related to the pathogenesis of a number of endocrine and metabolic disorders, not to mention the essential limitations of the social functions of obese people and the occurrence of enormous psychological and personality problems. Consequently, the fight against obesity and prevention of obesity should be considered to be priority strategic goals of the XXI century medicine [1]. At the same time, as the results of the latest scientific research show, the mechanism of the development of obesity is extremely complicated and can include the violation of many regulatory factors that control body mass. Today it is almost impossible to answer the question why the same diet in two people of the same sex, age, and having practically the same muscular energy expenditure, often leads to highly significant differences in their body mass. One person, even getting excess calories, preserves the

normal body weight without any problems, while the other, consuming a hygienically normalized amount of calories, has a clear propensity for obesity. In part, this probably depends on the different ability of people to absorb nutrients. To create the same diet does not present any difficulties, but it is probably impossible to simulate the same degree of assimilation of nutrients, because each person has an absolutely individual, genetically determined system of digestive enzymes. Moreover, each person forms a unique intestinal microbiota during ontogeny, and this, undoubtedly, influences nutrient assimilation. In addition, until now, many people and even some doctors have a very simplistic idea of the applicability of the law of conservation of energy to living systems. For example, they believe obesity to be solely the result of consuming excess calories compared to the necessary costs for physical activity [2]. In fact, the body can distribute excess calories from food at least in three ways:

1. Conversion of part of the energy of nutrients into reserve substances (fat and glycogen);
2. "Burning" of a certain proportion of metabolic fuel in tissues to carry out various types of work:

- Mechanical work (muscle contraction, the work of molecular machines, the creation of electric gradients of ions Na +, K +, Ca2 +, H + and their use for generation of a nervous impulse, cellular signaling, synthesis of ATP, etc.)
- Osmotic work (providing energy of various types of active transport of substances through biological membranes),
- Anabolic work (energy supply for the synthesis of proteins, lipids, carbohydrates, nucleic acids, various regulatory molecules, etc.)
- Activation work (energy-dependent activation of various organic molecules before their including into metabolism),
- Detoxification (energy-dependent reactions of neutralizing endogenous toxins and xenobiotics),
- Thermal work (generation of heat necessary to maintain a constant body temperature);

3. Nonspecific ("useless", futile) energy losses of nutrients and endogenous metabolic fuel. This kind of energy expenditure is almost imperceptible to man. The participation of the first and the second ways in the regulation of body weight has been studied quite well, but the role of the third is not so clear. The practical recommendations that should be the result of understanding this role are also unclear. The terms "useless" or "futile", in our opinion, are not correct, since this energy dissipation protects the body from obesity and, therefore, are very useful. The purpose of this review is to analyse in detail this energy expenditure of the body and to assess the possibilities and prospects for using fundamental scientific achievements in this area to prevent and treat obesity.

The main stages associated with nonspecific energy expenditure and changes in body mass

Nonspecific energy expenditure is possible at all stages of assimilation of nutrients such as (Figure 1):

- Primary processing of food in the oral cavity,
- Food digestion in the stomach, small intestine,
- Diet-induced thermogenesis,
- Interacting with small and large intestine microbiota,
- Intracellular transformations of metabolites,
- Final metabolic reactions associated with the transport of protons and electrons in the
- Mitochondrial electron transfer chain and the oxidative synthesis of ATP.

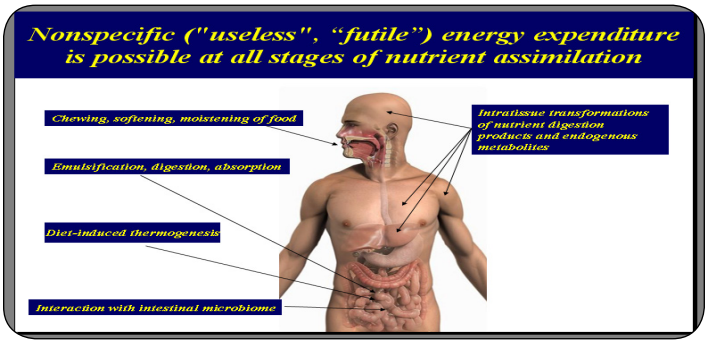


Figure 1: Levels of nutrient energy transformations associated with nonspecific energy expenditure.

The stage of primary food processing, chewing, digestion, absorption of basic nutrient digestion products: The regulating role of the quality of primary processing of food in the oral cavity, associated with its mechanical grinding, wetting, impregnation with enzymes and viscous components of saliva, having the properties of natural lubricants, seems quite obvious. It is at this stage these conditions are created for the further digestion of complex nutrients in more distal regions of the gastrointestinal tract. The effectiveness of the primary processing of food depends on the condition of teeth, gums, the functioning of large and small salivary glands, as well as the nature of masticatory organs. It would seem that in people prone to obesity, food in the

cavity should be processed most efficiently, ensuring the use of the maximum potential energy of nutrients. In fact, in such individuals, tooth loss [3-5], dental caries [6] and periodontal disease [7] are more often observed than in people with normal body mass. Such people, as a rule, eat hurriedly, badly chewing food, trying to satisfy hunger more quickly. The causal relationship here is not entirely clear, but the fact itself is unquestionable. As a result, in obese people, food is poorly chewed and insufficiently processed by oral fluid components. However, it should be borne in mind that ineffective primary processing of food in obese people is more than compensated by increased food intake due to a violation of the secretion of hormones that limit appetite and the amount of food consumed. In healthy people, effective fragmentation, softening and wetting of food as a result of a more complete chewing act leads to more complete satiety as a result of the consistent action of hormones (orexins and anorexins) responsible for the formation and successive change in hunger and satiety feeling. In people prone to obesity, this sequence is usually disordered [8,9]. In this connection, the truly plausible foresight is the slogan of I. Ilf and E. Petrov from the "The Twelve Chairs": "Carefully chewing food, you help society" (now this slogan can be interpreted not only in a sense that by this you save food, so necessary for a society, but also reduce the likelihood of developing obesity in yourself, and therefore, in a society as a whole). Nonspecific energy expenditure at this stage is also associated with the increase in heat generation during food intake or in the postprandial period. The effect is called "diet-induced thermogenesis". It appears as a result of energy use for production and secretion of enzymes, absorption of digestion products, resynthesis of lipids and proteins, gut motility, production of gastrointestinal hormones etc. This thermogenesis makes up 5-15% of daily energy expenditure [10]. Food components have a different effect on the size of the energy expenditure. The highest thermogenesis is induced by dietary proteins, but it is also dependent on the type of proteins [11]. Diet-induced thermogenesis may be a target for controlling body energy consumption in obesity [12].

The stage of digestion and assimilation of nutrient digestion products, intestinal microbiome as one of the regulators of nonspecific energy expenditure of the body: The same food is digested quite differently in different subjects who do not have an identical activity of digestive enzymes. Differences, in this case, can be explained by well-defined genetic causes (congenital enzymopathies of digestive enzymes that lead to the development of malabsorption phenomena) and acquired defects of digestive enzyme systems caused by the inhibitory effect of various internal and external factors. Undigested nutrients inevitably appear in the feces, representing nonspecific energy losses in the form of energy losses of the initial energy of nutrients (a typical example is steatorrhea). Inhibitors of digestive enzymes have been used for a long time as medicines in the treatment of severe forms of obesity to create artificial malabsorption of nutrients. This approach to the treatment of obesity continues to develop actively [13-17]. Disclosure of the detailed mechanism of the development of obesity, associated with energy metabolism disorders at this stage, requires the description of the role of various hormones, not only those produced by the "classical" endocrine glands, but also by cells of the gastrointestinal tract, liver, adipose tissue, various parts of the brain, muscles and other tissues. Many of these hormones affect directly or indirectly the food behavior, as well as the efficiency of the enzymatic systems of the digestive tract, the activity of which the body weight depends on. Another part of hormones affects adiposeness and metabolism in adipose tissue. In this paper? We will not analyze the contribution of each of these hormones to the regulation of body weight, nor the characteristics of the mechanism of their regulatory effect, since a large number of review articles are devoted to these questions, including our previously published review [18]. On the other hand, it is at the stage of digestion and absorption of food components that the human and animal body is forced to "share" a part of the potential nutrient energy with an intestinal microbiome, an evolutionary symbiont living in mutually beneficial coexistence with the host organism, and this is also part of the nonspecific energy expenditure. The degree and nature of these energy inputs depend, first of all, on a set of microorganisms in the microbiota. In recent time, the effect of the intestinal microbiota composition as a potential factor influencing the energy balance and fat accumulation has been particularly intensively studied. Nonspecific energy expenditure at the stage of the interaction of the organism with the microbiome largely depends on the intake of prebiotic food fibers- polysaccharides, not digested by host enzymes, but contributing to the development of normal intestinal microflora [19-22]. The intestinal microbiome can affect the intestinal motility, the ingestion of the products of its metabolism into the blood, and the regulatory functions of the brain that control the energy balance. The latter manifests itself both at the level of nutritional sensitivity mechanisms and potentially at integration sites in the central nervous

system (reaction to increasing fermentation of indigestible polysaccharides and obtaining additional energy from a part of the food, reducing the expression of a number of gut hormones and increased release of the YY peptide, which slows the mobility of the intestine, etc). Therefore, changes in the microbiome species composition can lead to both a decrease in body mass due to the loss of part of the nutrients as a result of the development of diarrhea, and to the development of obesity because of the slowing of peristalsis. Disturbances in the microbiome (e.g. under antibiotics) can affect body mass along several routes, including differences in energy exchange between the intestinal microbiota and the host's organism, the formation of new metabolites that are not typical for the host organism, as well as changes in immunity and the development of inflammation in adipose tissue [22-24].

Some authors attach particular importance to microbiome disorders in the pathogenesis of obesity, considering this condition to be a special form of intestinal infection, in particular caused by *Clostridium Difficile* and this infection is believed to be transmitted by the fecal-oral route. This form of obesity can be transmitted, for example, from one member of a family to another and can simulate the "hereditary" nature of the disease. According to some authors, the most radical way to prevent and treat such forms of obesity is to transplant the microbiome from a healthy donor [25-28].

Intracellular metabolic processes and energy dissipation, futile cycles

Energy dissipates inevitably in many anabolic and catabolic processes taking place in the cells, since common intermediates appear to take part in reversible chemical transformations. These transformations are not isoenergetic and catalyzed by different enzymes [29]. Typically, such transformations form the so-called futile (useless) cycles, the functioning of which leads to the dissipation of energy. Examples of such cycles are fructose-6-phosphate / fructose-1,6 bisphosphate cycle; glycerol / glycerol-3-phosphate cycle; pyruvate / phosphoenolpyruvate cycle, creatine / creatine phosphate cycle; futile cycle of calcium in the mitochondria, and many others [30-33]. The constant "rotation" of such cycles leads to the occurrence of self-oscillation of the substrate concentrations involved in the cycle. The works of Russian biophysics E.E. Selkov and his followers proved for the first time the association of oscillations of futile cycles with circadian rhythms that allows considering these cycles as part of the mechanism of "biological clocks" [34].

The speed of functioning of the futile cycles can vary significantly under the changing functional states of the organism and, consequently, the amount of energy dissipated can vary. Thus, these "useless" cycles can perform a very useful function of maintaining the energy homeostasis of the body [35]. A significant slowdown of some futile cycles during the development of obesity has been demonstrated. [36]. Most futile cycles have many different hormonal and allosteric regulators, which are likely to become targets for the creation of pharmacological agents aimed at the prevention and treatment of obesity [37].

