Obesity and Protein Metabolism

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Abstracts: A conceptual model of the interdependence between the metabolism of proteins, fats and carbohydrates taking into account the transport of the carbon skeleton and the stages of the relationship between the processes of formation and utilization of ATP (Adenosine Triphosphate) energy, which demonstrates the key role of protein metabolism and the maintenance of glucose homeostasis with different organism availability in energy was proposed. In supporting the processes of vital activity of the body, two periods should be analyzed. The first one is absorptive period, which is for providing rehabilitation processes, the expression of which is the “food pyramid” and the second one is postabsorptive period, which is for the energetic provision of physical and mental work, the expression of which is the “energy pyramid”. These pyramids differ in the ratio of macronutrients, and in their composition, which must be taken into account when developing the principles of human nutrition. Although obesity is seen as a simple discrepancy between the amount of intake of food calories and their utilization for physical activity, however, do not take into account the large energy expenditure on volatile processes, in particular, the process of protein synthesis. The process of protein synthesis depends on the availability in the substrate (amino acids), the intensity of mRNA expression (transcription) and the speed of reproduction (translation), so the violation at each of these stages will affect the energy balance and promote the development of obesity. Half of the protein mass is muscle, so it largely determines the homeostasis of glucose and the development of energy balance, which is presented in the form of an interdisciplinary model for the development of diabetes, obesity and cardiovascular diseases. In conclusion, technologies were proposed to support the process of protein synthesis and ways of preventing and treating obesity.

Key words: Obesity, protein metabolism, food model, energy homeostasis, non-communicable disease.

1. Introduction

Obesity is seen as a simple discrepancy between the amount of incoming calories and the amount of their use for physical activity. This way of thinking has led the whole problem into a dead end and all of the weight loss technologies are aimed at reducing the consumption of food calories and increasing physical activity. However, on the one hand, the number of obese persons is increasing from year to year, and, on the other hand, many technologies have proven unsafe for human health. It is known that some people can eat a lot and little move and they stay thin, while others try to limit themselves in food and move a lot and they stay fat. It means that the matter is in the metabolism. But, unfortunately, what actually happens in the body doctors do not know. Nutritionists constantly offer variants of different ratios in the diet of macronutrients (proteins, fats and carbohydrates), but adequate models of the relationship between the metabolism of proteins, fats and carbohydrates are not suggested. Glucose homeostasis may be maintained on the account of auto-regulation of enzymes involved in its utilization and synthesis [1]. However, such a regulation has limited potential, and one can observe considerable fluctuations of glucose levels at excessive or deficient intake of carbohydrates with food, as well as at various physiological and pathological conditions that determine the existence of more powerful systems for maintaining glucose homeostasis of the body.

Even though carbohydrates usually constitute over half of energy value of daily ration, however, the body is forced to balance on the edge of their deficit and to save glucose molecule from complete oxidation, for instance, by recycling it via lactate (Cori cycle). Later Feling [2] proposed a model of recycling of glucose via amino acid alanine (glucose-alanine cycle). This model considers the involvement of protein metabolism in

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maintaining glucose homeostasis.

Based on the ways of transporting the carbon skeleton and the stages of the interconnection between the processes of formation and utilization of ATP energy at various energy supply in the absorptive and postabsorptive periods a conceptual model was developed for the interconnection between the metabolism of proteins, fats and carbohydrates (Fig. 1).

Thus, during the “Surplus energy—Sancho Pancho” the process of glucose dissimilation is associated with the two assimilation processes: with lipogenesis in regard of carbon skeleton, and with protein synthesis in regard of generation and utilization of ATP energy.

Even though glycolysis and protein synthesis are interconnected via generation and utilization of ATP energy, however, these metabolic flows are closely interrelated since no protein synthesis occurs without energy supply while reduced utilization of ATP energy blocks ATP generation or glycolysis. In such case an excess carbon skeleton will be redirected to lipid synthesis resulting in obesity.

