



(RESEARCH ARTICLE)



Metabolic blocks and insulin resistance

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Abstract

Violation of glucose intake and oxidation in muscle tissue can occur at various stages and, according to the feedback principle, this will lead to inhibition of glucose utilization or the development of insulin resistance. In this regard, the process of violation of an excess glucose stream deposition in the form of glycogen (glycogen block) is considered. The processes of violation of glucose oxidation at various stages are considered: 1) pyruvate conversion (pyruvate block); 2) excessive accumulation of lactate (lactate block); 3) deterioration of the process of transamination of pyruvate (BCAA block); 4) impaired transport of reduced equivalents to mitochondria (aspartate block); 5) deficiency of cofactors for the conversion of pyruvate to acetyl-CoA and oxaloacetate; 6) carnitine deficiency for the transfer of acetyl-CoA to mitochondria (carnitine block); 7) a decrease in the rate of acetyl CoA entry into mitochondria due to a decrease in their number (mitochondrial block); 8) a decrease in the level of coenzyme Q10 and a decrease in the rate of oxidative phosphorylation (oxidative block). These disorders (metabolic blocks) can be corrected by providing substrate for these reactions, which may be the principle for the prevention and treatment of insulin-resistant conditions.

Keywords: Insulin resistance; Metabolic blocks; Diabetes; Prevention; Treatment

1. Introduction

Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide, and the number of patients with DM has continued to increase in recent years. Patients with DM exhibit hyperglycemia caused by an impairment in insulin secretion (type 1), insulin action (type 2), or both. Type 1 diabetes mellitus (T1DM), which accounts for less than 10% of diabetes cases, is characterized by an immune-mediated destruction of β cells in the pancreatic islets of Langerhans, leading to insulin deficiency [1]. On the other hand, type 2 diabetes mellitus (T2DM), which accounts for less than 90% of diabetes cases, involves insulin resistance in peripheral tissues and increased levels of blood glucose due to overnutrition accompanied by deficient insulin secretion [2]. DM is often associated with the development of secondary complications in various organs, such as eyes, kidneys, heart, brain, and skeletal muscle [3].

2. Material and methods

The article used PubMed data and the results of our own theoretical developments regarding the metabolic blocks for individual stages of glucose utilization.

3. Results and discussion

While infectious agents were the major causes of disease at the beginning of the 20th century, infectious diseases were replaced by type 2 diabetes mellitus (T2DM) and diabetic complications, cardiovascular diseases (CVD) and cancer as major causes of death by the 21st century. At present, westernized populations are plagued by a plethora of chronic degenerative diseases, including obesity, T2DM, atherosclerosis, coronary heart disease, stroke, autoimmune diseases,

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essential hypertension, cancer, osteoporosis and other more, and the number of these diseases is also rapidly increasing in developing countries [4].

Since the main negative manifestation of diabetes is hyperglycemia, all technologies for the prevention and treatment of diabetes are aimed to reduce amount of carbohydrate intake and increase amount spent on physical activity [5]. This principle has been supported since the last century, but the number of patients with diabetes is increasing from year to year and the disease has become epidemic of non-communicable origin. It should be noted that a person is a weak creature and wants to eat and lie on the couch, so the bulk of the population does not listen to medicinal advice, so the world is still losing the fight against diabetes.

It is currently believed that impaired glucose homeostasis is associated with the development of insulin resistance (IR) [6], which is the main step in the pathogenesis of diabetes and development of side effects of this disease.

Oxidation of glucose is a multi-stage process and at its stages problems with its course may appear. A decrease in the rate of glucose oxidation at any stage automatically leads to inhibition of all previous reactions (metabolic blocks), since the reaction product inhibits the reaction itself and, ultimately, leads to inhibition of glucose into the cell, therefore, in this article we will try to understand the reasons of impaired glucose oxidation and ways to prevent them.

Carbohydrates make up half of the diet calorie content and for an ordinary person with a need of 3000 kcal they make up 375 g. In the blood (with a norm of blood sugar of 100 mg% and a total blood volume of 5 l), only 5 g of glucose is contained. In the liver in the form of glycogen contains about 70 g, and in the muscles about 300 g [7,8], i.e. in total, this also amounts to 375 g or there is a correspondence (homeostasis) between intake and carbohydrate content.

It can be seen from the above data that 80% of glucose stores are in the muscles, which is consistent with the data that the muscles determine 80% of glucose uptake stimulated by insulin, [9,10], therefore, in the development mechanism of IR, we must first consider why metabolic blocks of glucose oxidation occur skeletal muscle.