Dissipation of energy as a result of oxidative phosphorylation uncoupling

The main way to convert the energy of nutrients in the body is the synthesis of ATP as a universal high energy substance that can participate as an energy donor in performing various types of ATP-dependent endergonic functions. In eukaryotes, ATP is mainly synthesized in mitochondria by oxidative phosphorylation, a process discovered in 1930 by a Russian biochemist and molecular biologist V.A. Engelhardt. The rate of mitochondrial respiration depends on many factors, including the ratio of [ADP] / [ATP]. Mitochondrial oxygen consumption rises sharply with an increase in the concentration of ADP (respiratory control) and spontaneously decreases when all ADP is converted to ATP. Transport of electrons using oxygen as the final electron acceptor (mitochondrial respiration) and the synthesis of ATP catalyzed by proton ATP synthetase are coupled processes, and the degree of coupling can be quantified by calculating the P: O or ADP: O ratios that express the number of ATP molecules, formed upon the uptake of 1 oxygen atom. Even if the coupling is maximally complete, not all of the energy released in the transfer of electrons towards oxygen is used for ATP synthesis. A certain share of the energy turns inevitably into heat, necessary to maintain body temperature. Moreover, the ideal complete coupling of respiration and oxidative synthesis of ATP is apparently impossible and dangerous because of the increased formation of reactive oxygen species and free radicals. Endogenous uncouplers of oxidative phosphorylation, such as fatty acids, calcium ions, uncoupling proteins, etc., protect mitochondria and cells from excessive accumulation of active forms of oxygen (ROS), chemical modification of proteins and the cell death program initiation [38-41].

Regulators of oxidative phosphorylation: There

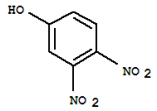
are many regulatory factors that control the rate and effectiveness of oxidative phosphorylation. These factors include a number of mineral and organic substances of endogenous and exogenous genesis that change the activity of transport systems delivering the necessary substrates and removing products of their transformations through the mitochondrial membranes, as well as the activity of the enzyme systems of electron transport and oxidative synthesis of ATP. At present, it is firmly established that all these factors are directly related to the regulation of body weight and are potential targets for the development of new methods for the prevention and treatment of pathological conditions associated with obesity [42].

Uncouplers as inducers of nonspecific energy expenditure of the organism: Uncouplers of oxidative phosphorylation are the substances that reduce the proton membrane potential of the inner mitochondrial membrane (ΔμH+). They activate mitochondrial oxygen consumption and turn off the ATP synthesis reaction catalyzed by proton ATP-synthetase (H+ -ATPase). Under the influence of uncouplers, the energy of electron transport from the initial substrates to oxygen is dissipated as heat. That part of the heat energy, which exceeds its required level to maintain constant body temperature, should be attributed to the nonspecific energy expenditure of the body. The action of the uncouplers is directed not at the enzymatic systems of the mitochondria, but onto the lipid bilayer of the inner membrane. Depending on the mechanism of the uncoupling effect, all these substances can be divided into 3 main classes:

Protonophores: Substances that induce the proton conductivity of the inner mitochondrial membrane and reduce or completely remove both components of the proton membrane potential (Δψ and ΔpH) are called protonophores. Most of these substances are weak hydrophobic acids that induce transport of H + ions through the impermeable inner mitochondrial membrane and release these ions within the mitochondrial matrix by the dissociation of the acid molecules. According to the Mitchell chemiosmotic theory, the oxidation-reduction reactions occurring in the respiratory chain are the direct energy generator in the form of the chemical potential ΔμH+ (proton-moving force). The action of protonophores is based on the decrease of ΔμH+ as the most important link in the coupling phenomenon. As a result, the ΔμH+ energy are dissipated as heat. Protopophores are the potential candidates for the role of anti-obesity drugs, especially through their ability to prevent excessive accumulation of ROS in mitochondria [33]. By now, a large number of substances possessing precisely such type of the uncoupling action have been isolated or synthesized. The structural classification of protonophor uncouplers was developed by T. Hiroshi in 1990 [43]. In accordance with this classification, substances of this class are as follows:

Phenols

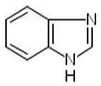
A classic example of the uncouplers of this class is 2,4-dinitrophenol (DNP).



In the early 30s of the last century it was found that the 2,4-dinitrophenol substance, which was widely used in industry, reduced the body mass of workers who were in contact with this substance. Maurice Teiner, a clinical pharmacologist of Stanford University, studied the substance as a pharmaceutical for treating obesity, and as a result, for two decades, DNP was used for this purpose in the US and several European countries. But soon the drug DNP was found to have a very narrow therapeutic range and a wide range of toxic effects, so now its clinical use is legally banned in most countries [44]. However, curently it's enough to go on some Internet sites to find criminal attempts to advertise DNP as a regulator of body weight.

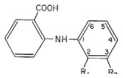
A number of human and animal hormones are iodine-containing phenol derivatives (di- and triiodothyronines). As has been shown by many studies, these hormones have a distinct caloric effect at the level of the whole organism, and therefore it seemed logical to assume their direct protonophoric dissociative effect. However, as it turned out later, the uncoupling effect was actually observed in vitro, but at concentrations significantly higher than physiological and pharmacological. It has now been proved that the action of these hormones in vivo is not direct, but mediated by their activating influence on the hormone-sensitive triglyceride lipase of adipocytes, the uncoupling action of free fatty acids and the activation of transcription of the genes of uncoupling proteins (UCP) [45,46]. The latter effects will be discussed below in the corresponding section of this paper.

Benzimidazoles



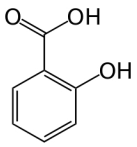
These uncouplers are typical weak aromatic acids whose kinetics of penetration through lipid bilayers has been studied both on isolated mitochondria and on artificial membranes. There have been a few attempts to use this class of uncouplers to correct experimental obesity and diabetes [47,48], but these studies have not been further undertaken, possibly because of the same reasons that restrict the use of DNP for these purposes.

N-phenylanthranilates

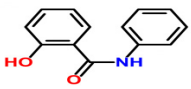


We could not find direct evidence of the possibility of using this class of uncouplers as a means to combat obesity, but given the fact that these substances have anti-inflammatory effect, and that the development of severe obesity is necessarily accompanied by inflammation of adipose tissue, it can be assumed that these substances might be tested on their ability to reduce body mass [49].

Salicylic acid and its derivatives



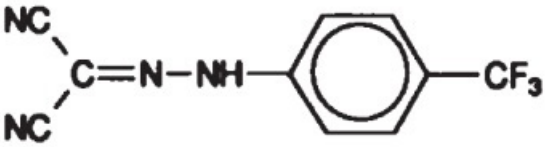
In recent years salicylic acid derivatives (aspirin, salsalate, sodium salicylate) have attracted increasing attention of researchers as relatively low-toxic agents for the prevention and treatment of obesity, metabolic syndrome and diabetes mellitus. The effect of aspirin is largely potentiated by some other substances used to reduce body mass (ephedrine, xanthines). However, the decrease in body mass under the influence of salicylic acid derivatives is probably due not so much to their uncoupling effect but to the anti-inflammatory and anticoagulant effect, as well as to the inhibition of cytokines responsible for the proliferation and differentiation of white adipocytes [50-52].



This group of substances has a powerful uncoupling effect. However, the uncouplers of this group are most likely not used for regulation of body mass because they have various inhibitory properties in addition to the uncoupling action [53-55], and they are therefore very toxic even at minimal concentrations. The derivatives of salicylanilides are used in experimental and clinical medicine, mainly as antibacterial and cytotoxic agents. They suppress the growth of mycobacteria tuberculosis, gram-positive microflora, and a number of fungi, some mollusks, helminths and tumors [56-60]. Despite this, attempts have recently been made to incorporate salicylanilide into drug compositions for treatment of metabolic syndrome [61].

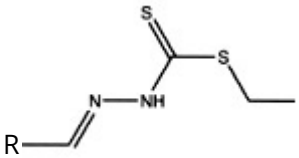
Phenylhydrazones

Phenylhydrazones are products of the interaction of phenylhydrazine with aldehydes or ketones. A number of phenylhydrazones have a powerful uncoupling action. Carbonyl cyanide p- (trifluoromethoxy) phenylhydrazone (FCCP) is most often used in experiments on the study of respiration of mitochondria:



Recently, new phenylhydrazone derivatives have been synthesized which, in the opinion of the authors, can be used to treat and prevent obesity, type II diabetes, insulin resistance, impaired glucose tolerance, or cardiovascular diseases [62].

Acyl dithiocarbazates

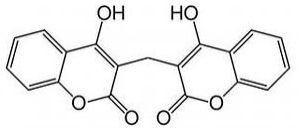


We did not find any information about the influence of this type of uncouplers on free energy expenditure at the level of the whole organism, as well as their influence on the body weight of animals and humans. This is probably due to the high toxicity of dithiocarbazates, many of which possess the properties of metal chelators with variable valency [63], and exhibit the properties of cytotoxic and antimicrobial agents [64,65].

Coumarins

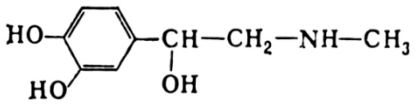
Dicumarol is the most known of the coumarin

uncouplers.



As early as the 1920s, its anticoagulant effect, due to his anti-vitamin K activity, was discovered, and in the 1940s this substance was isolated from the clover and its uncoupling effect was shown. It is unlikely that this uncoupler, actively acting as a protonophore *in vitro*, could be used to regulate body mass precisely because of its strong anticoagulant and antivitamin effect.

Aromatic amines



Epinephrine and other catecholamines are the uncouplers of this type, the thermogenic effect of which is undoubted *in vivo*, but their direct uncoupling effect on isolated mitochondria is not so obvious and is only observed if catecholamines are introduced into the incubation medium at concentrations many times higher than physiological ones. A detailed retrospective analysis of the works devoted to this problem is given in the A.M. Babsky thesis [66]. In all likelihood, the effect of adrenaline on the level of free energy expenditure and thermogenesis is not a direct uncoupling, but is mediated either by fatty acids released from adipose tissue by activation of the hormone-sensitive triacylglycerol lipase of adipocytes, or by UCP [67], whose role in body weight control will be discussed below.

Ionophores: These substances induce cationic or anionic conductivity of the inner mitochondrial membrane and reduce or completely remove only the electrical (Δψ), but not the acid-base component (ΔpH) of the proton membrane potential. This class includes potassium ionophores valinomycin and monaktin, sodium ionophores nigericin and gramicidin, calcium ions, magnesium, a carrier of bivalent ions A23187, a carrier of ammonium ion, nonactin, etc. [68]. All these substances are commonly used as tools for artificially reducing Δψ for *in vitro* experiments on isolated mitochondria. For other purposes, as well as for *in vivo* introduction, they are usually not used. The only exception is calcium, the introduction of which is widely used in experimental and clinical practice for many purposes. In particular, the effect of calcium ions, especially in combination with vitamin D3 on body mass and prevention of obesity, is well known, but this effect can hardly be explained as a direct effect of Ca ++ ions acting on mitochondria of adipocytes as ionophores. It is assumed that the body mass loss can be associated with activation of β-oxidation of fatty acids and induction of UCP(s) [69].

In recent time V.P. Skulachev et al. have used synthetic ionophores, particular phosphonium fatty acids. Thus, a dodecyltiphenylphosphonium (C12TPP) cation capable of penetrating the membranes at a dose of 500 μM/kg significantly reduced the body mass and fat mass of mice for 7 days of oral use. C12TPP also increased the level of oligomycin-sensitive consumption of oxygen by mitochondria of brown adipose tissue [70]. There is the reason to suppose that other compounds of this type, referred to as Skulachev ions (SkQ), will be very promising in terms of further clinical studies because they are used in catalytically low concentrations without any side effects.

Detergents: This type of uncouplers disrupts the structural integrity of the lipid bilayer of mitochondrial membranes and completely removes the proton membrane potential due to equalization of proton concentrations on both sides of the inner membrane. Among this group of uncouplers it is impossible to single out any substances that can cause the effect of "soft" uncoupling, even partial destruction of the membrane is a very crude effect of an irreversible nature. It is for these reasons that we do not see the possibility of using uncouplers of this type as regulators of body mass. Therefore, we omit a detailed analysis of these substances in this paper.

