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Review Article

Biochemistry of the Human Lens

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ABSTRACT: The main function of the crystalline lens is to transmit and focus light onto the retina by accommodation, just like the lens in a camera. At the beginning of embryonic life, the lens is opaque, but it becomes transparent over time as a result of nutrition. The main reasons for its transparency are the hexagonal structure of the fibrils, which are the main structural elements of the lens, and very little intercellular space. Lens transparency is maintained at both the cellular and molecular levels. The transparency of the lens is largely due to the very regular arrangement of the macromolecular components of the lens cells and the very small refractive index differences in the light-scattering components. The loss of the transparency of the lens is known as a cataract.

Maintaining cellular homeostasis between protein and carbohydrate metabolism, cell division, cell differentiation, oxidative damage and protective mechanisms supports the maintenance of lens transparency. Regulation of water and electrolyte balance plays a critical role in maintaining normal lens water content and transparency. As a result of the regression of the tunica vasculosa lentis, which nourishes the lens during intrauterine life, the lens obtains its metabolic requirements from the aqueous humour and vitreous humour.

Keywords: *Human Lens, lens biochemistry, human eye.*

1 INTRODUCTION

Up to 60% of the total mass of the lens may consist of proteins, much higher than in almost any other tissue. The lens is covered by a collagen capsule. The capsule acts as a barrier to diffusion and contributes to the remodelling of the lens during accommodation. Its major components are type IV collagen, laminin, entactin, perlecan, type XVIII collagen, heparin sulphate, proteoglycan and fibronectin. The capsular filaments, which are uniform in size and parallel in orientation, are thinnest at the posterior pole and reach their maximum thickness at the equator, where the lens zonules are located. The lens capsule first appears in humans at 5-6 weeks of gestation and is

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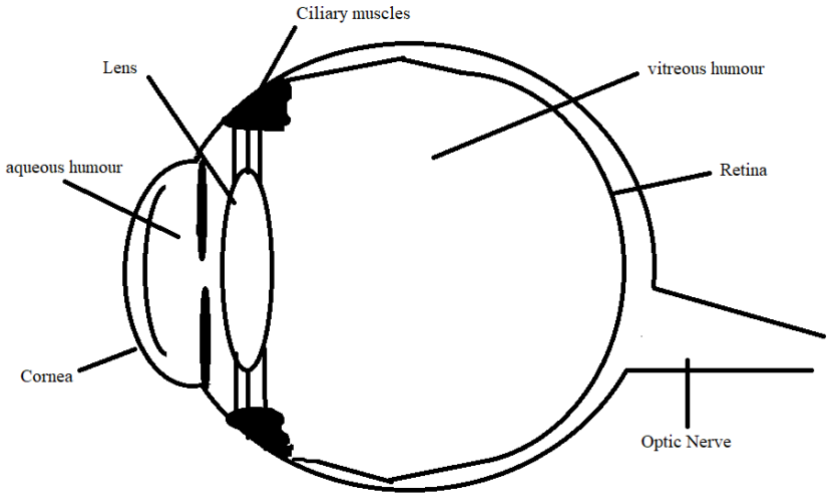

