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THE ROLE OF HOMOCYSTEIN IN THE PATHOGENESIS OF ARTERIAL HYPERTENSION IN OBESITY AND COMORBID DISEASES

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Abstract. Homocysteine (Hc) is an amino acid that is involved in the pathogenesis of arterial hypertension (AH) by inducing prothrombotic and pro-inflammatory effects, by increasing oxidative stress, endothelial dysfunction and smooth muscle cell proliferation. However, its role in the development of hypertension with comorbid pathologies, such as obesity and related metabolic disorders, has not been studied enough.

Key words: *homocysteine; obesity; metabolic syndrome; insulin resistance.*

РОЛЬ ГОМОЦИСТЕИНА В ПАТОГЕНЕЗЕ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ ПРИ ОЖИРЕНИИ И КОМОРБИДНЫХ ЗАБОЛЕВАНИЯХ

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Резюме. Гомоцистеин (Гц) — это аминокислота, которая принимает участие в патогенезе артериальной гипертензии (АГ) путем индукции протромботических и провоспалительных эффектов, путем увеличения окислительного стресса, эндотелиальной дисфункции и пролиферации клеток гладких мышц. Однако его роль в развитии АГ при коморбидных патологиях, например при ожирении и связанных с ним нарушениях обменных процессов, изучена недостаточно.

Ключевые слова: *гомоцистеин; ожирение; метаболический синдром; инсулинорезистентность.*

INTRODUCTION

By the end of the XX century, a cluster of major risk factors for cardiovascular disease (CVD) has been described, which includes simultaneous presence of obesity, type 2 diabetes mellitus (T2DM), hyperlipidaemia and arterial hypertension (AH). This simultaneous occurrence of risk factors led researchers to assume the existence of a peculiar pathophysiological state, later described as "metabolic syndrome", which emphasize the presence of pathogenetic links between these conditions. However, at the moment some researchers differentiate abdominal obesity as a separate independent risk factor for the development of atherosclerosis, coronary heart disease (CHD) and hypertension (HT) [1, 2].

According to the data published in recent years, hyperhomocysteinaemia plays an important role

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in the development of metabolic syndrome (MS) [3]. High homocysteine levels are associated with cardiovascular risk, risk of insulin resistance syndromes (IR), presence of nonalcoholic fatty liver disease (NAFLD) and many other diseases [4–6]. However, the relationship between abdominal obesity (as one of the main elements of MS) and hyperhomocysteinaemia has been insufficiently studied by the moment. Taking into account the prevalence of these conditions and their proven impact on the development and progression of cardiovascular pathology, the study of this problem has a great scientific and practical interest [7].

OBJECTIVE

The aim of this review is to present and analyze the current data concerning the role of homocysteine in the pathogenesis of arterial hypertension in obesity and related comorbid conditions.

MATERIALS AND METHODS

To reach this objective, scientific publications in Russian and English have been analuzed for the period from 2016 to 2022, the publications were indexed in RINC, PubMed, MEDLINE, and Cochrane Library databases. In isolated cases, earlier publications were used due to their priority or historical value.

HOMOCYSTEINE, ITS METABOLISM, NORMS AND CAUSES OF ELEVATION

In 1932, chemists Butz and Vigneaud described a previously unknown amino acid synthesized by exposing high concentration of sulfuric acid to metionine. The obtained compound differed from cysteine by one carbon atom and was therefore named "homocysteine". Homo (from Greek ομος) is a component of compound words meaning "similar" [8, 9].

Homocysteine (Hcy) is an intermediate metabolite in the folate cycle containing thiol groups, which is produced in all cells through transmethylation reactions of dietary methionine [10, 11].

The level of Hcy in human blood depends on age, sex, nutritional quality and genetic characteristics. During life, the level of Hcy in blood gradually increases. In children before puberty, the levels of Hz in boys and girls are approximately the same (about 5 μmol/L). During puberty, Hcy levels rise to 6–7 μmol/L, and this increase is more pronounced in boys than in girls. In adults, the balance is also maintained, and Hcy levels in males are usually higher than in females, which is attributed to greater muscle mass. Hcy levels gradually increase with age, women have a higher rate of increase than men. The gradual increase in Hcy levels connected with age has been attributed to a decline in the renal function [9, 12].

Homocysteine is metabolized by two pathways: by the transfer of the sulfate group in the presence of vitamin B6, or by remethylation in the presence of vitamin B12 and folic acid. Approximately 5–10% of the total daily cellular production of Hcy, which is not metabolized within the cell, passes into the blood plasma, where about 80% is in the albumin-bound state and about 1% is in the free form. The remaining part is presented as disulfides with cysteine, homocysteine (homocystine), and other compounds. All homocysteine-containing derivatives are defined as "total plasma homocysteine" [11, 12].