The skeletal muscle is notably affected by DM. It has been shown that DM induces atrophy [11], fiber-type transition from oxidative to glycolytic [12], and impaired energy metabolism in skeletal muscle [13]. These alterations result in skeletal muscle dysfunction, such as muscle weakness and exercise intolerance [14].

There is no pure glucose in the muscle cell, since when it is received from the blood, it undergoes phosphorylation (ATP energy is expended) with the participation of the hexokinase enzyme and glucose-6-phosphate (G-6-P) is formed. This, on the one hand, prevents the return of glucose from the cell, since the enzyme glucose-6-phosphatase is absent in the muscles, and, on the other hand, activated glucose undergoes further conversion more easily.

The amount of glycogen in the muscles does not exceed 1%, since glycogen has a branching structure and attracts a lot of water due to hydrophilicity, therefore it takes up a lot of space in the cell. In connection with a change in the lifestyle of a modern person, a decrease in physical activity has occurred, which leads to a decrease in glycogen utilization. Therefore, the possibility of turning G-6-P into glycogen is reduced, since the place simply turns out to be occupied. This is the so-called "**glycogen block**", therefore, programs to increase physical activity, which are aimed at removing the glycogen block, are quite legitimate.

In repeated phosphorylation with the participation of the enzyme phosphofructokinase, conditions are created for the reaction of decomposition of hexose to triosis and the subsequent formation of pyruvic acid (pyruvate). In this case, formation of 4 ATP molecules occurs. If we take into account that at first 2 ATP molecules were expended, then the ATP yield during glycolysis is 2 ATP molecules per glucose molecule.

In patients with diabetes, the absorption of glucose by the muscles decreases under the influence of insulin [15,16], therefore, it is believed that insulin should activate the key glycolysis enzymes, but insulin does not affect the activity of hexokinase and phosphofructokinase, and only the allosteric principle is detected [17].

Pyruvate formed during glycolysis can be converted in several directions, and all compounds lying at the crossroads of metabolic pathways should be maintained at the homeostatic level. Therefore, in case of violation of the further conversion of pyruvate, its formation is automatically inhibited or glucose uptake is stopped. This is the so-called "**pyruvate block**". Indeed, violation of pyruvate metabolism is the reason for development of a number of metabolic diseases [18,19].

During glucose oxidation or its dehydrogenation, reduced equivalents are released in the form of NAD.H₂. However, the accumulation of NAD.H₂ leads to disruption of redox reactions activity, which is a threat for vital processes and the task of its fraternal oxidation to NAD arises. NAD.H₂ oxidation occurs in the mitochondria, but the mitochondrial membrane is not permeable to NAD.H₂. The malate/aspartate shunt acts as the carrier of the reduced equivalents, the limiting link in which is the amino acid asparticity (aspartate), therefore, with aspartate deficiency, the possibility of NAD.H₂ transfer to mitochondria decreases and the so-called **aspartate block** develops. Indeed, in sports practice, aspartate feed is used as an ergogenic compound to increase physical performance [20].

Under anaerobic conditions, hydrogen (H₂) can join pyruvate and lactic acid (lactate) is formed. However, accumulation of lactate leads to the development of lactic acidosis and impaired contractile function of muscle fiber. In addition, developing acidosis can cause development of oxidative stress, which negatively affects the muscle fiber vital activity, so the cell must protect itself from excessive lactate formation by reducing glucose intake or developing IR [21], therefore, development of "**lactate block**" and IR in this case should be considered as an adaptive reaction of the body to prevent cell death. The cell is forced to free itself from lactate by transporting it into the circulation. Further, lactate enters the liver, in which it serves as a substrate for gluconeogenesis, but insulin inhibits gluconeogenesis and activates the process of converting lactate into lipids, which contributes to the development of lipidemia and increased fat deposition in adipocytes, therefore, one of the markers of obesity is an increase in blood lactate [22].

For reduction of lactate formation, it is advisable to convert pyruvate to the amino acid alanine, but this requires donors of amino groups, which are branch chain amino acids (BCAAs), therefore, when they are deficient, the possibility of converting pyruvate to alanine decreases and the manifestations of the BCAA block develop, which contributes to the development of pyruvate block. Therefore, when taking BCAAs, glucose utilization increases [23,24].

