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PHYSIOLOGICAL ROLE OF GLUTATHIONE IN THE HUMAN BODY (LECTURE)

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Abstract. Glutathione tripeptide is a small thiol molecule, which protects the body from reactive oxygen forms, aging, exposure to xenobiotics, destructive inflammation, various forms of cell death, and many diseases that are the leading causes of mortality worldwide. Glutathione is found in all animal cells. It ensures optimal performance under the effect of various adverse environmental factors. The report gives an overview of the structure and synthesis of glutathione in the body, its key role in the formation of antioxidant protection, detoxification of exogenous and endogenous xenobiotics. We discuss the participation of the glutathione system in the innate and acquired immune response processes, programmed cell death, cell proliferation, DNA repair and synthesis. The article provides a list of factors that cause glutathione system depletion followed by a decrease in the reserve capacity of the cell, up to its death. The content of glutathione in food products and the possibility of its transport into the internal environment from food are discussed. Changes in the content of glutathione depending on the methods of its introduction into the body are considered. The objective was to provide the variety of physiological aspects of the role of glutathione, to give a complex impression of the importance of this molecule for the body, to demonstrate the significance and possibility of preventing depletion of the glutathione system.

Keywords: glutathione, antioxidant, glutathione peroxidase, detoxification, glutathione transferase, glutathione transporters, disease prevention

ФИЗИОЛОГИЧЕСКАЯ РОЛЬ ГЛУТАТИОНА В ОРГАНИЗМЕ (ЛЕКЦИЯ)

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Резюме. Трипептид глутатион — небольшая тиольная молекула, защищающая организм от активных форм кислорода, старения, воздействия ксенобиотиков, разрушительного воспаления, различных форм клеточной смерти, многих заболеваний, являющихся ведущими причинами смертности во всем мире. Глутатион содержится во всех животных клетках, обеспечивая оптимальное функционирование в условиях воздействия различных неблагоприятных факторов внешней среды. В лекции рассматриваются строение и синтез глутатиона в организме, его ключевая роль в формировании антиоксидантной защиты, в обеспечении детоксикации экзогенных и эндогенных ксенобиотиков. Обсуждается участие системы глутатиона в протекании процессов врожденного и приобретенного иммунитета, запрограммированной клеточной смерти, в пролиферации клеток,

в процессах репарации и синтеза ДНК. Приводится перечень факторов, которые способны истощать систему глутатиона, что сопровождается снижением резервных возможностей клетки, вплоть до гибели. Обсуждается содержание глутатиона в продуктах питания и возможности транспорта его во внутреннюю среду из пищи. Рассматриваются изменения содержания глутатиона при различных способах его введения в организм. Автор ставил перед собой задачу показать читателю многообразие физиологических аспектов роли глутатиона, дать целостную картину значимости этой молекулы для организма, продемонстрировать важность и возможность профилактики истощения системы глутатиона.

Ключевые слова: глутатион, антиоксидант, глутатионпероксидаза, детоксикация, глутатионтрансфераза, транспортеры глутатиона, профилактика заболеваний

INTRODUCTION

Glutathione is a water-soluble tripeptide formed from the residues of three amino acids: glutamic acid, cysteine and glycine. Glutathione is found in many plant, microbial and animal cells. A decrease in its intracellular content is an important factor in the development of aging, Alzheimer's disease, Parkinson's disease, autism, schizophrenia, cataract, macular degeneration, glaucoma, osteoporosis, carcinogenesis, coronary heart disease, hemorrhagic and ischemic stroke, atherosclerosis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), bronchial asthma, cystic fibrosis, immunodeficiency, viral infections and diabetes mellitus [3, 5, 14, 20, 21].

The molar concentration of glutathione in animal cells (1–10 mM) is higher than the concentration of most organic substances [4]. Glutathione is synthesized in the cytosol, and is also found in the nucleus, mitochondria, and endoplasmic reticulum, where it enters via intracellular transport [53]. Liver provides up to 90% of all circulating glutathione and is called the main organ of glutathione synthesis [48].

Cytosolic GSH synthesis occurs via two ATP-dependent reactions. The first reaction is catalyzed by glutamate-cysteine ligase (also known as gamma-glutamylcysteine synthetase), which combines glutamate and cysteine. Regulation of the activity of this enzyme is carried out, firstly, by competitive inhibition by glutathione according to the negative feedback principle, and secondly, by the availability of cysteine [4]. The physiological concentration of cysteine in the cell is significantly lower than the concentration of glutamate. With a dietary deficiency of amino acids, a decrease in the level of glutathione in blood plasma is recorded, and with an increase in the intake of cysteine into the body, the level of glutathione increases [32].