Normal levels of Hcy range from 5 to 15 μmol/L, and this baseline is maintained in healthy individuals due to constant renal clearance[11]. According to other sources, normal rates of Hcy ranges from 10–11 μmol/L. Homocysteine concentration in blood plasma within 15–30 μmol/L indicates moderate hyperhomocysteinaemia, from 30 to 100 μmol/L — intermediate, and more than 100 μmol/L — severe [9].

The main causes of hyperhomocysteinaemia (HHcy is a condition characterized by elevated levels of Hcy in the blood) can be divided into hereditary (genetic) and non-hereditary (acquired). Thus, genetic factors are gene mutations that encode the synthesis of an enzyme involved in the processes of homocysteine formation. The most studied is a defect in the enzyme 5,10-methyleneteterahydrofolate reductase (MTHFR). MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyl-tetrahydrofolate. The latter is the major circulating form of folic acid, high concentrations of which are required for the conversion of excess homocysteine to methionine by the methionine-synthase enzyme. Thus, a decrease in the activity of the MTHFR enzyme caused by single nucleotide polymorphisms contributes to the accumulation of homocysteine [13].

Non-genetic factors of HHcy include autoimmune processes, consumption of large amounts of methionine-rich foods, large amounts of caffeine, smoking, alcohol consumption, sedentary lifestyle, vitamin deficiency states (especially deficiencies of B_1, B_6, B_{12}, folic acid), and kidney diseases [8]. Elevated Hcy levels are also observed in people who take certain medications, such

as methotrexate, cholestyramine, niacin, and a number of antiepileptic drugs, all of which affect folic acid metabolism. Drugs that affect vitamin B_{12} absorption (e.g., было выделено H_2-receptor antagonists) or drugs that inhibit vitamin B_6 activity (e.g., euphylline) may also increase Hz in the blood [9].

Although the description of Hcy and studies on the role of this amino acid began more than 90 years ago, the most active study concerning Hcy significance has taken place in recent decades [14]. Thus, nowadays there is a large number of publications regarding the association of hyperhomocysteinaemia with various pathologies: CVDs, neuropsychiatric disorders (autism spectrum disorders, migraines, etc.), neurodegenerative, allergic, oncological and autoimmune diseases, vasculitis, end-stage kidney disease, osteoporosis, undifferentiated connective tissue dysplasia, various lesions of the reproductive system (pregnancy abnormalities, polycystic ovary syndrome — PCOS) and others. [3, 8, 9, 14, 15].

A correlation between HHcy and obesity is seen in the structure of many studies, but the data remain contradictory. In 2020, Jinxiang Wang and Dingyun You conducted a meta-analysis based on 14 publications selected using NOS and AHRQ to evaluate the relationship between blood homocysteine concentration and obesity. The meta-analysis showed significantly lower homocysteine concentrations in the control group than in obese patients, regardless of nutritional status, dietary habits, insulin resistance (IR) status, special disease history, history of medications taken, genetic background, etc. Homocysteine concentration was higher in patients with obesity and PCOS than in PCOS patients without obesity, suggesting that obesity increases the concentration of Hcy in the blood even if there are conditions that already include an increase in this laboratory parameter [16].

The role of HHcy in pathogenesis of comorbid diseases (atherosclerosis, Hypertention, IR, T2DM, NAFLD, etc.) is well studied , while its place in the direct development of obesity remains controversial. However, the analysis of literature make it possible to indicate common links between the pathogenesis and HHcy, which will be discussed below.

INFLAMMATION IN ADIPOSE TISSUE AND THE ROLE OF HOMOCYSTEINE

According to numerous studies, it has been proved that obesity leads to subclinical systemic inflammation, which influence on forming vicious circles in the pathogenesis of this disease and related comorbid conditions (cardiovascular diseases, type 2 diabetes mellitus, uric acid metabolism disorder, sex hormone imbalance, non-alcoholic fatty liver disease, oncologic diseases) [17, 18].