Figure 1. Human eye schematic

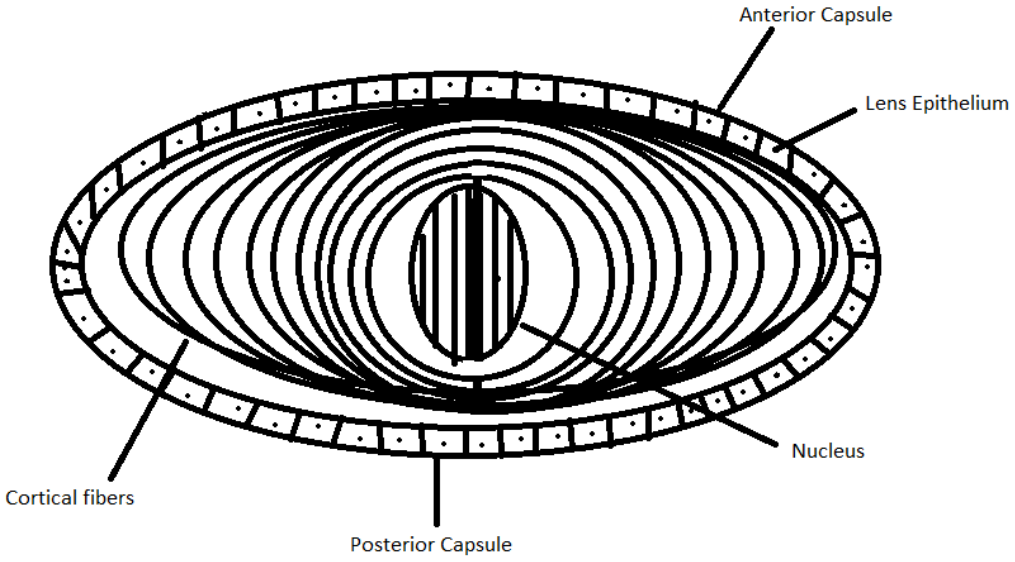

Figure 2. Lens Capsule, Epithelial Cells and Lens Fibrils

continuously produced throughout life, anteriorly by cuboidal epithelium and more slowly posteriorly by fibre cells (Figure 1,2) [1-3].

Except for a few tissues and organs in our body, nutrition is generally provided by the blood vessels. Fenestrated capillaries extend into the tissues and carry the oxygen

that the tissues need with the erythrocytes and the nutrients with the serum part of the blood. After receiving the metabolites it needs, the tissue returns the residues through the fenestrated capillaries and lymphatic vessels. The lens is one of the few structures in the body that is not actively circulated and maintains its own vitality. It relies on the aqueous humour for nutrition and waste removal. The metabolism of the lens therefore has a specialised cycle. The basic building block of all organs and tissues in the body is protein. The lens is one of the tissues with the highest protein content by volume in the body. The high protein content provides the high refractive index required by the lens. At the same time, lens proteins play an important role in maintaining the transparency of the lens. They are also responsible for the exchange of substances between the lens cells. Proteins within the lens cells are involved in maintaining cell shape [4,5].

In this review, we aim to focus on how the human lens reflects light and maintains its transparency through biochemical reactions.

2 METOBOLISM OF THE LENS

2.1 Carbohydrate Metabolism

Much of the energy production in the lens is provided by glucose metabolism. Glucose is imported into the lens from the aqueous humour by simple diffusion and facilitated diffusion. Most of the glucose that enters the lens is converted to glucose-6-phosphate by the enzyme hexokinase. The amount of glycolysis is limited by the amount of hexokinase. With age, the hexokinase enzyme decreases and energy production decreases. As a result, control of electrolyte metabolism becomes difficult. Glucose-6-phosphate is mainly used in two different metabolic pathways.

2.1.1 Anaerobic Glycolysis Pathway: 78% of glucose enters this pathway. The end product of this pathway is lactate. In this pathway, 2 ATP is formed from each glucose molecule. 70% of the energy requirements of the lens are

met by anaerobic glycolysis. Due to the low oxygen pressure in the lens, only 3% of the glucose enters the citric acid cycle. Nevertheless, the citric acid cycle provides 25% of the ATP requirement of the lens.

2.1.2 Hexose Monophosphate Pathway: Also known as the pentose phosphate pathway. Five percent of lens glucose enters this pathway. This pathway is usually stimulated by elevated glucose levels. The importance of this pathway is the formation of nicotinamide adenine dinucleotide phosphate (NADPH). In the lens, NADPH is required for the activities of glutathione reductase and aldose reductase. Aldose reductase is a key enzyme in the sorbitol pathway, another pathway of glucose metabolism.