The role of fatty acids and substances involved in their metabolism in the regulation of body mass: There is no doubt that the likelihood of developing obesity, insulin resistance, and type II diabetes, is to some extent related to an increase in the content of free and bound fatty acids in a human diet. Excessive fatty acids of food are directed to adipose tissue, which plays the role of the main energy reservoir in the body. Fat deposition and the associated increase in the number of white adipocytes in adipose tissue, caused by a chronic positive energy balance, resulting in the development of obesity. A high level of fat consumption and low physical activity characterize the current lifestyle of people in developed countries. Excessive fat accumulates in the white fatty tissue, liver, heart and muscles. In these organs, intracellular lipids serve as an easily accessible source of energy during, for example, physical activity or fasting. However, in conditions of an elevated level of fatty acids in plasma and an increased intake of fats with food, such

forms of pathology as obesity and type 2 diabetes with insulin resistance are increasingly developing. Recent evidence suggests that intramuscular lipids peripherally surrounded by the protein *perilypin* are especially harmful in combination with impaired mitochondrial function, which is very typical for obesity and diabetes mellitus 2 [71]. On the other hand, it has been proven that the addition of certain fatty acids (eg omega-3 polyunsaturated fatty acids) to the diet of animals with experimental obesity caused by the high-fat diet (HFD) leads to a decrease in the body mass of these animals and a decrease in the probability of insulin resistance development [72]. Such regulating effect of fatty acids on body mass has been studied since the middle of the last century, and this effect was initially postulated as a classic example of protonophor uncoupling of oxidative phosphorylation, accompanied by the dissipation of free energy as heat (thermogenesis) and reduction in body mass. However, later the mechanism of this action of fatty acids turned out to be not so simple as it seemed at first. First of all, the effect of fatty acids on body mass was found to largely depend on their structure, in particular on the length of their carbon chains (radicals), as well as on the presence and a number of double bonds in radicals (ie., on the degree of unsaturation). In addition, it turned out that the mechanism of the action of fatty acids on nonspecific energy expenditure of the body is not so unambiguous and is mediated by a number of other substances, such as UCP(s), adenine nucleotide translocase (ANT), substrate translocases in mitochondria, receptors, hormones, and messengers that are involved in the body mass control [73-75]. Consequently, not only fatty acids, but also antiporter enzyme systems that mediate their uncoupling action, are of undoubted interest as potential targets for the development and testing of pharmacological drugs that regulate nonspecific energy expenditure of the body.

Short chain fatty acids, such as acetate, propionate, butyrate, etc, enter the body mainly as exogenously introduced food substances and nonspecific metabolites of the intestinal microbiome metabolism [76,77]. Recently, a number of authors have studied the effect of short chain fatty acids on energy expenditure in tissue mitochondria. Thus, it has been established that acetic acid enhances the expression of the enzymes of fatty acid oxidation in the liver, activating catabolism of lipids and thus suppressing the accumulation of fat [78]. In addition, acetate reduces appetite, acting through central homeostatic mechanisms [79].

In other studies, it has been found that the addition of butyrate to food can prevent obesity caused by a high-calorie diet and partially eliminate insulin resistance in mice by activating an adiponectin mediated mechanism for stimulating mitochondrial function in skeletal muscle [80].

Fatty acids with short and medium chain (SCFA and MCFA), regardless of their role in cellular signaling, are important substrates for energy metabolism and anabolic processes in mammals. SCFAs are mainly generated by colon bacteria and are predominantly metabolized by enterocytes and the liver, whereas MCFA are most often derived from food triglycerides, including milk and dairy products. A common feature of SCFA and MCFA is their independence on carnitine-associated mitochondrial transport and intramitochondrial activation with the formation of acyl-CoA thioesters. These fatty acids modulate the tissue metabolism of carbohydrates and lipids. It is manifested through their inhibitory effect on glycolysis and stimulation of lipogenesis or gluconeogenesis. They have no or generally have only weak protonophor activity in the mitochondria and do not significantly affect the transfer of electrons in the respiratory chain. SCFA and MCFA modulate the production of mitochondrial energy by two mechanisms: first, they produce NADH and FADH2 for the respiratory chain, secondly, reduce partially the efficiency of the oxidative synthesis of ATP, that is, they have the properties of "mild" uncouplers of oxidative phosphorylation [81].

At the same time, the physiological effects of SCFA cannot be interpreted as being exclusively positive for the host organism. In particular, the direct connection of short chain fatty acids with the development of inflammation in the wall of the intestine and adipose tissue in obesity has been proved. [82]. It is possible that the positive and negative effects of SCFAs depend on their concentration.

The regulatory effects of long-chain fatty acids (LCFA) depend on the presence and number of double bonds in the structure of their radical. Saturated long chain fatty acids are involved in the development of adipose tissue inflammation in obesity, activating caspase 4/5 in monocytes, and also including the release of interleukins IL-1β and IL-18 from these cells [83].

In contrast to saturated fatty acids, monounsaturated LCFA, additionally introduced into the diet, reduce central obesity in volunteers tested, followed by a decrease in the risk factors for the development of the metabolic

syndrome. Such a diet, according to the authors, could be useful for treatment and, perhaps, to prevent the development of the metabolic syndrome [84,85].

Additional introduction of polyunsaturated LCFA (docosahexaenoic and eicosapentaenoic acids) to humans and animals has many positive effects for maintaining energy homeostasis, including differentiation of adipocytes, activation of lipolysis, inhibition of lipogenesis, an increase in energy expenditure in the oxidation of fatty acids in mitochondria and peroxisomes, etc., that can help reduce the likelihood of developing obesity and concomitant diseases [86-89].

Cellular fatty acid receptors, fatty acid binding proteins (FABPs) as potential targets for body mass control: Fatty acid binding proteins, FABP(s), were discovered at the beginning of 70s of the last century. Initially, it was assumed that this is the only protein with a molecular mass of about 12 kDa, capable of binding long-chain fatty acids and some other lipids, localized in the cytosol of intestinal cells, the liver, myocardium, adipose tissue and kidneys. Later it was revealed that there were a few different proteins with similar structural domains. These proteins were detected in macrophages, the brain, testes and other cell types. Their molecular weight (14-15 kDa) was defined and the primary structure was determined. At present, 9 main genetic variants of these proteins are identified, designated by the first letter of the name of the tissue in which the expression of this protein is most pronounced. For example, A-FABP, also known as aP2 or FABP4, is the most important cytosolic protein of adipocytes and macrophages responsible for the accumulation of neutral fat and the development of inflammation in adipose tissue [90,91]. An increased level of FABP4 expression is observed with the development of obesity and insulin resistance [92]. Mice deficient in FABP4 and FABP5 had normal fat mass and were less likely to develop hepato-steatosis, insulin resistance, and inflammation in adipose tissue induced by obesity. The improving effects of FABP deficiency are mediated by the powerful anti-expression effect of palmitoleic acid in adipocytes and macrophages. Palmitoleate also enhances muscle insulin action and inhibits de novo lipogenesis in the liver. FABP4 is the main adipokine whose production is strictly controlled by the fatty acids released during lipolysis. This protein is supposed to function as a lipid sensor in adipocytes, capable of transferring fatty acids into blood plasma to meet the needs of certain organs and cells in this type of metabolic fuel [93].

In general, it can be stated that in physiologically optimal concentrations, proteins that bind fatty acids, promote the transfer of fatty acids and their utilization. When they are over expressed, especially the adipocyte forms of FABP4 and FABP5, inflammation, metabolic syndrome, breast cancer, and insulin resistance are developed. Therefore, the control over the expression level of the genes of these proteins is one of the promising fields for the prevention and treatment of obesity and its associated syndromes [94]. The determination of various types of FABP in serum can serve as a predictor and objective measure of the severity of obesity, cardiovascular disease, diabetes mellitus 2, pre-eclampsia of pregnant women and a number of other pathological conditions [95].

Carnitine and its role in body mass control: In recent time, researchers in the field of body mass control pay great attention to a highly effective regulator - L-carnitine, a low molecular weight amphiphilic substance involved in the transport of fatty acids from the cytoplasm to the mitochondrial matrix, where their β-oxidation proceeds. Carnitine was discovered by the Moscow biochemist V. S. Gulevich together with his Kharkov colleague R. P. Crinberg in 1905. Later, this substance was given the name vitamin B_t (B_{11}) and became widely used in medicine for various purposes. In this case, the biological activity was proved to be inherent only in the L-stereoisomer of this substance. The logic in carnitine using for prevention and treatment of obesity was based on the following well-known assumptions:

a) Carnitine deficiency and impaired carnitine acyltransferase activity may contribute to the development of mitochondrial dysfunction in obesity,

b) Carnitine is able to increase the body's non-specific energy inputs in metabolic syndrome and obesity.

c) The additional introduction of carnitine into the body reduces the body weight in animals with experimental obesity, reduces the fat content in the blood and liver, restores the activity of carnitine acyltransferase, impaired by the development of obesity, prevents the development of negative effects associated with the activation of transcription of fatty acid synthase genes 3-hydroxy-3-methyl-glutaryl-CoA reductase, cholesterol-7 α-hydroxylase and some other enzymes involved in the pathogenesis of obesity, atherosclerosis, and metabolic syndrome [95-98].

Obesity changes the ratio of contractile elements in muscle tissue in the direction of increasing the proportion of type II fibers (white fibers, poor in mitochondria and myoglobin, characterized by the prevalence of anaerobic

metabolism). Carnitine, administered to animals with experimental obesity caused by excessive fat diet, reduces the proportion of type II fibers, but increases the proportion of type I fibers (red fibers rich in mitochondria and myoglobin, characterized by a high level of oxidative phosphorylation), respectively [99].

Carnitine deficiency in obesity develops due to the replacement of a part of muscle tissue with adipose tissue (the sarcopenia phenomenon), and due to the splitting of part of dietary carnitine to form trim ethylamine N-oxide under the influence of altered intestinal microflora [100-102].

In recent years, there has emerged the evidence about the participation of carnitine in increasing the share of nonspecific energy expenditure by inducing a mild uncoupling effect. This mild uncoupling is partly due to the fact that catabolism of fatty acids to acetyl coenzyme A produces FADH2 as an electron donor for the mitochondrial respiratory chain, which has a lower P: O ratio than NADH. This is in good agreement with the phenomenon of mild uncoupling effect of excess fatty acids. In addition, an increased level of fat oxidation during physical exercises is associated with lower respiration efficiency in state 3 [103]. However, it is not entirely clear whether the latter effect belongs to carnitine itself or is mediated by any other endogenous uncouplers of oxidative phosphorylation.

Uncoupling proteins, prospects for controlling their regulation and induction to combat obesity:

Nonspecific energy expenditure of the body inevitably arises in the implementation of interstitial metabolic transformations of various substances. In this case, a special role belongs to UCP(s) [104]. These proteins are directly involved in thermogenesis and the dissipation of a certain part of the energy of metabolic fuels [105]. The first of these proteins was a thermogenin (UCP-1) isolated more than 40 years ago - a protein of brown adipocytes with a molecular mass of 32 kDa [106]. For a long time this protein was believed to be produced only in brown adipocytes and only in young children, and in adults, it allegedly disappears due to the involution of brown adipose tissue. At present, it has been proven that the expression of the thermogenic gene takes place not only in adipose tissue, but also in different tissues (liver, kidneys) of an adult organism [107]. Moreover, the activity of UCP1 in adults is positively correlated with an increase in energy consumption during cold exposure and negatively with age, body mass index and fasting glycemia, which indicates regulatory links between brown adipocytes, cold thermogenesis and energy metabolism [108].

There are two alternative models of the mechanism of the uncoupling action of the UCP(s), and both postulate the participation of fatty acids. The difference between these models is how which ions are transferred. In the Klingenberg model, UCP(s) are proton-pores, i.e. they transfer hydrogen ions back to the mitochondrial matrix. In the Garlid model, UCP(s) conduct anions, namely they transfer the anionic head group of fatty acids from one side of the membrane to the other. The cycle ends with a quick flip-flop movement of protonated fatty acids through the lipid bilayer, which leads to a decrease in ΔμH + [109].