Inflammation of adipose tissue begins with the recruitment of monocytes and their extravasation from blood vessels into adipose tissue, where they acquire the status of macrophages. Chemokines, among others, are responsible for the processes of their adhesion and migration. Chemokines are produced in huge quantities by hypertrophied adipocytes in adipose tissue. One of the most known and active variants of chemokines is MCP-1 (monocyte chemoattractant protein 1), which stimulates the migration of monocytes into the vessel intima [17]. The study of G. Wang and Y.L. Siow proved that the increased expression of MCP-1 was associated with increased concentrations of homocysteine [19]. Thus, it can be assumed that hyperhomocysteinaemia aggravates extravasation of monocytes and further infiltration of adipose tissue by macrophages. The latter, in turn, prevent the transformation of preadipocytes into mature adipocytes, blocking the development of adipose tissue hyperplasia and promoting further hypertrophy of fat cells.

Assuming that chemokines are produced not only in hypertrophied adipocytes but also by macrophages infiltrating adipose tissue, this process acquires the character of a "vicious circle", which is probably maintained and aggravated in the presence of high homocysteine concentrations [17, 19].

IMPAIRED MICROCIRCULATION IN OBESITY AND THE RELATIONSHIP WITH HYPERHOMOCYSTEINAEMIA

In 2004, Trayhurn and Wood were first to propose the idea of obesity-related white adipose tissue hypoxia (WAT) as the cause of adipose tissue dysfunction. Since then, a number of studies have been conducted and there is much debate about the cause of adipose tissue dysfunction associated with hypoxia. These dysfunctions are proposed as a major cause for the development of a pro-inflammatory phenotype of adipose tissue, despite limited data of human studies [20].

Hyperhomocysteinaemia may serve as an additional provocative factor in the development of hypoxia through mechanisms of vascular endothelial dysfunction. Numerous publications

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correlate high plasma homocysteine rates with various pathologies of the vascular tract. Different studies present various mechanisms of homocysteine-induced endothelial dysfunction. Specifically, there is evidence that hyperhomocysteinaemia counteracts the vasodilatory properties of nitric oxide (NO) through the formation of S-nitrosohomocysteine, which contributes to the maintenance and induction of endothelial pathology [21]. Other sources indicate that homocysteine triggers smooth muscle cell proliferation and increases collagen synthesis, which leads to intima thickening and myocyte hypertrophy. Hcy provokes accumulation of reactive oxygen species, as a consequence, endothelial cell damage occurs [22]. Glutathione synthesis is also inhibited in HHcy conditions, resulting in accumulation of extra reactive oxygen species which triggers endothelial damage as well [6, 22].

The combination of the above mentioned processes eventually leads to the development of endothelial dysfunction, impaired microcirculation and hypoxia. Consequently, hypoxia-sensitive genes are expressed, which provokes the attraction of immune cells and the development of aspetic inflammation of adipose tissue [18, 20].

In addition, directly damaging the endothelium, homocysteine promotes the release of cytokines and other inflammatory factors (IL-6, IL-8, TNFα, etc.), which also supports inflammation in adipose tissue [22]. At the same time, the inflammation intensifies the processes of angiogenesis, they become extremely active and subsequently may lead to endothelial dysfunction as well. There is a tendency to form another vicious circle.

RELATIONSHIP BETWEEN HYPERHOMOCYSTEINAEMIA, INSULIN RESISTANCE AND OBESITY

Insulin resistance (IR) positively correlates with hyperhomocysteinaemia in many studies. Generally, this relationship is attributed to impaired liver function in the presence of high blood insulin concentrations (e.g., in non-alcoholic fatty liver disease, which will be discussed later). However, there is a hypothesis that hyperhomocysteinaemia is a factor in the development of IR. This theory is supported by animal studies. To name a few, J. Golbahar et al. conducted a study on two groups of male rats (the test group received Hcy daily with drinking water, the control group did not receive Hcy) in order to confirm the hypothesis that hyperhomocysteinemia may cause hyperinsulinemia leading to insulin resistance in rats. The study evaluated plasma glucose, insulin, total Hcy concentrations, oral glucose tolerance tests in the control and test groups twice (before the study and after 50 days). Based on the results, the mean fasting plasma insulin level was significantly higher in the test group, whereas the mean glucose/insulin rate was significantly lower in the test group than in the control group. In addition, the mean insulin resistance index as assessed by homeostasis was significantly higher in the experimental rats, but the mean plasma glucose levels were not significantly different. Additionally, the results of oral glucose tolerance tests showed the development of insulin resistance in experimental rats after 50-day of homocysteine consumption [23].