Another pathway used in glucose metabolism is the sorbitol pathway, and 5% of the glucose in the lens enters this pathway. In this pathway, glucose is converted to sorbitol by the enzyme aldose reductase and then to fructose, which can diffuse into the aqueous humour by polyol dehydrogenase. The affinity of aldose reductase for glucose is much lower than that of hexokinase. As the glucose level in the lens increases, the sorbitol pathway is activated more than the glycolysis pathway and the formation of sorbitol and fructose, the end products of this pathway, increases in the lens. At the same time, the hexose monophosphate pathway is also stimulated, further contributing to the increase in aldose reductase activity required for sorbitol formation. As the permeability of the lens to sorbitol is low, sorbitol accumulates in the lens. With the increase in osmotic pressure, water enters the lens, resulting in swelling of the fibrils, changes in lens structure and opacification. This mechanism is known to play an important role in the development of diabetic cataract [6-9].

2.2 Energy Production in the Lens

Due to the lack of blood circulation, the concentration of oxygen in and around the lens is much lower than in other parts of the body. The lens therefore relies on glycolytic metabolism to produce most of its ATP. The

glucose required for glycolytic metabolism is derived from the aqueous humour. Aqueous glucose levels are maintained by facilitated diffusion across the ciliary epithelium. However, lens epithelial cells and superficial fibre cells also contain mitochondria. Therefore, cells near the lens surface use both glycolytic and oxidative pathways to obtain energy from glucose [10].

2.3. Protein Metabolism

Proteins make up about 33% of the weight of the lens. The lens has the highest protein content in the human body. There are two main types of protein: soluble crystalline and insoluble albuminoid. Water-soluble proteins are found inside the cell, while water-insoluble proteins are found in the membranes of the lens fibres. There are 3 groups of soluble crystallins. These are the alpha, beta and gamma fractions. Beta-crystallins are the most abundant (55%). Alpha crystallins account for 32% of water-soluble proteins. Gamma crystallins make up 15%. Alpha-crystallin has the largest molecular structure, is formed before birth, is present throughout life and is known as the embryonic lens protein and is closely related to the non-water soluble albuminoids. In young people, the amount of alpha-crystallin is highest in the cortex and the amount of albuminoids is highest in the nucleus. With age, alpha-crystallin decreases and albuminoids increase. With age, the rate of water-insoluble protein increases, leading to the formation of aggregates. This results in lens opacities that cause more light to be scattered. Over time, the total amount of protein in the lens decreases. This decrease is more pronounced in eyes with cataracts. With age, the polypeptides degrade, dissolve and lose their sulfhydryl groups. As a result, the lens becomes less transparent. While the ratio of water-soluble proteins in a clear adult lens is 81%, this ratio is only 51.4% in a cataractous lens. This suggests a loss of crystallin from the lens capsule [11-14].

2.4 Lens Lipids

Most lens lipids are associated with the cell membrane. Lens lipids are mostly found in the

protein-lipid complex. The lipids found in the lens are cholesterol, phospholipids and glycosphingolipids. The major phospholipid of the lens cell membrane is sphingomyelin. The combination of high levels of cholesterol and sphingomyelin makes the lens cell membrane more stable [15].

2.5 Water and Electrolyte Balance of the Lens

Electrolyte and water balance, which is essential for maintaining lens transparency, is the most important topic in lens physiology. Disturbances in cellular hydration lead to lens opacity. The lens cortex is more hydrated than the nucleus. The lens contains high levels of potassium ions and amino acids, unlike the aqueous and vitreous humours. In contrast, the lens contains less sodium ions, chlorine ions and water than the surrounding structures. The maintenance of this cation balance depends on the permeability properties of the lens cell membrane and the activity of the sodium pump. The function of the sodium pump is to release sodium ions and take up potassium ions. This mechanism is triggered by the breakdown of ATP, which is controlled by the enzyme Na-K-ATPase. Na-K-ATPase activity is most intense in lens epithelial cells and superficial cortical fibre cells. Inhibition of the Na-K-ATPase enzyme results in an imbalance of cations and an increase in the water content of the lens. The combination of active transport and cell membrane permeability is considered to be the pumpless system of the lens. According to the pump-less theory, various molecules such as potassium and amino acids are taken up from the aqueous humour by the epithelial cells in the anterior part of the lens. They are then transported to the posterior part of the lens by passive diffusion due to the difference in concentration, without an active transport mechanism. Most of the passive diffusion in the lens content is provided by the low resistance gap junctions between the cells. However, the opposite transport is observed for sodium ions. Due to the unilateral electrolyte distribution along the cell membrane, there is an electrical potential