For conversion of pyruvate under aerobic conditions, carbon must be removed from it with participation of the pyruvate dehydrogenase complex or, conversely, carbon should be attached with the participation of pyruvate carboxylase. At the same time, acetyl-CoA and oxaloacetate are formed, but the activity of these enzymes requires cofactors, which are vitamin B1, magnesium ions and lipoic acid, so when they are deficient, [25,26,27] conversion of pyruvate to acetyl-CoA and oxaloacetate decreases and manifestations of the pyruvate block develop IR.

Acetyl-CoA is formed in the cytoplasm, and its oxidation occurs in the mitochondria, but the mitochondrial membrane is not permeable to acetyl-CoA, therefore, a carrier, which is carnitine, is required, therefore, if it is deficient, acetyl-CoA transfer is disrupted, which leads to a feedback principle of inhibition of its formation or a violation of the pyruvate conversion, and a pyruvate block develops. Consumption of carnitine improves acetyl-CoA transport and oxidation [28]. This is the so-called "**carnitine block**".

Acetyl-CoA also can not enter the mitochondria with a decrease in their number [29], functional impairment [30], in particular under the influence of excess free radical production [31]. This is the so-called **mitochondrial block**. In this case, according to the feedback principle, the conversion of pyruvate to acetyl-CoA is inhibited and the manifestations of the pyruvate block develop.

Upon entry into mitochondria, acetyl-CoA dehydrogenation occurs and reduced equivalents are formed, which enter the biological oxidation chain. At the first stage of biological oxidation, ubiquinone or coenzyme Q₁₀. (CoQ₁₀) appears. However, CoQ₁₀ decreases with age [32], which leads to a decrease in the value of oxidative phosphorylation and acetyl-CoA dehydrogenation and its entry into mitochondria are inhibited by the feedback principle. This is the so-called "**oxidative block**". When taking CoQ₁₀, the oxidative phosphorylation process improves and the manifestations of IR are reduced. [33].

In case of impaired glucose metabolism at various stages of its oxidation, the mechanism of maintaining homeostasis is activated by transferring accumulating metabolites by including alternative pathways for their metabolism. Since the possibilities of G-6-F deposition in the form of glycogen are limited, the conversion of G-6-F to fructose and sorbitol is enhanced, the accumulation of poorly digestible carbohydrates in the cell leads to the formation of conglomerates and impaired cell function, therefore, the cell protection mechanism in the form of the development of IR and a decrease in the intake of glucose in the muscles. Another alternative way is to convert under-oxidized metabolic products with excessive secretion of insulin into fats. In metabolic terms, this pathway is shown in Figure 1.