For today, four more genetic variants of uncoupling proteins (UCP2, UCP3, UCP4, and UCP5) have been described. These proteins are produced in different tissues of the body. They carry out the functions of regulation of bioenergy and metabolism [95]. Thus, the UCP2 and UCP3 genes are expressed in the heart tissue and protect it from cell death and development of heart failure in obesity [110]. UCP2 is also formed in the brain, lungs, spleen and liver, where it participates in antioxidant defense reactions [111-115]. UCP3 is actively involved in the regulation of proton leakage in the inner membrane of mitochondria, oxidative status and thermogenesis in muscle tissue, and, therefore, in the regulation of nonspecific energy expenditure of the body [116].

UCP4 is present in the brain already from 12-14 days of the embryonic period, which coincides with the onset of neuronal differentiation. The content of UCP4 in mitochondria decreases with increasing age. The preferential expression of UCP4 and UCP 5 in neurons and the dynamics of expression under physiological conditions may indicate the involvement of these proteins in the differentiation of neuronal cells, as well as in the antioxidant protection of the brain [117].

Thus, the presence of uncoupling proteins in tissues is closely related to the numerous physiological and pathological processes occurring in these tissues, as evidenced by the simple enumeration of the functions of these proteins described today:

- Adaptive thermogenesis [118],
- Participation in the oxidation of fatty acids and the regulation of energy efficiency mitochondrial

β-oxidation of fatty acids [119,120],
- Reduced ROS [121],
- Regulation of the ATP / ADP ratio in cells by changing the activity ANT [122],
- Prevention of the development of atherosclerosis, diabetes, obesity [123],
- Participation in the realization of the effects of thyroid hormones and leptin [124,125],
- Participation in the development of inflammation in adipose tissue [126].

Expression of uncoupling proteins is regulated by physical activity, starvation and saturation, exposure to low ambient temperature, a number of hormones, some nutrients and metabolites, such as nitrous oxide, lipids, conjugated linolenic acid, reactive oxygen species, etc. [127-129].

It is easy to see that almost all functions of uncoupling proteins are violated with the development of obesity. Therefore, the task of using these proteins as targets for developing methods of nutritional prevention and pharmacological correction of impaired nonspecific energy expenditure, and, consequently, of body weight correction seems so urgent.

Bile acids and thermogenesis

Bile acids are the final products of cholesterol metabolism in the liver. In recent years, in addition to the role of bile acids in emulsification, digestion and absorption of food lipids, their regulatory or hormone-like function is increasingly being studied [130-132]. So in 2014, experiments on mice chenodeoxycholic acid (CDCA) was shown to reduce obesity in HFD mice. The authors attributed this effect not so much to the influence of CDCA administered on the amount of food consumed as to the ability of CDCA to induce the synthesis of the uncoupling protein UCP 1 and to increase thermogenesis in brown adipocytes [133]. The following year, similar results were obtained in experiments with volunteers. The administration of CDCA to 12 healthy women increased the activity of brown adipose tissue and heat production. In experiments *in vitro* the uncoupling effect of CDCA in the mitochondria of brown adipocytes mediated by the activating action of CDCA on iodothyronine deiodinase type 2 (D2) was demonstrated. This enzyme is involved in the synthesis of the most active hormone of the thyroid gland - triiodothyronine (T3). These data, according to the authors, allow the bile acids to be considered a target for the activation of brown adipose tissue in humans [134,135].

Microorganisms of the gastrointestinal tract play a central role in the metabolism of host bile acids by deconjugation and dehydroxylation reactions that generate unconjugated free bile acids and secondary bile acids, respectively. These converted bile acids are in part potential signal molecules that interact with the host bile acid receptors (including the farnesoid X receptor, the vitamin D receptor and the TGR5 receptor) to induce cellular responses that play a key role in lipid metabolism of the host, transport of electrolytes and immune regulation. Disorders of microbial intestinal populations can, therefore, significantly alter the bile acid profiles of the host. A number of recent scientific studies have demonstrated that the occurrence of microbial perturbations can lead to changes in the bile acid profiles of the host, which leads to complications in the course of diseases. Intestinal pathology, in particular irritable bowel disease, the syndrome after the resection of a part of the intestine and the infection caused by *Clostridium Difficile*, are all accompanied by competitive changes in microbiome composition and changes in bile acid profiles of the host [136,137].

Two amino acids are actively involved in the metabolism of bile acids: glycine and taurine. The role of the latter is not limited to its use in the formation of paired (conjugated) bile acids. Taurine is a sulfur-containing amino acid that is found in the tissues of mammals in fairly significant (millimolar) concentrations. It takes part in various ways associated with the physiological functions of the body, including conjugation of bile acids, osmoregulation, and stabilization of membranes, calcium modulation, antioxidant action and immunomodulation. Studies have shown that the 24-hour excretion of taurine as a marker of its consumption with food was inversely associated with BMI, blood pressure and plasma cholesterol concentration in humans. In addition, taurine-chloramine, an endogenous product produced by activated neutrophils, inhibits obesity-induced oxidative stress and inflammation in adipocytes. Synthetic activity and the concentration of taurine in adipose tissue and plasma are reduced in humans and animals during the development of obesity, and this leads to the conclusion that there is a correlation between insufficiency of taurine and obesity [138].

To better understand the relationship between microbial dysbiosis and bile acid metabolism disorders, large-scale metagenomic, metatranscriptomic and metaproteomic studies are needed to create a catalog of

the functional diversity of healthy and sick populations of microorganisms. It is necessary to further search for active probiotics capable of restoring the normal metabolic level of the microbiome and use them for therapeutic purposes [139].

Sarcolipin: A new target for nonspecific energy expenditure control

In the last two decades, the close attention of researchers of nonspecific energy expenditure of the body was given to brown adipose tissue. It was traditionally assumed that the tissue was responsible for the function of thermogenesis performed with the participation of uncoupling proteins (UCP). At the same time, thermogenesis is directly related to the functioning of not only fat, but also muscle tissue. The participation of skeletal muscles in thermogenesis is known to any person, for everyone experienced the influence of cold, manifested in a form of involuntary trembling. However, the role of skeletal muscles in nonshivering thermogenesis, and consequently, in the regulation of nonspecific energy losses of the organism, until recently was not completely understood [140]. Much has been clarified in this issue in 2012 after the discovery of the function of the protein sarcolipine [141]. Sarcolipin (Sln), a small protein containing 31 amino acid residues, was identified as a regulator of the Ca^{2+} -ATPase of the sarco-endoplasmic reticulum (SERCA) [142]. It turned out that this protein is absolutely necessary for nonshivering thermogenesis [143]. It plays a key role in the formation of the level of basal metabolism, and its over expression increases the total energy expenditure of the body and leads to the development of resistance to obesity [144].

The regulating effect of Sln in obesity can be considered as an alternative possibility of increasing nonspecific energy expenditure with some neuroendocrine mechanisms realized through β-adrenoreceptors and UCP proteins [145]. The mechanism of the thermogenic action of Sln can be characterized as the separation of two conjugated events: the transport of calcium by means of SERCA and the hydrolysis of ATP, which provides energy for this type of active transport. The uncoupling action of Sln is functionally linked to its N-terminal amino acid residue. Removal of this residue from the structure of Sln deprives it of uncoupling and thermogenic action [146].

Can brown fat defeat white in the fight against obesity?

This very intriguing title of the section almost entirely repeats the title of one of the recently published articles on the problem of the plasticity of adipose tissue and its ability to transform white and brown adipocytes into each other [147-149].

The interest in the development of this direction originates from the time when the Virtanen group obtained new results on the distribution of brown adipose tissue cells in adults using the positron emission tomography method [150]. In the work of these authors, not only the fact of the existence of metabolically active brown fat in adults was demonstrated, but it was also proved that the mass and activity of this tissue decreases in the aging and development of obesity. These results aroused great interest in studying the mechanisms of the development and differentiation of adipose tissue, as well as natural and artificial regulators of these processes. It was found that an increase in the number of brown or beige adipocytes (browning, beigeing), and, consequently, nonspecific energy expenditure can be achieved by the following factors:

- Exposure to cold [151];
- The introduction of phytopreparations, such as resveratrol, curcumin, genistein, xanthohumol, quercetin, capsaicin, cinnamon, extractives rose hips, etc. [152-155,], as well as inorganic nitrates [156], and polyunsaturated fatty acids [157];
- Changes in neuroendocrine regulation of preadipocyte differentiation [158];
- Physical exercise [159].

In January 2012, Boström and his colleagues identified a new secreted protein of muscle tissue, which they called irisin. It is secreted by the muscles as a product of an alternative splicing of the FNDC5 gene, which encodes a larger fibronectin III protein [160]. It turned out that the secreted protein has a molecular weight of about 12 kDa and contains 112 amino acids. It was called “irisin” in honor of the goddess Irida, the messenger of the gods. The authors showed that the increased expression of the gene of this protein is observed under the influence of physical exercises. Irizin affects white fat cells in vitro and in vivo, stimulating the synthesis of thermogenin and other proteins typical for brown adipocytes in adipocytes of white adipose tissue. Such adipocytes are called “brite adipocytes” (brown-in-white.) Irisin is induced with exercises in mice and humans, and moderately increased levels of irisin in the blood cause an increase in energy expenditure in mice without changes in movement or consumption of food. Reducing obesity and improving the homeostasis of glucose. Irizine, according to the authors, could be a therapeutic agent for the treatment

of metabolic disorders and other diseases that can be controlled with exercise [161].

This discovery caused a stormy but very contradictory reaction in the scientific and medical community: from total enthusiasm in connection with the emergence of another "panacea" for the treatment of obesity to declaring all the beneficial effects of irisin described above as a myth [162-165].

In recent years, researchers in different countries have paid special attention to the study of genes involved in browning adipocytes in order to develop new methods of gene therapy for obesity [166-171].

Conclusion

The main targets of nonspecific energy expenditure control and the prospects of their use for prevention and treatment of obesity

As shown by the analysis of scientific papers presented in this review, nonspecific energy expenditure of the organism makes a very significant contribution to the regulation of body mass. The main objects of the energy expenditure are the digestive tract, intestinal microbiota, hormonal control systems for appetite and satiety, mitochondrial oxidative phosphorylation, expression of UCP, Ca++-ATPase/sarcolipin system, fatty acids, bile acids and regulatory systems controlling the differentiation of preadipocytes into white or brown adipocytes. Each of these objects is a potential target for the development of new methods of influencing the regulatory systems of body weight control, and consequently, for the prevention and treatment of obesity. From the presented review materials, it is possible to draw quite definite practical conclusions and new recommendations for dieticians, physiotherapy specialists, sports physicians and physicians of different specialties dealing with patients suffering from obesity or having a high risk of developing this most common pathology. The essence of these recommendations is as follows:

1. It is necessary to carefully monitor the condition of the teeth, gums, salivary glands and other structures of the oral cavity because there is a positive correlation between the presence of caries, periodontal disease, anodontia, the speed of moisturizing and chewing food, on the one hand, and the likelihood of developing obesity, on the other.
2. The level of secretion of orexigenic and anorexigenic hormones, directly or indirectly affecting the nonspecific energy expenditure of the body (ghrelin, leptin, proopiomelanocortins, amylin, galanin, visfatin, omentin, adipolin, etc.), should be controlled. To determine the majority of these hormones there are no methodological limitations, since modern methods of analysis have been developed, and ready-made sets of reagents (kits) are on sale.
3. Special attention is required by intestinal microbiota, changes in which can cause inflammation in adipose tissue, increased proliferation of white adipocytes, slowing intestinal peristalsis and, ultimately, the development of obesity. Probably, the most dangerous type of microbiome infringement is the replacement of beneficial microflora by anaerobic bacteria such as Clostridium difficile, which should be eliminated by all means, up to the transplantation of the donor microbiota.
4. In patients with obesity, especially those suffering from severe forms, substances stimulating the oxidation of fatty acids with dissipation of free energy-carnitine (vitamin B or B11), soft uncouplers of oxidative phosphorylation, polyunsaturated fatty acids (linoleic, linolenic, arachidonic, docospentenoic), which are also regulators of lipolysis, lipogenesis and differentiation of adipocytes, should be used. There is a large amount of evidence about the effectiveness of such therapy, which are given in Section 4.1.
5. Great hopes for the rapid development of new management tools for nonspecific energy losses of the body are associated with clinical studies of bile acids, taurine, sarcolipin, substances that regulate the expression of UCP proteins, and Skulachev ions. There is every reason to believe that these substances will soon be tested as very effective pharmaceutical preparations for obesity therapy.
6. To stimulate the differentiation of preadipocytes in the direction of brown cells, the tactics of increasing tolerance to cold and physical stresses. Winter sports and diet containing optimal level of polyunsaturated fatty acids, should be recommended to activate the production of irisin and other regulators of such differentiation that increase the nonspecific energy expenditure of the body.