difference between the inside and outside of the lens. The inside of the lens is electronegative at approximately -70 millivolts. There is a potential difference of -23 millivolts between the anterior and posterior sides of the lens. Calcium hemostasis is also very important for the lens. The difference in calcium concentration between intracellular and extracellular calcium is mainly provided by Ca-ATPase. Disruption of calcium hemostasis can cause damage to lens metabolism. There may be some adverse changes such as impaired glucose metabolism, formation of high molecular weight protein aggregates, destructive protease activation due to high calcium levels. Cell membrane permeability and active transport are important for lens nutrition. With the concentration difference created by sodium pumps, amino acids in the lens epithelium are transported into the lens by active transport. Glucose is delivered directly to the lens by facilitated diffusion, where active transport is not involved [16-19].

2.6 Oxidative Damage and Protective Mechanisms in the Lens

Free radicals are formed as a result of normal cellular metabolic activity in the lens. Free radicals can also be produced by external factors such as radiant (electromagnetic) energy from the sun. These highly reactive free radicals can damage the lens fibres and are thought to be one of the causes of lens opacity. During lipid peroxidation, the oxidant converts saturated fatty acids into radical fatty acids by removing the hydrogen atom. The fatty acid radical is converted to a lipid peroxy radical by binding to molecular oxygen. During this chain reaction, lipid peroxy (LOOH) is formed. LOOH is then converted to malondialdehyde (MDA), a potent cross-linking agent. Because of the low oxygen pressure in and around the lens, free radicals react directly with other molecules instead of molecular oxygen. DNA is easily damaged by free radicals. Some of the damage in the lens can be repaired and some cannot. Free radicals damage proteins in the cortex and lipids in the cell membrane. There

is no repair mechanism to correct this damage, which increases over time. In the lens fibres, where protein synthesis can no longer take place, free radicals cause polymerisation and cross-linking of lipids and proteins. This increases the amount of water-insoluble protein in the lens.

Oxidation-reduction mechanisms are particularly important in the lens. Oxidative damage leads to many molecular changes and contributes to the development of cataracts. Glutathione plays a very important role in protecting against this damage. Almost all glutathione in the lens is in reduced form (GSH). It has functions such as protecting thiol groups in proteins, preventing protein aggregation between disulfide bonds, and protecting sulfhydryl groups necessary for normal cation transport. Glutathione levels are significantly reduced in human and experimental cataracts. The lens becomes susceptible to oxidative damage. Glutathione is the major antioxidant in the lens. It exerts its antioxidant effect by detoxifying H2O2 and organic peroxides through reactions in which the enzyme glutathione peroxidase acts as a cofactor. The enzyme superoxide dismutase (SOD) is also present in the lens. Although it is found in high concentrations in normal lenses, its concentration decreases in cataractous lenses [20-24].

3 CONCLUSION

As a result, the human lens must maintain a healthy biochemical structure in order to maintain its transparency and its role in the visual system. Damage to the lens biochemistry, which can occur as a result of oxidation, leads to deterioration of the lens transparency and permanent damage to the visual system.

4 AUTHOR CONTRIBUTIONS

Hypotesis: Ö.Ç.; Design: Ö.Ç.; Literature review: Ö.Ç.; Data Col”lection: Ö.Ç.; Analysis and/or interpretation: Ö.Ç.; Manuscript writing: Ö.Ç.

5 CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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