During the “Energy deficiency—Donkichot” (for utilization endogenous nutrition flow) glucose homeostasis is maintained on the account of its endogenic synthesis from amino acids, those results in protein catabolism to supply the required substrates while lipolysis and lipid oxidation get activated to supply the energy for gluconeogenesis. This stage is characterized with combination of two dissimilation processes (protein catabolism and lipid oxidation) and one assimilation process (gluconeogenesis). Glucose synthesis is associated with lipid oxidation through the generation and utilization of ATP energy, while with protein catabolism—via routes of transportation of carbon skeleton.

Though gluconeogenesis and lipid oxidation are associated with each other through the generation and utilization of ATP energy, these metabolic flows are inter-dependent. For example, blockade of lipolysis [3] or lipid oxidation [4] automatically causes the decline of gluconeogenesis resulting in hypoglycemia, and on the contrary, the reduction of concentration of the substrate for gluconeogenesis blocks ATP synthesis from acetyl-CoA and results in condensing of excess acetyl groups in acetoacetate and oxybutyrate, leading to ketosis, for instance, in diabetes or fasting [5].

Thus, glucose homeostasis in the body depends to considerable extent on interrelations between the metabolism of proteins, lipids and carbohydrates. This dependence is determined by the capacity of any component of the food to affect individual steps of conversion of other nutrients with involvement of regulatory function of hormones. This model may serve as a theoretical basis to develop a dynamic model of balanced nutrition.

**Fig. 1** The model of the interconnection between metabolism of proteins, fats and carbohydrates, based on the ways of transporting the carbon skeleton and the stages of the interconnection between the processes of formation and utilization of ATP energy in the absorptive (Sancho Pancho) and postabsorptive (Donkichot) periods.
Metabolism intensity is controlled by neuro-endocrine system. The “Surplus energy” is signaled by acetylcholine and insulin levels while the “Energy deficiency” is mediated through noradrenaline and glucagon levels. Therefore, on the one hand, the neuro-hormonal status reflects energy balance of the body, and on the other hand, it depends on the intensity and ratio of nutrient flows.

Extensive studies on the specifics of metabolism in fasting or intake of individual nutrients are available; therefore these states are a convenient model to assess the intensity of metabolic flows from the position of the proposed model.

Hepatic glycogen stores almost completely disappear after a 24-48 hour fasting [6, 7], therefore the body is supplied with glucose due to protein catabolism [8] and lipid oxidation. Introduction of the key gluconeogenic amino acid (alanine) causes an increased glucose production in the liver [9] while oleic acid (energy substrate for gluconeogenesis) increases hepatic glucose production almost two fold [10], and on the contrary, the inhibition of lipolysis [3] or fatty acid oxidation [4] result in hypoglycemia.

Muscular alanine synthesis in fasting is completely dependent on the levels of branched amino acids produced in protein catabolism, and their levels are elevated during the first week of starvation [11]. A two-week feeding of rats with low-protein chow did not affect blood glucose level [12], but the starvation caused more expressed hypoglycemia. A low level of alanine in blood plasma of adults [13] and children [14] is mentioned at protein-energy deficiency, and fasting caused more pronounced hypoglycemia.

Obesity causes activation of metabolic flows during the “Surplus energy”, therefore obese patients have an increased blood concentration of insulin [18] while on the contrary glucagon levels are lower [19].

A certain balance between individual nutrient flows should be maintained. During the “Surplus energy” such balance should be met between the flows of glucose and amino acids. Excess glucose flow induces hyperglycemia and lipemias, while inadequate glucose intake with food leads to a lower inclusion of amino acids in proteins resulting in hyperaminoacidemia. Therefore, adequacy between these nutrient flows is the most important principle of balanced nutrition.

If in the food pyramid the main nutrient is carbohydrates, then in the energy pyramid—fats. In addition to the ratio of macronutrients, these pyramids differ in the composition of food compounds necessary to ensure the activity of their metabolic processes (Fig. 3).
fats; as proteins—gluconeogenic amino acids (alanine, serine and glycine); as carbohydrates—polysaccharide inulin, monosaccharides fructose and galactose.