STRUCTURE AND BIOLOGICAL FUNCTION

Glutamate-cysteine ligase consists of two subunits encoded by different genes. Their expression is induced by the action of active forms of oxygen and nitric oxide, physical inactivity, pro-inflammatory cytokines, lycopene, beta-carotene, and vitamin D [4, 19, 44].

Being the smallest intracellular thiol molecule, glutathione has a high reducing ability, providing antioxidant protection to the body.

Glutathione (GSH) is a hydrogen donor. Each of two GSH molecules donates a hydrogen atom to form a dimer (GSSG), which is the oxidized form of glutathione: $2GSH \rightarrow GSSG + 2H\bullet$. Concentration of GSSH in tissues is not higher than 0,5–1% of GSH [4, 48].

Oxidized glutathione (GSSG) can be reconverted into two molecules of reduced GSH by the enzyme glutathione reductase and NADP-H: $GSSG + NADP\text{-}H + H_2 \rightarrow 2GSH + NADP\text{-}H_2$.

The most reactive group in the glutathione molecule is a sulfhydryl group of cysteine residue –SH, which easily enters into reactions of one- and two-electron oxidation, thiol-disulfide exchange, alkylation and acetylation, providing numerous functions of glutathione in the cell [4, 42].

Being a powerful antioxidant, glutathione interacts directly with free radicals, superoxide, singlet oxygen, and hydroxyl radicals [7, 13].

Glutathione also performs its antioxidant function as a coenzyme of glutathione peroxidase. This enzyme is known to catalyze the reduction of hydrogen peroxide and hydroperoxides to water or alcohol ROH. It should be noted that currently 7 isoforms of glutathione peroxidases are known [4], the function of which is not limited to the antioxidant effect. For example, the 4th isoform is involved in the inhibition of inflammatory processes by influencing lipoxygenases and cyclooxygenases [66]. The glutathione peroxidase deficiency, which is directly associated with a decrease in glutathione concentration, contributes to the development of acute and chronic inflammation of the cardiovascular system and intestines, accelerates the formation of atherosclerosis, and increases embryonic mortality [42].

In the glutathione-ascorbate-tocopherol chain, which is part of the body's antioxidant defense system, glutathione plays a key role, carrying out the reduction of oxidized ascorbic acid and tocopherol [47].

It is important to remember that for the normal functioning of the body, a small amount of reactive oxygen species is necessary, which are involved in the transmission of signals in cells [31]. This is why introducing excess amounts of glutathione into the body can lead to adverse effects.

Glutathione is associated with energy metabolism in the cell. Its level is critical for optimal and efficient oxidation of mitochondrial fatty acids. With insufficient glutathione levels, oxidation of non-esterified fatty acids in mitochondria is reduced, which has been demonstrated in both animals and humans [51]. Correction of glutathione deficiency results in restoration of impaired mitochondrial fatty acid oxidation.

In the process of nutrient oxidation in mitochondria, reactive oxygen species are formed, which can damage the mitochondria. GSH deficiency results in mitochondrial dysfunction, which can be corrected by correcting glutathione levels [40].

Glutathione transferases play a major role in the metabolism of endogenous and exogenous xenobiotics, catalyzing reactions of conjugation, reduction, isomerization, etc. [48]. Numerous glutathione transferases are grouped into three families: cytosolic, mitochondrial, and microsomal. Some of them are involved in the synthesis of prostaglandins and leukotrienes, testosterone and progesterone, and tyrosine degradation [4].

Detoxification processes occur in all cells, and are especially active in the liver, where electrophilic xenobiotics of almost all classes are neutralized. These xenobiotics include a variety of substances: pesticides, drugs, smoking products, paints, carcinogens and mutagens. The addition of glutathione helps reduce toxicity by decreasing their activity and leads to a more rapid elimination of these compounds from the body, as their hydrophilicity increases.

As early as the 1980s, it was believed that detoxification of exogenous xenobiotics was the main function of glutathione transferases. Nowadays, it is clear that the primary function of glutathione transferases is to participate in the metabolism of toxic endogenous substances. Already in prokaryotes, glutathione transferases perform the conjugation of GSH with secondary metabolites of oxidative stress — aldehydes, quinones, epoxides [42].