References

1. Villalobos JÁC. Obesity: the real pandemic of the 21st century. *Cirugía y Cirujanos (English Edition)*.

2016;84(5):351-355. Doi: http://dx.doi.org/10.1016/j.circen.2016.08.013

2. Martin M, Krystof S, Jiri R, et al. Modulation of energy intake and expenditure due to habitual physical exercise. *Curr Pharm Des*. 2016;22(24):3681-3699.
3. Singh A, Peres MA, Peres KG, Bernardo C de O, Xavier A, D'Orsi E. Gender differences in the association between tooth loss and obesity among older adults in Brazil. *Rev Saude Publica*. 2015;49:44. Doi: http://dx.doi.org/10.1590/S0034-8910.2015049005590
4. Urzua I, Mendoza C, Arteaga O, et al. Dental caries prevalence and tooth loss in chilean adult population: First national dental examination survey. *International Journal of Dentistry*. Doi: http://dx.doi.org/10.1155/2012/810170
5. Nakamura M, Ojima T, Nakade M, et al. Poor oral health and diet in relation to weight loss, stable underweight, and obesity in community-dwelling older adults: a cross-sectional study from the jages 2010 project. *J Epidemiol*. 2016;26(6):322-329. Doi: http://dx.doi.org/10.2188/jea.JE20150144
6. Östberg A-L, Bengtsson C, Lissner L, Hakeberg M. Oral health and obesity indicators. *BMC Oral Health*. 2012;12(1):50. Doi: http://dx.doi.org/10.1186/1472-6831-12-50
7. Khan S, Saub R, Vaithilingam RD, Safii SH, Vethakkan SR, Baharuddin NA. Prevalence of chronic periodontitis in an obese population: a preliminary study. *BMC Oral Health*. 2015;15(1):114. Doi: http://dx.doi.org/10.1186/s12903-015-0098-3
8. Yagi T, Ueda H, Amitani H, Asakawa A, Miyawaki S, Inui A. The Role of Ghrelin, Salivary Secretions, and Dental Care in Eating Disorders. *Nutrients*. 2012;4(8):967-989. Doi: http://dx.doi.org/10.3390/nu4080967
9. Tada A, Miura H. Association of mastication and factors affecting masticatory function with obesity in adults: a systematic review. *BMC Oral Health*. 2018;18(1):76. Doi: http://dx.doi.org/10.1186/s12903-018-0525-3
10. Ho KKY. Diet-induced thermogenesis: fake friend or foe? *J Endocrinol*. 2018;238(3):R185-R191. Doi: http://dx.doi.org/10.1530/JOE-18-0240
11. Kassis A, Godin J-P, Moille SE, et al. Effects of protein quantity and type on diet induced thermogenesis in overweight adults: A randomized controlled trial. *Clin Nutr*. August 2018. Doi: http://dx.doi.org/10.1016/j.clnu.2018.08.004
12. Vázquez Cisneros LC, López-Espinoza A, Martínez Moreno AG, Navarro Meza M, Espinoza-Gallardo AC, Zepeda-Salvador AP. [Effect of feeding frequency and schedules on diet induced thermogenesis in humans, a systematic review]. *Nutr Hosp*. 2018;35(4):962-970. Doi: http://dx.doi.org/10.20960/nh.1611
13. Davis HC. Can the gastrointestinal microbiota be modulated by dietary fibre to treat obesity? *Ir J Med Sci*. 2018;187(2):393-402. Doi: http://dx.doi.org/10.1007/s11845-017-1686-9
14. de la Garza AL, Milagro FI, Boque N, Campión J, Martínez JA. Natural inhibitors of pancreatic lipase as new players in obesity treatment. *Planta Med*. 2011;77(8):773-785. Doi: http://dx.doi.org/10.1055/s-0030-1270924
15. Kumar S, Alagawadi KR. Anti-obesity effects of galangin, a pancreatic lipase inhibitor in cafeteria diet fed female rats. *Pharm Biol*. 2013;51(5):607-613. Doi: http://dx.doi.org/10.3109/13880209.2012.757327
16. Sales PM, Souza PM, Simeoni LA, Silveira D. α-Amylase inhibitors: a review of raw material and isolated compounds from plant source. *J Pharm Pharm Sci*. 2012;15(1):141-183.
17. Hamzaoui S, Ben Salah B, Hamden K, Rekik A, Kossentini M. Synthesis and evaluation of new bis-1,3,4,2-triazaphospholinoalkane derivatives as in vitro α-amylase and lipase inhibitors. *Arch Pharm (Weinheim)*. 2015;348(3):188-193. Doi: http://dx.doi.org/10.1002/ardp.201400283
18. Zagoskin PP, Zagoskina IP, Savelieva NA, Lyalyaev VA. Modern approaches to the problem of body weight regulation (Review). *Современные технологии в медицине*. 2014;6(3 (eng)). https://cyberleninka.ru/article/n/modern-approaches-to-the-problem-of-body-weight-regulation-review. Accessed March 15, 2019.
19. Cani PD. Human gut microbiome: hopes, threats and promises. *Gut*. 2018;67(9):1716-1725. Doi: http://dx.doi.org/10.1136/gutjnl-2018-316723
20. Leong KSW, Derraik JGB, Hofman PL, Cutfield WS. Antibiotics, gut microbiome and obesity. *Clin Endocrinol (Oxf)*. 2018;88(2):185-200. Doi: http://dx.doi.org/10.1111/cen.13495
21. Parnell JA, Reimer RA. Prebiotic fiber modulation of the gut microbiota improves risk factors for obesity and the metabolic syndrome. *Gut Microbes*. 2012;3(1):29-34. Doi: http://dx.doi.org/10.4161/gmic.19246
22. Zak-Gołąb A, Olszanecka-Glinianowicz M, Kocełak P, Chudek J. [The role of gut microbiota in the pathogenesis of obesity]. *Postepy Hig Med Dosw*

(Online). 2014;68:84-90. Doi: http://dx.doi.org/10.5604/17322693.1086419

23. Calvani R, Brasili E, Praticò G, et al. Application of NMR-based metabolomics to the study of gut microbiota in obesity. *J Clin Gastroenterol*. 2014;48 Suppl 1:S5-7. Doi: http://dx.doi.org/10.1097/MCG.0000000000000236
24. Ferreira CM, Vieira AT, Vinolo MAR, Oliveira FA, Curi R, Martins F dos S. The central role of the gut microbiota in chronic inflammatory diseases. *J Immunol Res*. 2014;2014:689492. Doi: http://dx.doi.org/10.1155/2014/689492
25. Vassallo A, Tran M-CN, Goldstein EJC. Clostridium difficile: improving the prevention paradigm in healthcare settings. *Expert Rev Anti Infect Ther*. 2014;12(9):1087-1102. Doi: http://dx.doi.org/10.1586/14787210.2014.942284
26. Thorkildsen LT, Nwosu FC, Avershina E, et al. Dominant fecal microbiota in newly diagnosed untreated inflammatory bowel disease patients. *Gastroenterol Res Pract*. 2013;2013:636785. Doi: http://dx.doi.org/10.1155/2013/636785
27. Shankar V, Hamilton MJ, Khoruts A, et al. Species and genus level resolution analysis of gut microbiota in Clostridium difficile patients following fecal microbiota transplantation. *Microbiome*. 2014;2:13. Doi: http://dx.doi.org/10.1186/2049-2618-2-13
28. Wang W, Xu S, Ren Z, Jiang J, Zheng S. Gut microbiota and allogeneic transplantation. *J Transl Med*. 2015;13:275. Doi: http://dx.doi.org/10.1186/s12967-015-0640-8
29. Curi R, Newsholme P, Marzuca-Nassr GN, et al. Regulatory principles in metabolism-then and now. *Biochem J*. 2016;473(13):1845-1857. Doi: http://dx.doi.org/10.1042/BCJ20160103
30. Kiskinis E, Chatzeli L, Curry E, et al. RIP140 represses the "brown-in-white" adipocyte program including a futile cycle of triacyclglycerol breakdown and synthesis. *Mol Endocrinol*. 2014;28(3):344-356. Doi: http://dx.doi.org/10.1210/me.2013-1254
31. Zhang Y, Li C, Li H, et al. MiR-378 Activates the pyruvate-pep futile cycle and enhances lipolysis to Ameliorate Obesity in Mice. *EBioMedicine*. 2016;5:93-104. Doi: http://dx.doi.org/10.1016/j.ebiom.2016.01.035
32. Kazak L, Chouchani ET, Jedrychowski MP, et al. A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. *Cell*. 2015;163(3):643-655. Doi: http://dx.doi.org/10.1016/j.cell.2015.09.035
33. De Stefani D, Rizzuto R, Pozzan T. Enjoy the trip: calcium in mitochondria back and forth. *Annu Rev Biochem*. 2016;85:161-192. Doi: http://dx.doi.org/10.1146/annurev-biochem-060614-034216
34. Sel'kov EE, Sozinov LA. Stable circadian rhythms as a property of cell populations. *Life Sci Space Res*. 1970;8:157-167.
35. Hers HG. The usefulness of "futile cycles." *Biochem Soc Trans*. 1976;4(6):985-988.
36. Fried SK, Watford M. Leucing weight with a futile cycle. *Cell Metab*. 2007;6(3):155-156. Doi: http://dx.doi.org/10.1016/j.cmet.2007.08.009
37. Betz MJ, Enerbäck S. Targeting thermogenesis in brown fat and muscle to treat obesity and metabolic disease. *Nat Rev Endocrinol*. 2018;14(2):77-87. Doi: http://dx.doi.org/10.1038/nrendo.2017.132
38. Handy DE, Loscalzo J. Redox regulation of mitochondrial function. *Antioxid Redox Signal*. 2012;16(11):1323-1367. Doi: http://dx.doi.org/10.1089/ars.2011.4123
39. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev*. 2014;94(3):909-950. Doi: http://dx.doi.org/10.1152/physrev.00026.2013
40. Chouchani ET, Kazak L, Jedrychowski MP, et al. Mitochondrial ROS regulate thermogenic energy expenditure and sulfenylation of UCP1. *Nature*. 2016;532(7597):112-116. Doi: http://dx.doi.org/10.1038/nature17399
41. Rokitskaya TI, Ilyasova TM, Severina II, Antonenko YN, Skulachev VP. Electrogenic proton transport across lipid bilayer membranes mediated by cationic derivatives of rhodamine 19: comparison with anionic protonophores. *Eur Biophys J*. 2013;42(6):477-485. Doi: http://dx.doi.org/10.1007/s00249-013-0898-9
42. Childress ES, Alexopoulos SJ, Hoehn KL, Santos WL. Small molecule mitochondrial uncouplers and their therapeutic potential. *J Med Chem*. 2018;61(11):4641-4655. Doi: http://dx.doi.org/10.1021/acs.jmedchem.7b01182
43. Terada H. Uncouplers of oxidative phosphorylation. *Environ Health Perspect*. 1990;87:213-218. Doi: http://dx.doi.org/10.1289/ehp.9087213
44. Colman E. Dinitrophenol and obesity: an early twentieth-century regulatory dilemma. *Regul Toxicol Pharmacol*. 2007;48(2):115-117. Doi: http://dx.doi.org/10.1016/j.yrtph.2007.03.006
45. Maslov LN, Vychuzhanova EA, Gorbunov AS, Tsybul'nikov SI, Khaliulin IG, Chauski E. [Role of

thyroid system in adaptation to cold]. *Ross Fiziol Zh Im I M Sechenova*. 2014;100(6):670-683.