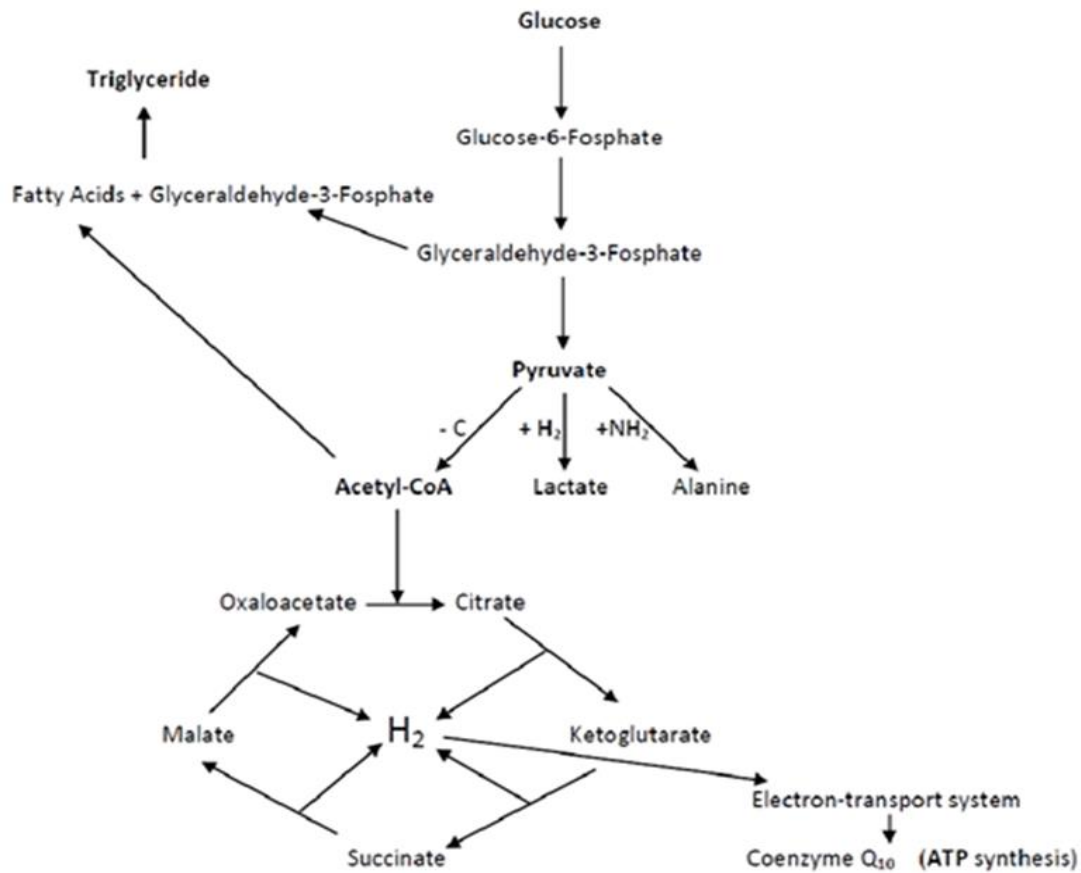


Figure 1 Diagram of glucose oxidation and lipogenesis activation pathway in case of impaired conversion of glyceraldehyde-3-phosphate and acetyl-CoA

As can be seen from Figure 1, if glucose oxidation worsens at the stages of glyceraldehyde-3-phosphate and acetyl-CoA oxidation, their carbon skeleton is discharged into fats or lipogenesis is activated. These manifestations are noted when trying to increase the flow of glucose into the muscles under the influence of pharmaceuticals. Therefore, it is more advisable to improve the course of glucose oxidation, rather than just trying to increase its uptake into tissues with the help of pharmaceuticals, since in this case we can get negative manifestations in the form of activation of lipogenesis. The accumulation of lipids in the muscles can also have a negative effect on their function and, accordingly, prevent the negative effects of lipid accumulation, glucose intake decreases due to the development of IR [34]. This manifestation can be called a **"lipid block"**.

ATP is formed in the biological oxidation chain, but the ATP level in the muscle cell is at a constant level even during the feeding / starvation cycle or during exercise. Therefore, the ATP/ADP coefficient is an information signal for regulatory systems in relation to maintaining ATP homeostasis. With a decrease in the use of ATP, an increase in the coefficient and inhibition of hexokinase, i.e. muscle glucose is inhibited and IR develops. This is a kind of **"energy block"**. With an increase in ATP utilization, the ATP/ADP coefficient decreases and hexokinase is activated, which contributes to an increase in the supply of glucose to the muscles and decreases the manifestations of IR.

The main consumers of ATP in muscles are physical activity and protein synthesis. There are many serious works on the role of physical activity in the regulation of glucose homeostasis, but virtually no attention is paid to the role of protein synthesis in the regulation of glucose homeostasis. It is known that 3 ATP is expended on the formation of a peptide bond. The average protein contains 100 peptide bonds. Thousands of proteins are synthesized per day, so protein synthesis is the most energy-intensive process in a muscle cell.

Insulin is an anabolic hormone; therefore, it is involved only in the processes of storage of glucose either in the form of glycogen or in the form of lipids. But it does not show catabolic properties or does not affect the process of glucose catabolism, therefore, insulin should be considered as a marker of "excess" glucose and amino acids.

Protein synthesis occurs on ribosomes even under fasting conditions (energy deficiency) to preserve the synthesis of important functional proteins. With an excess of glucose and amino acids after eating (excess energy), insulin secretion is enhanced and anabolic processes are activated.

The effect of insulin on protein metabolism is associated with its ability to initiate aggregation of ribosomes into polysomes or its effect on protein metabolism is manifested at the stage of translation [35]. Translation is the fastest process for regulating the rate of protein synthesis (Fig. 2).

