ASPECTS OF THE LENS CHEMISTRY AND PATHOCHEMISTRY

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The lens (*lens cristalina*) is part of the light conducting and light refracting system of the eye. Transparency and light refraction are the main properties of the lens. Nutrients are supplied to the lens through the capsule by diffusion and active transport. The energy needs of the avascular epithelial structure are 10–20 lower compared to that of other organs and tissues. Such needs are satisfied through anaerobic glycolysis. Currently, there is insufficient information about the fundamental chemical mechanism underlying the existence of the lens in the healthy body, the mechanisms of its functional "survival" against the background of somatic disorder, such as diabetes. The paper reports the authors' view of certain chemical aspects clarifying pathochemical alterations of the lens with the possible mechanisms underlying its "adaptation"/"protection" associated with the systemic disorder at the molecular level. In particular, the view of the involvement of glucose-6-phosphate dehydrogenase/transketolase, the enzymes of the oxidative and non-oxidative phases of the pentose phosphate pathway belonging to the native crystalline fraction protein family, in the mechanisms underlying protection of the lens against the oxidative and osmotic stress, involvement of aldo-keto reductases in pathochemical alterations of the lens, as well as the role the NO, NO_3-, B_6, PQQ small molecules having an antioxidant cytoprotective effect is reported.

Keywords: lens, aldo-, ketoreductase, transketolase, crystallines, key pathochemistry aspects

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АСПЕКТЫ ХИМИИ И ПАТОХИМИИ ХРУСТАЛИКА

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Хрусталик (*lens cristalina*) является частью светопроводящей и светопреломляющей системы глаза. Главные свойства хрусталика — прозрачность и светопреломление. Питательные вещества поступают к нему через капсулу путем диффузии и активного транспорта. Энергетические потребности бессосудистого эпителиального образования в 10–20 раз ниже, чем потребности других органов и тканей. Они удовлетворяются посредством анаэробного гликолиза. На сегодняшний день недостаточно сведений, отражающих особенности базового химического механизма существования хрусталика в норме, механизмы его функциональной «выживаемости» на фоне соматической патологии, в частности, диабета. В работе представлен взгляд авторов на отдельные химические аспекты, проясняющие патохимические изменения хрусталика с возможными механизмами его «адаптации»/«защиты» на фоне системной патологии на молекулярном уровне. В частности, на участие ферментов окислительного и неокислительного этапов пентозофосфатного шунта — глюкозо-6-фосфатдегидрогеназы/транскетолазы, относящихся к семейству белков собственной кристаллиновой фракции, в механизмах защиты хрусталика от окислительного и осмотического стресса, участие альдо- и кеторедуктаз в патохимических изменениях хрусталика, а также роль «малых молекул» NO, NO_3-, B_6, PQQ с антиоксидантным цитопротекторным эффектом.

Ключевые слова: хрусталик, альдоредуктаза, кеторедуктаза, транскетолаза, кристаллины, ключевые аспекты патохимии

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The lens (*lens cristalina*) is a component of the light conducting and light refracting system of the eye. Transparency and light refraction are the main lens properties. It is second to the cornea in the degree of light refraction. The optical power of this living biological lens is within 19.00 diopters. The lens has a layered structure. Nutrients are supplied through the capsule by diffusion and active transport. The energy needs of this avascular epithelial structure that are 10–20 lower compared to the needs of other organs and tissues are satisfied mainly through anaerobic glycolysis [1, 2]