46. Festuccia WT, Blanchard P-G, Oliveira TB, et al. PPARγ activation attenuates cold-induced upregulation of thyroid status and brown adipose tissue PGC-1α and D2. *Am J Physiol Regul Integr Comp Physiol*. 2012;303(12):R1277-R1285. Doi: http://dx.doi.org/10.1152/ajpregu.00299.2012
47. Kwak HJ, Pyun YM, Kim JY, et al. Synthesis and biological evaluation of aminobenzimidazole derivatives with a phenylcyclohexyl acetic acid group as anti-obesity and anti-diabetic agents. *Bioorg Med Chem Lett*. 2013;23(16):4713-4718. Doi: http://dx.doi.org/10.1016/j.bmcl.2013.05.081
48. Tamura Y, Hayashi K, Omori N, et al. Identification of a novel benzimidazole derivative as a highly potent NPY Y5 receptor antagonist with an anti-obesity profile. *Bioorg Med Chem Lett*. 2013;23(1):90-95. Doi: http://dx.doi.org/10.1016/j.bmcl.2012.11.005
49. Lee J, Ellis JM, Wolfgang MJ. Adipose fatty acid oxidation is required for thermogenesis and potentiates oxidative stress-induced inflammation. *Cell Rep*. 2015;10(2):266-279. Doi: http://dx.doi.org/10.1016/j.celrep.2014.12.023
50. Norgard NB. Obesity and altered aspirin pharmacology. *Clin Pharmacokinet*. 2018;57(6):663-672. Doi: http://dx.doi.org/10.1007/s40262-017-0611-8
51. Anderson K, Wherle L, Park M, Nelson K, Nguyen L. Salsalate, an old, inexpensive drug with potential new indications: a review of the evidence from 3 recent studies. *Am Health Drug Benefits*. 2014;7(4):231-235.
52. Nie L, Yuan X-L, Jiang K-T, et al. Salsalate activates skeletal muscle thermogenesis and protects mice from high-fat diet induced metabolic dysfunction. *EBioMedicine*. 2017;23:136-145. Doi: http://dx.doi.org/10.1016/j.ebiom.2017.08.004
53. Chen CL, Liu FL, Lee CC, et al. Modified salicylanilide and 3-phenyl-2 H -benzo[e][1,3]oxazine-2,4(3 H)-dione derivatives as novel inhibitors of osteoclast differentiation and bone resorption. *Journal of medicinal chemistry*. 2014;57(19):8072-8085. Doi: http://dx.doi.org/10.1021/jm5007897
54. Hu M, Ye W, Li J, et al. Synthesis and evaluation of salicylanilide derivatives as potential epidermal growth factor receptor inhibitors. *Chem Biol Drug Des*. 2015;85(3):280-289. Doi: http://dx.doi.org/10.1111/cbdd.12383
55. Krátký M, Vinšová J, Novotná E, Stolaříková J. Salicylanilide pyrazinoates inhibit in vitro multidrug-resistant Mycobacterium tuberculosis strains, atypical mycobacteria and isocitrate lyase. *Eur J Pharm Sci*. 2014;53:1-9. Doi: http://dx.doi.org/10.1016/j.ejps.2013.12.001
56. Krátký M, Volková M, Novotná E, Trejtnar F, Stolaříková J, Vinšová J. Synthesis and biological activity of new salicylanilide N,N-disubstituted carbamates and thiocarbamates. *Bioorg Med Chem*. 2014;22(15):4073-4082. Doi: http://dx.doi.org/10.1016/j.bmc.2014.05.064
57. Krátký M, Vinšová J, Novotná E, Mandíková J, Trejtnar F, Stolaková J. Antibacterial activity of salicylanilide 4-(trifluoromethyl)-benzoates. *Molecules*. 2013;18(4):3674-3688. Doi: http://dx.doi.org/10.3390/molecules18043674
58. Zhang X, Zhang H-M, Liu X, Rong X-B, Yang R. [Molluscicidal effect of 10% LDS in fields]. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi*. 2013;25(2):182-183, 186.
59. Mikhajlitsyn F, Gitzu G, Bekhlialla F, Rusak L, Krotov A. Salicylanilides possessing antihelmintic activity. *Patent SU697500 (A1) № SU19772456106* 19770214; 1979.
60. Yuan M, Li J-M, He G-W, Zhong G-C, Zhang Y-C. [Design, synthesis and antitumor activity of valproic acid salicylanilide esters]. *Yao Xue Xue Bao*. 2013;48(6):874-880.
61. Chen C-H. New composition for treating metabolic syndrome.. Patent RU 2486902 № RU20090131065 20080116; 2011.
62. Marguerie G, Giethlen B, Joubert M, Garrido F, Helin L. *New phenylhydrazone derivatives and their use as pharmaceuticals. Patent RU 2012129559(A) №RU1073165*(A1); 2011.
63. Basha MT, Chartres JD, Pantarat N, et al. Heterocyclic dithiocarbazate iron chelators: Fe coordination chemistry and biological activity. *Dalton Trans*. 2012;41(21):6536-6548. Doi: http://dx.doi.org/10.1039/c2dt12387h
64. Break MKB, Tahir MIM, Crouse KA, Khoo T-J. Synthesis, characterization, and bioactivity of schiff bases and their cd(2+), zn(2+), cu(2+), and ni(2+) complexes derived from chloroacetophenone isomers with s-benzyldithiocarbazate and the x-ray crystal structure of s-benzyl- β -n-(4-chlorophenyl)methylenedithiocarbazate. *Bioinorg Chem Appl*. 2013;2013:362513. Doi: http://dx.doi.org/10.1155/2013/362513

65. Low ML, Maigre L, Tahir MIM, et al. New insight into the structural, electrochemical and biological aspects of macroacyclic Cu(II) complexes derived from S-substituted dithiocarbazate schiff bases. *Eur J Med Chem*. 2016;120:1-12. Doi: http://dx.doi.org/10.1016/j.ejmech.2016.04.027

66. Babsky A. Influence of adrenaline on oxidative phosphorylation and calcium ions transport in mitochondria of rat liver and small intestinal mucosa : *Dissertation for the Degree of Candidate of Biological Sciences.*. Lvov ; Puchshino. 137 p ?; 1985.

67. Wikstrom JD, Mahdaviani K, Liesa M, et al. Hormone-induced mitochondrial fission is utilized by brown adipocytes as an amplification pathway for energy expenditure. *EMBO J*. 2014;33(5):418-436. Doi: http://dx.doi.org/10.1002/embj.201385014

68. Ling GN. Oxidative phosphorylation and mitochondrial physiology: a critical review of chemiosmotic theory, and reinterpretation by the association-induction hypothesis. *Physiol Chem Phys*. 1981;13(1):29-96.

69. Srinivasan K, Buys EM. Insights into the role of bacteria in vitamin A biosynthesis: Future research opportunities. *Critical Reviews in Food Science and Nutrition*. 2019;0(0):1-16. Doi: http://dx.doi.org/10.1080/10408398.2018.1546670

70. Kalinovich AV, Mattsson CL, Youssef MR, et al. Mitochondria-targeted dodecyltriphenylphosphonium (C12TPP) combats high-fat-diet-induced obesity in mice. *Int J Obes (Lond)*. 2016;40(12):1864-1874. Doi: http://dx.doi.org/10.1038/ijo.2016.146

71. Morales PE, Bucarey JL, Espinosa A. Muscle lipid metabolism: role of lipid droplets and perilipins. *Journal of Diabetes Research*. Doi: http://dx.doi.org/10.1155/2017/1789395

72. Cavaliere G, Trinchese G, Bergamo P, et al. Polyunsaturated fatty acids attenuate diet induced obesity and insulin resistance, *Modulating Mitochondrial Respiratory Uncoupling in Rat Skeletal Muscle*. *PLOS ONE*. 2016;11(2):e0149033. Doi: http://dx.doi.org/10.1371/journal.pone.0149033

73. Samartsev VN, Marchik EI, Shamagulova LV. Free fatty acids as inducers and regulators of uncoupling of oxidative phosphorylation in liver mitochondria with participation of ADP/ATP- and aspartate/glutamate-antiporter. *Biochemistry Mosc*. 2011;76(2):217-224.

74. Samartsev VN, Rybakova SR, Dubinin MV. Simulation of the uncoupling activity of fatty acids with the participation of ADP/ATP and aspartate/glutamate antiporters in liver mitochondria.. *Biofizika*. 2014;57:267-273.

75. Baraldi F, Dalalio F, Teodoro B, Prado I, Curti C, Alberici L. Body energy metabolism and oxidative stress in mice supplemented with conjugated linoleic acid (CLA) associated to oleic acid. *Free Radic Biol Med*. 2014;75 Suppl 1:S21. Doi: http://dx.doi.org/10.1016/j.freeradbiomed.2014.10.733

76. Murugesan S, Nirmalkar K, Hoyo-Vadillo C, García-Espitia M, Ramírez-Sánchez D, García-Mena J. Gut microbiome production of short-chain fatty acids and obesity in children. *Eur J Clin Microbiol Infect Dis*. 2018;37(4):621-625. Doi: http://dx.doi.org/10.1007/s10096-017-3143-0

77. Hu J, Lin S, Zheng B, Cheung PCK. Short-chain fatty acids in control of energy metabolism. *Crit Rev Food Sci Nutr*. 2018;58(8):1243-1249. Doi: http://dx.doi.org/10.1080/10408398.2016.1245650

78. Hanatani S, Motoshima H, Takaki Y, et al. Acetate alters expression of genes involved in beige adipogenesis in 3T3-L1 cells and obese KK-Ay mice. *J Clin Biochem Nutr*. 2016;59(3):207-214. Doi: http://dx.doi.org/10.3164/jcbn.16-23

79. Frost G, Sleeth ML, Sahuri-Arisoylu M, et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat Commun*. 2014;5:3611. Doi: http://dx.doi.org/10.1038/ncomms4611

80. Hong J, Jia Y, Pan S, et al. Butyrate alleviates high fat diet-induced obesity through activation of adiponectin-mediated pathway and stimulation of mitochondrial function in the skeletal muscle of mice. *Oncotarget*. 2016;7(35):56071-56082. Doi: http://dx.doi.org/10.18632/oncotarget.11267

81. Schönfeld P, Wojtczak L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J Lipid Res*. 2016;57(6):943-954. Doi: http://dx.doi.org/10.1194/jlr.R067629

82. Soldavini J, Kaunitz JD. Pathobiology and potential therapeutic value of intestinal short-chain fatty acids in gut inflammation and obesity. *Dig Dis Sci*. 2013;58(10):2756-2766. Doi: http://dx.doi.org/10.1007/s10620-013-2744-4

83. Pillon NJ, Chan KL, Zhang S, et al. Saturated fatty acids activate caspase-4/5 in human monocytes, triggering IL-1β and IL-18 release. *Am J Physiol Endocrinol Metab*. 2016;311(5):E825-E835. Doi: http://dx.doi.org/10.1152/ajpendo.00296.2016

84. Liu X, Kris-Etherton PM, West SG, et al. Effects of canola and high-oleic-acid canola oils on abdominal

fat mass in individuals with central obesity. *Obesity (Silver Spring)*. 2016;24(11):2261-2268. Doi: http://dx.doi.org/10.1002/oby.21584