Being a strong proinflammatory agent, Hcy provokes the release of a large number of cytokines, including TNFα and IL-6. They can similarly activate the insulin receptor, however, in contrast to a physiological pathway when insulin activates its receptor and phosphorylates tyrosine, cytokines activate serine kinase; accordingly, phosphorylation of another amino acid, serine, is triggered, including the substrate of the insulin receptor (SIR-1). This process inactivates SIR-1 or leads to its destruction by blocking tyrosine phosphorylation in both the insulin receptor and SIR-1, resulting in disruption of the intracellular insulin signaling pathway and insulin's characteristic actions. Thus insulin resistance develops.

However, TNFα stimulates the development of insulin resistance by another mechanism as well. It promotes an increase of free fatty acids in the blood, and this is another pathway for the development of insulin resistance in many tissues [17].

Increasing the concentration of cytokines (IL-1, IL-6, TNFα), homocysteine can probably lead to aggravated expression and secretion of resistin. Resistin is a peptide hormone mainly secreted by adipose tissue. Its effects play a key role in the development of insulin resistance and diabetes associated with obesity [10].

In addition, hyperhomocysteinaemia provokes inflammation in adipose tissue through the secretion of adiponectins and inflammatory mediators (leptin, TNFα, adiponectin, IL-6, IL-8, etc.) which may contribute to the development of IR, as presented above [17, 18].

Therefore, IR leads to a decrease in the synthesis of nitric oxide and prostacyclin and increases the synthesis of vasoconstrictors resulting in the

development of endothelial dysfunction, which was described in the previous section. The formation of another vicious circle is traced [24].

Additionally, there is a theory of primary obesity arising from blood hyperinsulinaemia and insulin resistance of body tissues — the so-called endocrine (carbohydrate-insulin) model of obesity. Deficiency of lipolysis and beta-oxidation in mitochondria against the background of high levels of insulin in the blood underlie the theory. It subsequently leads to energy deficiency, resulting in muscle weakness against the background of increased appetite, and, as a consequence, an increase in body weight [24, 25]. If the theory of hyperhomocysteinemia as a risk factor for the development of insulin resistance is correct, then Hcy may lead to an increase in body mass index through this mechanism. However, there is currently no scientific evidence to support this hypothesis, and further study is required.

HYPERHOMOCYSTEINAEMIA AND NON-ALCOHOLIC FATTY LIVER DISEASE

Recently, there has been increased interest in the positive relationship between homocysteine and the prevalence of nonalcoholic fatty liver disease (NAFLD) [26]. On the one hand, homocysteine is produced and catabolized in the liver. In case of liver damage the levels of Hcy in serum may feasibly increase. One of the possible mechanisms of HHcy is impaired homocysteine trans-sulfation against the background of the negative effect of high insulin concentrations in IR. Deterioration of liver function in obesity due to steatosis leads to a reduced activity of enzymatic systems, which slows down homocysteine metabolism and contributes to hyperhomocysteinaemia [10].

On the other hand, according to foreign studies, there is a suggestion that Hcy may contribute to the progression of liver damage independently. To name a few, in L. Yao et al. (2016) found that hyperhomocysteinaemia could promote liver steatosis in mice through activation of the aryl hydrocarbon receptor pathway. According to several experimental studies, lipid accumulation in the liver was induced in different models of hyperhomocysteinaemia in the Pediatric NAFLD study. In 2014, A. Pastore et al. indicated that Hcy levels strongly correlated with the severity of liver damage. These studies suggest that elevated blood Hcy is associated with the progression of NAFLD [27].

The pathogenesis of NAFLD includes a large number of pathogenetic mechanisms associated with abdominal obesity and IR: oxidative stress, endothelial dysfunction, chronic vascular inflammation, and altered secretion of adipocytokines, especially adiponectin, which increase as pathologic liver changes progress. It should be noted that IR is considered as an independent factor that can determine the development and progression of NAFLD. There are many studies indicating a close relationship between NAFLD and IR of liver, adipose and muscle tissue. Therefore, when metabolically obese but normal weight syndrome (MONW) develops, systemic insulin resistance is indicated in these patients. In light of the well-known association between NAFLD and insulin resistance (IR), NAFLD without obesity can be considered as a "hepatic" phenotype of MONW [28].

As discussed earlier, Hcy probably plays an important role in the development of IR, and it could theoretically participate in the pathogenesis of NAFLD. However, no reliable data supporting this theory have been found by the moment.

CONCLUSION

Thus, there is no doubt that Hcy is involved in many metabolic pathways which lead to the formation/maintenance/progression of hypertention in obesity and related comorbid conditions. However, there is insufficient data to form a unified theory. It is necessary to expand the laboratory practice of Hcy determination in order to collect additional statistical information on the correlation between Hcy, obesity and other conditions.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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