Features of chemical composition

Chemical analysis of the lens was first performed in the late 19th century, when U. Mörner extracted a soluble protein referred to as crystalline. In 1950s, V. N. Orechovich and then R. A. Reznik extracted three fractions with different molecular weight referred to as α-, β- and γ-crystallines from the soluble fractions of lens proteins. The lens is made up of about 35% proteins, 1% lipids and 64% water. The lens proteins are divided into water soluble and water insoluble. More than 90% of soluble proteins are represented by α-, β- and γ-crystallines. Heterogeneity of protein composition is typical for the lens: fractions of the α-, β- and γ-crystalline high molecular weight forms predominate in the nucleus, while α- and β_L-crystallines are the main cortical proteins. α-Crystallines (chaperones, molecular weight 160–1000 kDA) have two predominant isoforms (αA-crystallines and αB-crystallines), inhibit aggregation of damaged proteins, thereby maintaining the

lens transparency. β-Crystallines (up to 60%) include the acidic (β_A-crystallines) and alkaline (β_B-crystallines) subgroups, four isoforms per subgroup (designated with Arabic numerals, 1 to 4). And, finally, γ-crystallines are represented by seven isoforms designated with Arabic letters A–F and S. γ-Crystallines exist as 20 kDA monomers only and have a structural function, like the previous group [3, 4]. Of low molecular weight compounds, large amounts of vitamins have been found. Ascorbic acid plays a certain role in the energy production processes: it transports hydrogen to the lens, constitutes part of the lens antioxidant system. Vitamins A, B_1, B_2, B_5 have an impact on the mitotic activity of the lens epithelium; vitamin E is considered as a probable antioxidant factor preventing the lens opacification. Several glutathione analogues have been found in the lens, the content of which is lower; the cysteine residue is substituted in each of these analogues. The leucine aminopeptidase of the lens is an essential member of the crystalline fraction protein family, along with the transketolase [5].

Features of major metabolic pathways

To provide energy supply, glucose breakdown is accomplished through aerobic and anaerobic glycolysis, direct (apotomic) oxidation of glucose (pentose phosphate pathway), and the Krebs cycle. The sorbitol pathway for glucose uptake by the lens is also possible. However, against the background of the disorder, such as diabetic retinopathy, the other pathway for utilization of excess carbohydrates coming from the outside, the polyol pathway realized by means of the key enzyme, aldose reductase, is enhanced. This group of enzymes belonging to the first class of oxidoreductases deals with the nicotinamide coenzyme, specifically with its phosphorylated form essential for the tandem binding to the active center of this reductase [6–9]. Our question is: why does such a basic substance, as pyruvic acid, the final metabolite of glycolytic carbohydrate degradation, that shows high carbonyl activity, exerts no effect on the aldose reductase enzyme present here in the cytosol before entering the mitochondria (pyruvate dehydrogenase complex (PDC) of the inner membrane) in individuals with diabetes and tissue ketoacidosis? Moreover, the enol forms of bioorganic substances showing keto-enol tautomerism predominate under native conditions, and the presence of the conjugated carbonyl group with the multiple bond in the linear molecular structure allows such form to be a potent nucleophilic agent. Or is a certain effect still possible? And how is it realized under conditions of molecular environment in the cytosol? On the one hand, it may be mainly converted to lactate, and on the other hand, binding with the specific cytosolic/mitochondrial transporter is possible. The latter transports it using the proton symport mechanism (the energized, electrically charged inner membrane of the mitochondrion can be de-energized and discharged, which is mediated by the H^+/ATPase activity). Apparently, the pyruvate affinity for this protein is rather high, otherwise a certain pool of this could move to the appropriate cellular compartments and decrease the activity of the first phase of polyol pathway, specifically covalent interaction with the active structural motif of such reductases, such as the tyrosine amino acid, since monocarboxylic acids can be involved in the Friedel-Crafts reactions, in this case occurring in the form of the Fries rearrangement reaction that is most typical for phenols. The phenolic radical of the tyrosine amino acid can also be safely included in this group of compounds. According to the available research data, this reaction sometimes does not require a catalyst, especially when the final product representing an aromatic ketone is produced having lower activation energy of the molecule, which stabilizes the reaction product and makes it less active compared to the initial reagents due to the M- and I-effect of the carbonyl group. Perhaps, it is this mechanism that underlies partial blockage of the cytosolic aldo- and ketoreductases and preserves viability of the eye lens for a long time against the background of chronic diabetes. This issue requires more thorough investigation and conceptualization under the conditions of using NMR spectroscopy and the kinetic isotope effect that will probably allow the researchers to reveal more subtle mechanisms underlying the above pathochemical process.