85. Albracht-Schulte K, Kalupahana NS, Ramalingam L, et al. Omega-3 fatty acids in obesity and metabolic syndrome: a mechanistic update. *J Nutr Biochem*. 2018;58:1-16. Doi: http://dx.doi.org/10.1016/j.jnutbio.2018.02.012
86. Huang C-W, Chien Y-S, Chen Y-J, Ajuwon KM, Mersmann HM, Ding S-T. Role of n-3 polyunsaturated fatty acids in ameliorating the obesity-induced metabolic syndrome in animal models and humans. *Int J Mol Sci*. 2016;17(10). Doi: http://dx.doi.org/10.3390/ijms17101689
87. Laiglesia LM, Lorente-Cebrián S, Prieto-Hontoria PL, et al. Eicosapentaenoic acid promotes mitochondrial biogenesis and beige-like features in subcutaneous adipocytes from overweight subjects. *J Nutr Biochem*. 2016;37:76-82. Doi: http://dx.doi.org/10.1016/j.jnutbio.2016.07.019
88. Kim J, Okla M, Erickson A, Carr T, Natarajan SK, Chung S. Eicosapentaenoic acid potentiates brown thermogenesis through ffar4-dependent up-regulation of mir-30b and mir-378. *J Biol Chem*. 2016;291(39):20551-20562. Doi: http://dx.doi.org/10.1074/jbc.M116.721480
89. Cavaliere G, Trinchese G, Bergamo P, et al. Polyunsaturated fatty acids attenuate diet inducedobesity and insulin resistance, *Modulating Mitochondrial Respiratory Uncoupling in Rat Skeletal Muscle. PLOS ONE*. 2016;11(2):e0149033. Doi: http://dx.doi.org/10.1371/journal.pone.0149033
90. Hao Y, Ma X, Luo Y, et al. Associations of serum adipocyte fatty acid binding protein with body composition and fat distribution in nondiabetic chinese women. *J Clin Endocrinol Metab*. 2015;100(5):2055-2062. Doi: http://dx.doi.org/10.1210/jc.2014-4373
91. Iwamoto M, Miyoshi T, Doi M, et al. Elevated serum adipocyte fatty acid-binding protein concentrations are independently associated with renal dysfunction in patients with stable angina pectoris. *Cardiovasc Diabetol*. 2012;11:26. Doi: http://dx.doi.org/10.1186/1475-2840-11-26
92. Kralisch S, Ebert T, Lossner U, Jessnitzer B, Stumvoll M, Fasshauer M. Adipocyte fatty acid-binding protein is released from adipocytes by a non-conventional mechanism. *Int J Obes (Lond)*. 2014;38(9):1251-1254. Doi: http://dx.doi.org/10.1038/ijo.2013.232
93. Cao H. Adipocytokines in obesity and metabolic disease. *J Endocrinol*. 2014;220(2):T47-59. Doi: http://dx.doi.org/10.1530/JOE-13-0339
94. Greenhill C. A-FABP links obesity and breast cancer. *Nature Reviews Endocrinology*. 2018;14(10):566. Doi: http://dx.doi.org/10.1038/s41574-018-0085-2
95. Vasiukova OV, Okorokov PL. The role of specific chaperons in pathogenesis of obesity and related diseases. *Problems of Endocrinology*. 2012;58(4):48-53. Doi: http://dx.doi.org/10.14341/probl201258448-53
96. Wu T, Guo A, Shu Q, et al. L-Carnitine intake prevents irregular feeding-induced obesity and lipid metabolism disorder. *Gene*. 2015;554(2):148-154. Doi: http://dx.doi.org/10.1016/j.gene.2014.10.040
97. Seiler SE, Martin OJ, Noland RC, et al. Obesity and lipid stress inhibit carnitine acetyltransferase activity. *J Lipid Res*. 2014;55(4):635-644. Doi: http://dx.doi.org/10.1194/jlr.M043448
98. Choi JW, Ohn JH, Jung HS, et al. Carnitine induces autophagy and restores high-fat diet-induced mitochondrial dysfunction. *Metab Clin Exp*. 2018;78:43-51. Doi: http://dx.doi.org/10.1016/j.metabol.2017.09.005
99. Couturier A, Ringseis R, Mooren F-C, Krüger K, Most E, Eder K. Carnitine supplementation to obese Zucker rats prevents obesity-induced type II to type I muscle fiber transition and favors an oxidative phenotype of skeletal muscle. *Nutr Metab (Lond)*. 2013;10:48. Doi: http://dx.doi.org/10.1186/1743-7075-10-48
100. Batsis JA, Mackenzie TA, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity, and functional impairments in older adults: National Health and Nutrition Examination Surveys 1999-2004. *Nutr Res*. 2015;35(12):1031-1039. Doi: http://dx.doi.org/10.1016/j.nutres.2015.09.003
101. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576-585. Doi: http://dx.doi.org/10.1038/nm.3145
102. Zhu Y, Jameson E, Crosatti M, et al. Carnitine metabolism to trimethylamine by an unusual Rieske-type oxygenase from human microbiota. *Proc Natl Acad Sci USA*. 2014;111(11):4268-4273. Doi: http://dx.doi.org/10.1073/pnas.1316569111
103. Stephens FB, Wall BT, Marimuthu K, et al. Skeletal muscle carnitine loading increases energy expenditure, modulates fuel metabolism gene networks and prevents body fat accumulation in humans. *J Physiol*. 2013;591(Pt 18):4655-4666. Doi:

http://dx.doi.org/10.1113/jphysiol.2013.255364

104. Echtay KS, Bienengraeber M, Mayinger P, et al. Uncoupling proteins: Martin Klingenberg's contributions for 40 years. *Arch Biochem Biophys*. 2018;657:41-55. Doi: http://dx.doi.org/10.1016/j.abb.2018.09.006

105. Brondani L de A, de Almeida Brondani L, de Souza BM, et al. Association of the UCP polymorphisms with susceptibility to obesity: case-control study and meta-analysis. *Mol Biol Rep*. 2014;41(8):5053-5067. Doi: http://dx.doi.org/10.1007/s11033-014-3371-7

106. Crichton PG, Lee Y, Kunji ERS. The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism. *Biochimie*. 2017;134:35-50. Doi: http://dx.doi.org/10.1016/j.biochi.2016.12.016

107. Lee P, Swarbrick MM, Ho KKY. Brown adipose tissue in adult humans: a metabolic renaissance. *Endocr Rev*. 2013;34(3):413-438. Doi: http://dx.doi.org/10.1210/er.2012-1081

108. Garlid KD, Jaburek M, Jezek P. Mechanism of uncoupling protein action. *Biochemical Society Transactions*. 2001;29(6):803-806. Doi: http://dx.doi.org/10.1042/bst0290803

109. Bouillaud F, Alves-Guerra M-C, Ricquier D. UCPs, at the interface between bioenergetics and metabolism. *Biochim Biophys Acta*. 2016;1863(10):2443-2456. Doi: http://dx.doi.org/10.1016/j.bbamcr.2016.04.013

110. Ruiz-Ramírez A, López-Acosta O, Barrios-Maya MA, El-Hafidi M. Cell death and heart failure in obesity: role of uncoupling proteins. *Oxid Med Cell Longev*. 2016;2016:9340654. Doi: http://dx.doi.org/10.1155/2016/9340654

111. Mattiasson G, Shamloo M, Gido G, et al. Uncoupling protein-2 prevents neuronal death and diminishes brain dysfunction after stroke and brain trauma. *Nat Med*. 2003;9(8):1062-1068. Doi: http://dx.doi.org/10.1038/nm903

112. Jabůrek M, Ježek J, Zelenka J, Ježek P. Antioxidant activity by a synergy of redox-sensitive mitochondrial phospholipase A2 and uncoupling protein-2 in lung and spleen. *Int J Biochem Cell Biol*. 2013;45(4):816-825. Doi: http://dx.doi.org/10.1016/j.biocel.2013.01.010

113. Wu Q, Gong D, Tian N, et al. Protection of regenerating liver after partial hepatectomy from carbon tetrachloride hepatotoxicity in rats: roles of mitochondrial uncoupling protein 2 and ATP stores. *Dig Dis Sci*. 2009;54(9):1918-1925. Doi: http://dx.doi.org/10.1007/s10620-008-0650-y

114. Crescenzo R, Bianco F, Mazzoli A, Giacco A, Liverini G, Iossa S. Alterations in proton leak, oxidative status and uncoupling protein 3 content in skeletal muscle subsarcolemmal and intermyofibrillar mitochondria in old rats. *BMC Geriatr*. 2014;14:79. Doi: http://dx.doi.org/10.1186/1471-2318-14-79

115. Sreedhar A, Zhao Y. Uncoupling protein 2 and metabolic diseases. *Mitochondrion*. 2017;34:135-140. Doi: http://dx.doi.org/10.1016/j.mito.2017.03.005

116. Ramsden DB, Ho PW-L, Ho JW-M, et al. Human neuronal uncoupling proteins 4 and 5 (UCP4 and UCP5): structural properties, regulation, and physiological role in protection against oxidative stress and mitochondrial dysfunction. *Brain Behav*. 2012;2(4):468-478. Doi: http://dx.doi.org/10.1002/brb3.55

117. Bouillaud F, Alves-Guerra M-C, Ricquier D. UCPs, at the interface between bioenergetics and metabolism. *Biochim Biophys Acta*. 2016;1863(10):2443-2456. Doi: http://dx.doi.org/10.1016/j.bbamcr.2016.04.013

118. Serra D, Mera P, Malandrino MI, Mir JF, Herrero L. Mitochondrial fatty acid oxidation in obesity. *Antioxid Redox Signal*. 2013;19(3):269-284. Doi: http://dx.doi.org/10.1089/ars.2012.4875

119. Cole MA, Murray AJ, Cochlin LE, et al. A high fat diet increases mitochondrial fatty acid oxidation and uncoupling to decrease efficiency in rat heart. *Basic Res Cardiol*. 2011;106(3):447-457. Doi: http://dx.doi.org/10.1007/s00395-011-0156-1

120. Friederich-Persson M, Aslam S, Nordquist L, Welch WJ, Wilcox CS, Palm F. Acute knockdown of uncoupling protein-2 increases uncoupling via the adenine nucleotide transporter and decreases oxidative stress in diabetic kidneys. *PLOS ONE*. 2012;7(7):e39635. Doi: http://dx.doi.org/10.1371/journal.pone.0039635

121. Acosta A, Camilleri M, Shin A, et al. Association of UCP-3 rs1626521 with obesity and stomach functions in humans. *Obesity (Silver Spring)*. 2015;23(4):898-906. Doi: http://dx.doi.org/10.1002/oby.21039

122. Liu J, Li J, Li W-J, Wang C-M. The role of uncoupling proteins in diabetes mellitus. *J Diabetes Res*. 2013;2013:585897. Doi: http://dx.doi.org/10.1155/2013/585897

123. Lee J-Y, Takahashi N, Yasubuchi M, et al. Triiodothyronine induces UCP-1 expression and mitochondrial biogenesis in human adipocytes. *Am J Physiol, Cell Physiol*. 2012;302(2):C463-472. Doi: http://dx.doi.org/10.1152/ajpcell.00010.2011

124. Park H-K, Ahima RS. Physiology of leptin: energy

homeostasis, neuroendocrine function and metabolism. *Metab Clin Exp*. 2015;64(1):24-34. Doi: http://dx.doi.org/10.1016/j.metabol.2014.08.004

125. Wernstedt Asterholm I, Tao C, Morley TS, et al. Adipocyte inflammation is essential for healthy adipose tissue expansion and remodeling. *Cell Metab*. 2014;20(1):103-118. Doi: http://dx.doi.org/10.1016/j.cmet.2014.05.005

126. Kim D-H, Kim S-H, Kim W-H, Moon C-R. The effects of treadmill exercise on expression of UCP-2 of brown adipose tissue and TNF-α of soleus muscle in obese Zucker rats. *J Exerc Nutrition Biochem*. 2013;17(4):199-207. Doi: http://dx.doi.org/10.5717/jenb.2013.17.4.199

127. Yasrebi A, Hsieh A, Mamounis KJ, et al. Differential gene regulation of GHSR signaling pathway in the arcuate nucleus and NPY neurons by fasting, diet-induced obesity, and 17β-estradiol. *Mol Cell Endocrinol*. 2016;422:42-56. Doi: http://dx.doi.org/10.1016/j.mce.2015.11.007