Glutathione plays a key role in many forms of programmed cell death, including apoptosis, necroptosis, ferroptosis and autophagy [8, 25, 30, 55]. Apoptosis is initiated and triggered by the caspase family. A decrease in GSH/GSSG ratio in the cell precedes the activation of caspases and is considered an early event in the progression of apoptosis in response to various stimuli [28, 35]. In some cases, GSH depletion not only triggers one form of programmed cell death, but can also initiate multiple forms of cell death. These different forms of cell death can be initiated simultaneously or sequentially and then interact with each other [23, 27, 68].

Glutathione is directly involved in cell proliferation. Thus, when there is insufficient GSH content in the nucleus, the cell cycle stops at the G1 phase. At the onset of cell proliferation, GSH creates the necessary redox environment to stimulate chromatin degradation. Nuclear glutathione is required to control nuclear protein degradation by the nuclear proteasome [2, 30, 55].

The normal course of innate and acquired immunity processes cannot occur without GSH. Immune cells use active forms of oxygen to eliminate pathogens. Glutathione is used to contain this process within the infectious focus and prevent excessive impact on surrounding tissues. In addition, it is important for the regulation of such processes as proliferation of T-lymphocytes, the phagocytic activity of polymorphonuclear neutrophils, and the functions of dendritic cells [41, 54, 64, 65].

Glutathione is essential for cells to repair damaged areas of DNA, proteins and other biomolecules. Synthesis and repair of damaged DNA occurs with the participation of the enzyme ribonucleotide reductase (RNR). The GSH-glutathione reductase system is an electron donor for this enzyme, thereby supporting DNA synthesis and repair [30, 62].

Glutathione is the first protective barrier for the lens, cornea, retina, skin, lungs and intestinal mucosa [46, 50].

Thus, glutathione status is an indicator of cell viability. When the glutathione system is depleted, the functionality and resistance of cells decreases sharply, even to the point of death.

FACTORS THAT DEPLETE THE GLUTATHIONE SYSTEM

Various exogenous and endogenous factors of physical or chemical etiology can deplete the glutathione system. Viral infections [36], various radiations [52], including ultraviolet [24], toxins including alcohol, heavy metals, inflammation, household chemicals and dietary deficiency of glutathione and its precursors lead to a decrease in the concentration of reduced glutathione [6, 43].

With aging, the level of reduced glutathione decreases, and the oxidized one increases [42, 59, 67]. This deterioration of GSH homeostasis may participate, along with other physiological phenomena, in the development of age-related diseases.

Thus, oxidative depletion of glutathione can outpace its synthesis. In such situations, the body is extremely important to be able to obtain glutathione from exogenous sources. Naturally, questions arise about the presence and

quantity of glutathione in food, the possibility of transporting this substance from the gastrointestinal tract to blood plasma and its interorgan transport.

GLUTATHIONE CONTENT IN FOOD

Glutathione is a common component of human nutrition, as it is part of all animal cells, yeast and many plants [4, 7, 42, 49]. Human nutritional sources contain both reduced and oxidized glutathione. The total content of glutathione (GSH+GSSG) in 100 g of fresh liver is about 200 mg, in 100 g of meat is about 50 mg, in plant products its content ranges from 1 to 28 mg per 100 g of product [1, 6].

L. Pilat et al. (2012) provide lists of products that contain not only glutathione, but also its inactivating substances (GRU). The authors also indicate products that contain only glutathione, or only its inactivators, or both [6].

For example, in the list of products containing only glutathione (GSH+GSSG), boiled asparagus is in first place (916 nmol/g total GSH). This list also includes meat products, including veal chop and fried beefsteak — 774 and 434 nmol/g, respectively, vegetables (cauliflower, broccoli, tomatoes, carrots, cucumbers, etc.) — an average of 200 nmol/g, fruits (oranges, peaches) — 237 and 241 nmol/g, etc. In the list of products containing only GRU (where GRU was defined as the amount of GSH reacting with a food sample, nmol/g food), milk and some dairy products are in the first place, followed by cherries, blueberries, prunes, and among drinks, the most important are tea, coffee, etc. There is a fairly extensive list of products containing glutathione and substances that inactivate it. The authors note that fresh fruits and vegetables generally contain more glutathione than GRU, although the amount of glutathione varies widely. Cereals such as corn and fortified white bread contained GRU and very little GSH, while rice, oatmeal, and whole white bread had relatively high levels of GSH and low levels of GRU.