Effect of NO on the polyol pathway

It is well-known that the aldose reductase inhibitors (ARIs) and sorbitol dehydrogenase inhibitors (SDIs) cause changes in the content of sorbitol and fructose. The aldose reductase activity is decreased under exposure to the nitric oxide (NO). Since superoxide reduces the amount of NO, the aldose reductase activity increase is associated with oxidative stress, and reduction of the reactive oxygen species levels inhibits aldose reductase. Hyperosmolarity induced by sorbitol results in depletion of the organic osmolytes and antioxidants (such as taurine) [10].

Contribution of the nitrate ion as a donor of nitric oxide

Based on the chemical nature, this nitrogen compound is classified as a diatomic neutral molecule, however, it represents a free radical, colorless gas with the half-life of 2–30 s and the average lifetime in biological tissues of 5–6 s. The molecule has an unpaired electron in the outer ϖ orbital, which makes it a high-spin radical. The nitrate ion can well react with other free radicals and is capable of covalent bonding. This very property allows it to both activate and block (chain interruption) the free radical substitution reactions (S_R). Recently, the other source of the compound, other than oxidation of the proteinogenic L-arginine α-amino acid guanidine group supplying this vasoactive metabolite to the body's tissues, has been determined. Thus, it has been found that not only (1–3) NO-synthase (NOS) isoforms can generate NO in the lens and cornea of the eye; NO can be formed non-enzymatically from the other compound, nitrate, in the tissues. In particular, the reaction of direct asymmetric fission or reduction of the nitrate ion (heterolytic mechanism) is possible that results in the formation of the nitrite ion and NO (Fig. 1). Such a process may possibly occur predominantly under conditions of acidification of the environment, i.e. under conditions of ischemia, which can only affect the eye lens function. In our opinion, it is also necessary to consider the fact that breakdown of such one of the most potent oxidizing agents in the organic world, as peroxynitrite ion ($ONOO^-$) yielding nitrogen dioxide under conditions of acidosis (in the form of nitrite ion under native conditions) and the hydroxyl radical ($OH^•$), occurs under the same conditions. In this case the pool of intracellular nitrite ion is increased due to both first (heterolysis of nitrate) and second (breakdown of peroxynitrite associated with acidification of the environment) reactions, which is likely to shift equilibrium of the entire pathochemical process to the side of reagents (precursors) and reduces total NO levels, which is especially important for the process of peroxynitrite accumulation during realization of the lipid peroxidation (LOP) pathways. However, in the course of long evolution, essential NO levels became involved in the process of the lens "rescue" during such reactions. To ensure survival of the lens epithelial tissue, such

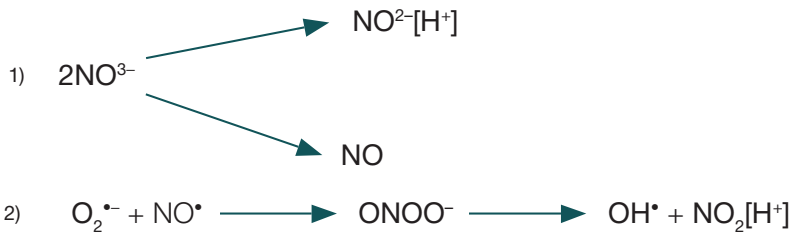

Fig. 1. Pathochemical pathways involving the oxygen-containing nitrogen compounds

levels are achieved through generation of S-nitrosoglutathione. It represents an endogenous long-lived donor of such an active small molecule, as NO. This is especially important in the context of ischemia with subsequent reperfusion, when the function of the lens capsule inflow vessels is impaired and the release of free radicals is enhanced, resulting in the NO biosynthesis limitation.