128. Yu L, Fink BD, Herlein JA, Oltman CL, Lamping KG, Sivitz WI. Dietary fat, fatty acid saturation and mitochondrial bioenergetics. *J Bioenerg Biomembr*. 2014;46(1):33-44. Doi: http://dx.doi.org/10.1007/s10863-013-9530-z

129. Shore AM, Karamitri A, Kemp P, Speakman JR, Graham NS, Lomax MA. Cold-Induced Changes in Gene Expression in Brown Adipose Tissue, White Adipose Tissue and Liver. *PLOS ONE*. 2013;8(7):e68933. Doi: http://dx.doi.org/10.1371/journal.pone.0068933

130. Pournaras DJ, le Roux CW. Are bile acids the new gut hormones? lessons from weight loss surgery models. *Endocrinology*. 2013;154(7):2255-2256. Doi: http://dx.doi.org/10.1210/en.2013-1383

131. Li T, Chiang JYL. Bile acid signaling in metabolic disease and drug therapy. *Pharmacol Rev*. 2014;66(4):948-983. Doi: http://dx.doi.org/10.1124/pr.113.008201

132. Teodoro JS, Zouhar P, Flachs P, et al. Enhancement of brown fat thermogenesis using chenodeoxycholic acid in mice. *Int J Obes (Lond)*. 2014;38(8):1027-1034. Doi: http://dx.doi.org/10.1038/ijo.2013.230

133. Broeders EPM, Nascimento EBM, Havekes B, et al. The bile acid chenodeoxycholic acid increases human brown adipose tissue activity. *Cell Metab*. 2015;22(3):418-426. Doi: http://dx.doi.org/10.1016/j.cmet.2015.07.002

134. Chen X, Yan L, Guo Z, et al. Chenodeoxycholic acid attenuates high-fat diet-induced obesity and hyperglycemia via the G protein-coupled bile acid receptor 1 and proliferator-activated receptor γ pathway. *Exp Ther Med*. 2017;14(6):5305-5312. Doi: http://dx.doi.org/10.3892/etm.2017.5232

135. Joyce SA, Gahan CGM. Disease-associated changes in bile acid profiles and links to altered gut microbiota. *Dig Dis*. 2017;35(3):169-177. Doi: http://dx.doi.org/10.1159/000450907

136. Bustos AY, Font de Valdez G, Fadda S, Taranto MP. New insights into bacterial bile resistance mechanisms: the role of bile salt hydrolase and its impact on human health. *Food Res Int*. 2018;112:250-262. Doi: http://dx.doi.org/10.1016/j.foodres.2018.06.035

137. Murakami S. Role of taurine in the pathogenesis of obesity. *Mol Nutr Food Res*. 2015;59(7):1353-1363. Doi: http://dx.doi.org/10.1002/mnfr.201500067

138. Jones ML, Martoni CJ, Ganopolsky JG, Labbé A, Prakash S. The human microbiome and bile acid metabolism: dysbiosis, dysmetabolism, disease and intervention. *Expert Opin Biol Ther*. 2014;14(4):467-482. Doi: http://dx.doi.org/10.1517/14712598.2014.880420

139. Rowland LA, Bal NC, Periasamy M. The role of skeletal-muscle-based thermogenic mechanisms in vertebrate endothermy. *Biol Rev Camb Philos Soc*. 2015;90(4):1279-1297. Doi: http://dx.doi.org/10.1111/brv.12157

140. Bal NC, Maurya SK, Sopariwala DH, et al. Sarcolipin is a newly identified regulator of muscle-based thermogenesis in mammals. *Nat Med*. 2012;18(10):1575-1579. Doi: http://dx.doi.org/10.1038/nm.2897

141. Autry JM, Thomas DD, Espinoza-Fonseca LM. Sarcolipin promotes uncoupling of the SERCA Ca2+ pump by inducing a structural rearrangement in the energy-transduction domin. *Biochemistry*. 2016;55(44):6083-6086. Doi: http://dx.doi.org/10.1021/acs.biochem.6b00728

142. Rowland LA, Maurya SK, Bal NC, Kozak L, Periasamy M. Sarcolipin and uncoupling protein 1 play distinct roles in diet-induced thermogenesis and do not compensate for one another. *Obesity (Silver Spring)*. 2016;24(7):1430-1433. Doi: http://dx.doi.org/10.1002/oby.21542

143. Maurya SK, Bal NC, Sopariwala DH, et al. Sarcolipin is a key determinant of the basal metabolic rate, and its overexpression enhances energy expenditure and resistance against diet-induced obesity. *J Biol Chem*. 2015;290(17):10840-10849. Doi: http://dx.doi.org/10.1074/jbc.M115.636878

144. Bombardier E, Smith IC, Gamu D, et al. Sarcolipin

trumps β-adrenergic receptor signaling as the favored mechanism for muscle-based diet-induced thermogenesis. *The FASEB Journal*. 2013;27(9):3871-3878. Doi: http://dx.doi.org/10.1096/fj.13-230631

145. Sahoo SK, Shaikh SA, Sopariwala DH, et al. The n terminus of sarcolipin plays an important role in uncoupling sarco-endoplasmic reticulum ca2+-atpase (serca) atp hydrolysis from ca2+ transport. *J Biol Chem*. 2015;290(22):14057-14067. Doi: http://dx.doi.org/10.1074/jbc.M115.636738

146. Elattar S, Satyanarayana A. Can brown fat win the battle against white fat? *J Cell Physiol*. 2015;230(10):2311-2317. Doi: http://dx.doi.org/10.1002/jcp.24986

147. Lee Y-H, Mottillo EP, Granneman JG. Adipose tissue plasticity from WAT to BAT and in between. *Biochim Biophys Acta*. 2014;1842(3):358-369. Doi: http://dx.doi.org/10.1016/j.bbadis.2013.05.011

148. Carpentier AC, Blondin DP, Virtanen KA, Richard D, Haman F, Turcotte ÉE. Brown adipose tissue energy metabolism in humans. *Front Endocrinol (Lausanne)*. 2018;9:447. Doi: http://dx.doi.org/10.3389/fendo.2018.00447

149. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med*. 2009;360(15):1518-1525. Doi: http://dx.doi.org/10.1056/NEJMoa0808949

150. Rosell M, Kaforou M, Frontini A, et al. Brown and white adipose tissues: intrinsic differences in gene expression and response to cold exposure in mice. *Am J Physiol Endocrinol Metab*. 2014;306(8):E945-964. Doi: http://dx.doi.org/10.1152/ajpendo.00473.2013

151. Azhar Y, Parmar A, Miller CN, Samuels JS, Rayalam S. Phytochemicals as novel agents for the induction of browning in white adipose tissue. *Nutr Metab (Lond)*. 2016;13:89. Doi: http://dx.doi.org/10.1186/s12986-016-0150-6

152. Zheng J, Zheng S, Feng Q, Zhang Q, Xiao X. Dietary capsaicin and its anti-obesity potency: from mechanism to clinical implications. *Biosci Rep*. 2017;37(3). Doi: http://dx.doi.org/10.1042/BSR20170286

153. Baskaran P, Krishnan V, Ren J, Thyagarajan B. Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms. *Br J Pharmacol*. 2016;173(15):2369-2389. Doi: http://dx.doi.org/10.1111/bph.13514

154. Cavalera M, Axling U, Berger K, Holm C. Rose hip supplementation increases energy expenditure and induces browning of white adipose tissue. *Nutr Metab (Lond)*. 2016;13:91. Doi: http://dx.doi.org/10.1186/s12986-016-0151-5

155. Roberts LD, Ashmore T, Kotwica AO, et al. Inorganic nitrate promotes the browning of white adipose tissue through the nitrate-nitrite-nitric oxide pathway. *Diabetes*. 2015;64(2):471-484. Doi: http://dx.doi.org/10.2337/db14-0496

156. Kim J, Okla M, Erickson A, Carr T, Natarajan SK, Chung S. Eicosapentaenoic acid potentiates brown thermogenesis through ffar4-dependent up-regulation of mir-30b and mir-378. *J Biol Chem*. 2016;291(39):20551-20562. Doi: http://dx.doi.org/10.1074/jbc.M116.721480

157. Bartness TJ, Ryu V. Neural control of white, beige and brown adipocytes. *Int J Obes Suppl*. 2015;5(Suppl 1):S35-S39. Doi: http://dx.doi.org/10.1038/ijosup.2015.9

158. Stanford KI, Middelbeek RJW, Goodyear LJ. Exercise effects on white adipose tissue: beiging and metabolic adaptations. *Diabetes*. 2015;64(7):2361-2368. Doi: http://dx.doi.org/10.2337/db15-0227

159. Stanford KI, Goodyear LJ. Exercise regulation of adipose tissue. *Adipocyte*. 2016;5(2):153-162. Doi: http://dx.doi.org/10.1080/21623945.2016.1191307

160. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481(7382):463-468. Doi: http://dx.doi.org/10.1038/nature10777

161. Novelle MG, Contreras C, Romero-Picó A, López M, Diéguez C. Irisin, two years later. *Int J Endocrinol*. 2013;2013:746281. Doi: http://dx.doi.org/10.1155/2013/746281

162. Fukushima Y, Kurose S, Shinno H, et al. Effects of body weight reduction on serum irisin and metabolic parameters in obese subjects. *Diabetes Metab J*. 2016;40(5):386-395. Doi: http://dx.doi.org/10.4093/dmj.2016.40.5.386

163. Zhang Y, Song H, Zhang Y, et al. Irisin inhibits atherosclerosis by promoting endothelial proliferation through microrna126-5p. *J Am Heart Assoc*. 2016;5(9). Doi: http://dx.doi.org/10.1161/JAHA.116.004031

164. Raschke S, Elsen M, Gassenhuber H, et al. Evidence against a beneficial effect of irisin in humans. *PLOS ONE*. 2013;8(9):e73680. Doi: http://dx.doi.org/10.1371/journal.pone.0073680

165. Albrecht E, Norheim F, Thiede B, et al. Irisin – a myth rather than an exercise-inducible myokine. *Scientific Reports*. 2015;5:8889. Doi: http://dx.doi.org/10.1038/srep08889

166. Wu L, Zhang L, Li B, et al. AMP-activated protein kinase (ampk) regulates energy metabolism through modulating thermogenesis in adipose tissue. *Front Physiol*. 2018;9:122. Doi: http://dx.doi.org/10.3389/fphys.2018.00122

167. Loft A, Forss I, Siersbæk MS, et al. Browning of human adipocytes requires KLF11 and reprogramming of PPARγ superenhancers. *Genes Dev*. 2015;29(1):7-22. Doi: http://dx.doi.org/10.1101/gad.250829.114

168. Dempersmier J, Sambeat A, Gulyaeva O, et al. Cold-inducible Zfp516 activates UCP1 transcription to promote browning of white fat and development of brown fat. *Mol Cell*. 2015;57(2):235-246. Doi: http://dx.doi.org/10.1016/j.molcel.2014.12.005

169. Zhang M, Zhang Y, Ma J, et al. The demethylase activity of fto (fat mass and obesity associated protein) is required for preadipocyte differentiation. *PLoS ONE*. 2015;10(7):e0133788. Doi: http://dx.doi.org/10.1371/journal.pone.0133788

170. Seki T, Hosaka K, Lim S, et al. Endothelial PDGF-CC regulates angiogenesis-dependent thermogenesis in beige fat. *Nat Commun*. 2016;7:12152. Doi: http://dx.doi.org/10.1038/ncomms12152

171. Waldman M, Bellner L, Vanella L, et al. Epoxyeicosatrienoic Acids Regulate Adipocyte Differentiation of Mouse 3T3 Cells, Via PGC-1α Activation, Which Is Required for HO-1 Expression and Increased Mitochondrial Function. *Stem Cells Dev*. 2016;25(14):1084-1094. Doi: http://dx.doi.org/10.1089/scd.2016.0072