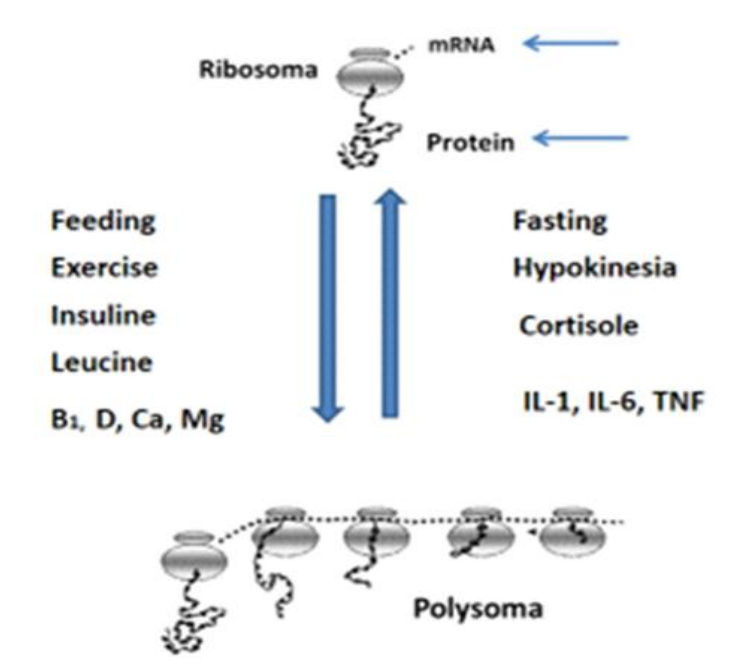


Figure 2 Factors affecting the regulation of protein synthesis at the translation stages

As can be seen from Figure 2, a number of factors affect the rate of protein synthesis. This is feeding, the hormone insulin, and physical activity, especially of a resistant nature [36]. Some vitamins have a positive effect on protein synthesis [37,38] and microelements [39]. This effect is achieved through the activation of mTOR kinase or translation kinase [40,41], which promotes aggregation of ribosomes into polysomes. In this case, the rate of protein synthesis increases by about 10 times. With an increase in the rate of protein synthesis, the ATP energy requirements automatically increase and, accordingly, glucose utilization increases and the manifestations of IR are removed.

It should be noted that under the influence of insulin the process of lipolysis and fat oxidation is inhibited, therefore lipids cannot serve as ATP energy sources for protein synthesis during food intake and ATP formed due to protein synthesis during this period can be used glucose catabolism. Therefore, when lowering blood glucose levels, insulin levels decrease and anabolic processes are inhibited, and all hypoglycemic states are only catabolic.

Polysomes can decay back to ribosomes. This occurs during fasting (deficiency of the substrate for protein synthesis), during hypokinesia (reducing the anabolic effect of physical activity), under the action of cortisol (hormone stress), and under the influence of inflammatory cytokines (switching the flow of energy to inflammatory processes). In all these cases, amount of protein synthesis decreases and, accordingly, need of glucose energy for anabolic process, therefore, under these conditions, amount of glucose utilization by the muscles decreases or the manifestations of IR develop [42,43].

Usually, muscles are considered as an organ providing mobility of the body, but muscles take an important role in the regulation of metabolic processes, in particular in glucose homeostasis. With insufficient glucose intake, for example, during fasting, homeostasis is maintained due to endogenous synthesis (gluconeogenesis), but proteins are used as a substrate.

Since muscles make up about 50% of the protein mass, respectively, they mainly provide the supply of the substrate for the gluconeogenesis process. Therefore, with a decrease in muscle mass - sarcopenia (from the Greek words sacra - meat and singing - deficiency), the amount of glucose utilization decreases, which is the main reason for the increase in

its concentration in the blood (glycemia) and there is an increase in insulin secretion (insulinemia). This is an important reason for the development of T2DM. Under the influence of insulin, the discharge of the carbon skeleton of glucose into fats is enhanced, which leads to the development of dyslipidemia. This contributes to increased fat deposition in adipocytes and the development of obesity.

During sarcopenia possibility of supplying a substrate (amino acids) for gluconeogenesis is reduced. These manifestations are especially dangerous during the period of nightly starvation, when the risk of developing deep hypoglycemia and even death develops. Therefore, maintenance of glucose homeostasis during feeding and fasting significantly worsens during sarcopenia, and in these cases it is necessary to increase attention to the development of measures to increase muscle mass.

Thus, diabetes is a violation of protein metabolism, so all measures to improve the process of protein synthesis will increase the need for ATP and indirectly increase the flow of glucose into the muscle cell to provide the anabolic process with energy. This requires a review of our understanding of the pathogenesis of diabetes and allows us to develop new technologies for the prevention and treatment of diabetes. These provisions apply to type 1 diabetes, when an improvement in protein synthesis can help reduce glycemia even without increasing the dose of insulin.

4. Conclusion

In the mechanism of insulin resistance development, deterioration of glucose oxidation during its anaerobic and aerobic conversion plays a significant role. These disorders or metabolic blocks can be eliminated by using of food compounds, which must be taken into account when developing preventive and therapeutic measures.

Compliance with ethical standards

Disclosure of conflict of interest

Disclosure of conflict of interest Conflicts Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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