Effects of vitamins B_6 and PQQ

The aldose reductase inhibitors were extensively studied using multiple compounds that were not chemically related.

Pyridoxamine was first described as inhibitor of production of the advanced glycation end products (AGEs) following the Amadori rearrangement, but it also inhibits formation of the advanced lipoxidation end products (ALEs) on protein during LOP. Administration of 1 g per 1 L of drinking water to rats with diabetes throughout 28 weeks decreased the diabetic capillary regression by 71%. To date, it is unclear whether such treatment inhibits the loss of pericytes, including in the inflow arterioles of the lens capsule, or not.

Vitamin PQQ (former name B_{14}) being a potent cytoprotective agent as an antioxidant is more active as a reducing agent than vitamin C; it is more active as an oxidizing and reducing agent than the vitamin B_2 derivatives; it is more active as a compound showing carbonyl activity than vitamin B_6 due to the fact that it represents a co-enzyme of glucose dehydrogenase (the first key enzyme of the eye lens crystalline family actually being one of the crystalline fractions of proteins). We believe that this is nothing less than bioorganic chemical reduction ("simplification") of the pentose phosphate pathway oxidative phase that has emerged over millions of years of evolution against the background of the lens functional specialization. By analogy with this statement, we can conclude that transketolase, in turn, can be considered as similar reduction of the phosphate pathway non-oxidative phase, which is quite enough for "survival" of the lens tissue when various changes of homeostatic conditions occur associated with the prominent organ (tissue) specialization.

The second key enzyme of the crystalline family: transketolase as the "reduced" pentose phosphate pathway of the eye lens

In mammals, transketolase links pentose phosphate pathway with glycolysis by dispatching excess sugar phosphates to the main carbohydrate metabolic pathways. The presence of transketolase is essential for NADPH production, especially in the tissues actively participating in the biosynthesis, including tissues of the lens. The co-enzyme form of vitamin B_1, thiamine pyrophosphate (TPP), is an important co-factor, along with calcium, and functions in a complex with the latter (this complex is similar to the ATP/ Mg^{2+} complex as an electron-deficient system). The entrance to the active site of this enzyme consists of several side chains of arginine, histidine, serine, and aspartate. Despite the fact that the enzyme is capable of binding various types of substrates, it shows high specificity for stereochemical arrangement of hydroxyl groups in sugars. These hydroxyl groups in the C-3 and C-4 positions of the ketose donor carbon chain should have a D-treo configuration to properly match positions C-1 and C-2 in the aldose acceptor. His263 is used as a donor of proteins for the substrate-acceptor-TPP complex, which can then generate erythrose 4-phosphate. The histidine and aspartate side chains used for effective stabilization of the substrate contribute to the substrate deprotonation. The phosphate group of the substrate also plays an important role in the substrate stabilization when it enters the active center, along with the ionic nature of the bond of the salt bridge connecting Arg359 with the phosphate group. Catalysis is initiated by B_1 deprotonation in the thiazolium ring. Then the carbanion binds to the carbonyl group of the donor substrate, thereby breaking the bond between C-2 and C-3. This keto-fragment remains covalently linked to the TPP C-2. After that the donor substrate is released. The acceptor substrate enters the active site, where the fragment bound to the α-β-dihydroxyethyl-TPP intermediate is transferred to the acceptor [11, 12].