GLUTATHIONE TRANSPORT

How is glutathione transported from food into the body's internal environment? It is known that intestinal epithelial cells have a special transporter for glutathione and are able to import it from the intestinal lumen in an intact form [42, 66]. In parallel to this process, enterocytes, using the enzymes gamma-glutamyl transferase and dipeptidase, hydrolyze glutathione into amino acids. Then, these amino acids are transported into the cell, where glutathione is synthesized again.

For intracellular transport of glutathione through internal membranes, dicarboxylate and oxoglutarate transporters are used [53]. Interorgan transport of glutathione is carried out with the help of three groups of proteins: multidrug resistance proteins, polypeptides that transport organic anions, and Ral-binding proteins [15, 16]. Glutathione, which is synthesized in hepatocytes, is transported into blood plasma, epithelial lining fluids and exocrine secretions (e.g. bile, unchanged, without degradation) [10, 15, 17]. In rat liver, approximately half of GSH is released into plasma and half passes through the tubular membrane into bile [16].

CHANGES IN GLUTATHIONE CONTENT IN THE BODY DEPENDING ON TYPE OF ADMINISTRATION

The effectiveness of glutathione in dietary supplements is highly controversial. Thus, animals have demonstrated good results from the use of glutathione, which were accompanied by an anticarcinogenic effect [60], an improvement in the immune status [29], and an increase in the detoxification function [38].

At the same time, the effectiveness of oral glutathione in humans is controversial. Researchers associate this with the amount and activity of the intestinal enzyme γ-glutamyl transpeptidase, which breaks down glutathione [9, 69].

However, there is a six-month randomized, double-blind, placebo-controlled study that showed that oral glutathione supplementation at 250 or 1000 mg/day resulted in significant increases in body glutathione stores in 54 non-smoking adults [58]. At the same time, good results have been shown using sublingual glutathione [22, 61]. The authors demonstrated that with a sublingual dosage form, the tripeptide GSH is directly assimilated through the buccal mucosa. Sublingual administration of glutathione (450 mg/day) resulted in an increase in plasma GSH. In addition, a secondary effect of glutathione administration was a significant increase in plasma vitamin E.

Based on the above studies, it can be assumed that dietary glutathione is partly absorbed through the oral mucosa, and partly through the gastrointestinal tract. Part of it is hydrolyzed by the intestinal and liver enzyme γ-glutamyl transpeptidase.

EFFECT OF DIFFERENT DIETS ON GLUTATHIONE HOMEOSTASIS

The Mediterranean diet, which is characterized by high consumption of vegetables, fruits, greens, extra virgin olive oil, cereals, legumes, nuts, moderate consumption of red wine, fish, dairy products, showed an inverse relationship with the level of GSSG and, accordingly, with an increase in the GSH/GSSG ratio, regardless of family and genetic factors [26]. In another study, adherence to the Mediterranean

diet in adult men and women showed a positive association with GSH levels and an inverse association with GSSG [18]. Calculations were made after adjustment for age, body mass index, sex, race, and history of chronic diseases.

The DASH diet, which was developed for the treatment and prevention of hypertension, promotes an increase in plasma GSH levels [11, 12, 57]. This diet includes 5 servings of fresh vegetables and fruits per day, 7 servings of carbohydrates (whole grains, legumes), 2 servings of meat and 2 of dairy products, nuts and seeds — 2–3 servings per week. The diet emphasizes reduced intake of saturated fat and sodium.

Analysis of the effects of vegetarian diets has shown conflicting results: a number of studies have recorded an increase in GSH in blood plasma, mainly in individuals with chronic diseases and reduced baseline glutathione levels [34, 63], while other studies, on the contrary, have demonstrated its decrease [39] or no changes there [33, 37, 56]. Such mixed results of vegetarian diets are most likely related to possible amino acid deficiency that disrupts GSH synthesis.

Diets typical of modern urban populations and containing insufficient amounts of fresh vegetables and fruits may be associated with decreased plasma GSH levels [45].

CONCLUSION

Optimal functioning of the glutathione system in the body is directly related to health reserves, prevention of many diseases, slowing down the aging process and increasing life expectancy. Maintaining normal glutathione levels is possible with dietary optimization, especially in cases where the body's antioxidant systems are depleted under the influence of unfavorable factors. Studies are needed to examine the effects of including glutathione-containing foods in the diet and, conversely, excluding glutathione-depleting foods from the diet during oxidative stress and other adverse effects on the body.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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