In other words, all food compounds should be divided into two groups: some are required for the food pyramid, but have a negative impact on the functioning of the energy pyramid. For example, glucose promotes the secretion of the hormone insulin and the activation of metabolic pathways that promote protein synthesis and repair and renew cellular structures (rehabilitation) and store excess energy, but at the same time inhibit energy generation processes. In other words, at the same time the working capacity decreases—“well-fed animal is not a hunter”.

When we work, we use the energy deposited in the body. This is the so-called endogenous nutrition. Nowadays the life style of a person has changed significantly. This is due to decline in physical labor and a predominance of intellectual and operator activities, which led to a reduction in fat consumption and increased need for glucose. This led to the development of a deficit of the one energy source (glucose), against an excess of the other—fats. An energy imbalance has been developed that contributes to the increase of metabolic pathologies—diabetes, obesity and cardiovascular diseases. It is necessary to adjust the energy imbalance by developing a specialized product for the work phase or the post-absorptive period. Based on such principles, we have developed a specialized product for feeding obese
patients, to which English patent GB 2496119 of January 22, 2014 was received. This product does not induce the secretion of insulin, so working capacity does not decrease; it contributes to the maintenance of glucose homeostasis, reducing fat deposit and prevents the development of functional disorders using technologies to reduce body weight.

On the other hand, food energy pyramid connections have a negative influence on the processes of rehabilitation. In the literature, a large amount of information about the negative effect of fructose monosaccharide (20-23) and palm oil (24-25) has accumulated. Many of these aspects have been repeatedly discussed in the scientific literature regarding sugar and its component of fructose as toxic compounds promoting the development of chronic non-communicable diseases (26). Fructose is not used as an energy source in humans, but in the liver it is converted into glucose and in this form is used as an energy source. During high carbohydrate diet, insulin secretion occurs, which is an information signal about the excess intake of glucose from food. Therefore, during insulinemia, gluconeogenesis is blocked in the liver and fructose from the food passes through the liver unchanged, which increases fructose level in blood (fructosemia) and lead to the development of its toxic effects. However when fructose enters the postabsorptive period, it totally turns into glucose and has not its toxic effects. Moreover, in the absorptive period fructose promotes activation of lipogenesis and obesity, but in the post-adsorption period it promotes fat oxidation and activation of energy use processes (6 ATP molecules are consumed to synthesize glucose from fructose) and lipid oxidation and a decrease in body mass index are noted. The same dependence is noted for palm oil. Palm oil is not required for rehabilitation processes and entering the absorption period it contributes to the development of lipidemia, but when it enters the postabsorptive period it enhances gluconeogenesis, improves glucose homeostasis and activates utilization and promotes weight loss. Therefore, the phasic nature of the intake of food compounds is an important aspect of maintaining health and developing preventive and curative measures against weight gain.

In this regard, protein metabolism is at the center of all metabolic processes and largely determines the energy homeostasis, so when the synthesis of myofibrillar proteins decreases, there is a decrease in the need for glucose energy and activation of the discharge of its carbon skeleton into lipids occurs, which is noted in obese individuals [20].

It is believed that insulin is necessary for the expression of genes [21], the transport of glucose into the cell, mainly in the muscle, as they determine the amount of glucose utilization under the influence of insulin by 80% [22]. To penetrate glucose into the cell, it must be phosphorylated with the participation of hexokinase and only in the form of glucose-6-phosphate enters the muscle cell, so the rate of glucose intake into muscles depends on the activity of hexokinase. In connection with this, it was suggested that insulin promotes the activation of hexokinase, but biochemical confirmation of this situation does not exist. Hexokinase is a kind of energy sensor for the cell’s energy needs, so its activity depends on the level of ATP or the ATP/ADP coefficient [23]. Insulin promotes the activation of protein synthesis by enhancing gene expression (at the level of transcription) and the aggregation of ribosomes into polysomes (at the translation level), which increases the consumption of ATP energy and activates hexokinase. Therefore, we can make the assumption that the stimulation of glucose utilization by the muscle cell occurs indirectly through the activation of the protein synthesis process.