Inhibition of transketolases by the AGE and LOP end products

Protein glycation (glycation) is a process referred to as the Maillard reaction. In the course of the Maillard reaction, intermediate products, such as glyoxal, methylglyoxal and 3-deoxyglucosone, are also yielded that can be formed as a result of both monosaccharide auto-oxidation (for example, glucose in the Wolf reaction) and Schiff base rearrangement (Namiki pathway) or Amadori rearrangement (Hodge's model — he discovered the fact of interaction between glucose and glycine yielding at least 24 compounds as early as in 1953). Since free amino groups are glycated, any protein can be potentially subject to this process, which is especially important for protein fractions of the lens that are mostly basic. AGEs, both free and bound to proteins, are found in plasma of the inflow blood vessels, including in the eye lens. At least 20 different AGEs have been reported, among them N-carboxymethyl-lysine, pentosidine and hydroimidazolones are relatively inert and can be used as biomarkers of the AGE content in the tissues. The Maillard reaction includes several phases. First, glucose (or other reducing carbohydrate, such as fructose, pentose, galactose, mannose, xylulose) react with the free amino groups of amino acids yielding an unstable compound, the Schiff base. The Schiff base (aldimine) is subject to spontaneous rearrangements yielding a relatively stable ketoamine (1-amino-1-deoxy-2-ketose), the Amadori compound [13–15]. Further degradation of these early glycation products yields a heterogeneous group of irreversible compounds, the AGEs. Fig. 2 presents one of possible (in our opinion) mechanisms underlying pathochemical blockage of transketolase involving switching off the enzyme itself. Malondialdehyde as a biomarker of oxidative stress in the epithelial cell of the eye lens plus arginine (2-amino-5-guanidino-pentanoic acid) of the transketolase represent the reaction of condensation and intermolecular cyclization yielding 2-aminopyrimidine. The reaction is based on the mechanism

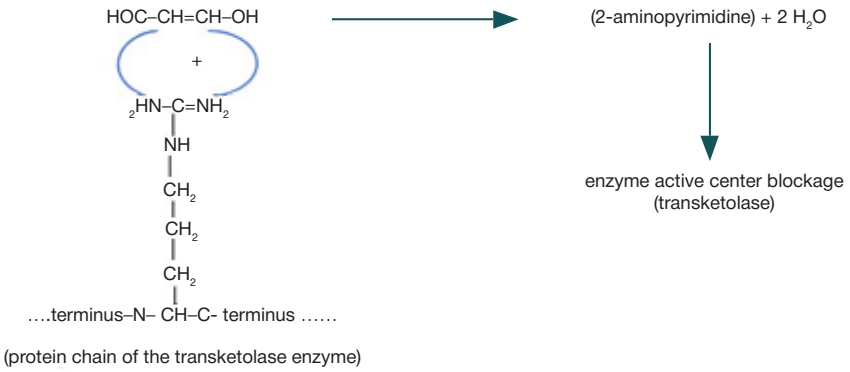

Fig. 2. One of possible mechanisms underlying blockage of the transketolase active center involving the malondialdehyde enol form

of nucleophilic bimolecular addition. Furthermore, due to the presence of malondialdehyde as a carbonyl group in the enol form, along with the conjugated multiple bond, it is converted to the potent nucleophile attacking the arginine electrophilic center in the form of imine nitrogen $=NH^{2+}$ in the first phase to yield pyrimidine derivatives (by analogy with the chalcones used for artificial synthesis of antitumor agents based on the aminopyrimidine framework when assessing molecular docking during production of new dosage forms).

CONCLUSION

We have tried to understand, what chemical substances and how they interact with each other in the context of the lens basic metabolism and pathochemistry. The cataract, representing partial or complete clouding of the lens substance and/or capsule, is among the most common causes of vision loss, that is why we have touched upon the issue of cataracts and fundamental chemical causes of their development against the background of diabetes mellitus, one of the most important medical and social problems. Pathogenesis of diabetic lens disorders is extremely complex and multifactorial. AGEs that realize their potential through the effects on the protein structure and activation of the AGE–RAGE axis contribute greatly to the diabetes progression, which results in a number of pathological changes. Since AGEs have many adverse effects, it is necessary to search for new chemical and pharmaceutical technological strategies, primarily targeted ones focused on reducing the AGE levels. Interruption of the cascade of pathochemical events triggered by the AGE–RAGE interaction can also represent a promising and reasonable direction of developing new approaches to prevention and treatment of the diabetic complications affecting such highly specialized functional structures of the eye, as the lens.

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