Synthesis of protein is the most energy-consuming process in the cell. This is due to the fact that 3 ATPs are used to form a peptide bond or to bind two amino acids (плата за точность и скорость). The average protein consists of 100 peptide bonds, thousands of proteins are synthesized per day. In the reverse decay of the peptide bond, 1 ATP is released. Therefore, with
an increase in the number of food calories, the processes of protein synthesis and proteins decay accelerate, i.e. the acceleration of protein turnover and the increase in energy expenditure, and, conversely, with a reduction in food calories, the process of protein turnover and energy expenditure also decreases. In this regard, protein metabolism is the physiological mechanism of controlling the weight of a person. Consequently, all factors contributing to the synthesis of protein, will help improve body weight control.

The rate of protein synthesis is accelerated by the aggregation of ribosomes into polysomes. This process is influenced by translation kinases, in particular mTOR, which are activated under the influence of amino acids and glucose [24] or signaling molecules to ensure the process of protein synthesis by building material and energy. The process of aggregation of ribosomes is influenced by many factors (Fig. 4).

However, when this adaptive mechanism fails to support the homeostasis of glucose, for example, when the building material (amino acids) is insufficiently supplied or the protein of the synthesizing apparatus deteriorates (reducing the ribosome aggregation factors and increasing the factors of polysomes disaggregation), the excess flow of food calories is predominantly deposited as fats, for example, in hypokinesia and inflammation [25]. Reduction of muscle mass (sarcopenia) is also an important factor in reducing the amount of energy utilization on the protein synthesis process and leads to the development of sarcopenia obesity [26].

Homeostasis of glucose is one of the most important principles of life support, so all forms of metabolism, all organs and tissues, all regulatory systems of the body participate in its maintenance, which must be integrated to maintain energy homeostasis [27]. We tried to express this interconnection in the form of a scheme (Fig. 5)

Reducing the size of muscle mass leads to a decrease in the amount of glucose utilization and there is an increase in the amount of glucose in the blood (glycaemia). In response to hyperglycemia, increased insulin secretion and increased the concentration of the hormone in the blood (insulinemia), i.e. the main manifestations of diabetes mellitus developed. These include glycaemia, insulinemia, and reduced glucose consumption by muscles. Under the influence of insulin the carbon skeleton of glucose is released into

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**Fig. 4** Factors affecting the aggregation of ribosomes.
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Figs. 5  The model of the relationship between muscle loss and the development of non-communicable diseases.

Fats, which leads to the development of lipidemia, increasing lipid deposition in adipocytes and the development of obesity.

Rapid growth of adipose tissue leads to a worsening of its blood supply and development of hypoxia, macrophage infiltration and secretion of inflammatory cytokines, so diabetes and obesity are related to chronic low-grade inflammation. Inflammatory cytokines enter the liver and promote the secretion of the CRP, which promotes increased blood pressure and marked the development of cardiovascular diseases.

Consequently, there is a decrease in the utilization of glucose and the development of non-communicable diseases (diabetes, obesity, cardiovascular) in sarcopenia, so it is necessary to carry out measures to increase muscle mass in order to interrupt this chain.

First of all, it is an adequate substrate support for the process of protein synthesis. In this regard, it is necessary to use high-grade proteins with a high content of anabolic amino acids, in particular whey protein [28].

Secondly, use technology to activate protein synthesis:

(a) Anabolic resistance exercise [29];
(b) Proteins and amino acids with a high of muscle protein synthesis activity [30];
(c) Vitamins having a positive effect on protein synthesis [31] and microelements (Ca and Mr);
(d) Can use anabolic sex hormones testosterone and estrogens;
(e) Technologies to restore the function of the insulin receptor [32];
(f) Reduce inflammation [33];
(g) Use nutraceuticals to reduce absorption and increase glucose utilization [34, 35].

Accordingly, it should completely change the ideology of the fight against obesity, taking as a basis the principles of maintaining glucose homeostasis and technology to combat sarcopenia. Strange as it may seem, these technologies have long been tested in vitro, in vivo and human studies, only in this review we tried to give them a theoretical basis.

References


[35] Jeong, Y.-T., Kim, Y. D., Jung, Y.-M., Park, D.-C., Lee,