Biochemistry & Pharmacology: Open Access

Pintor, Biochem Pharmacol 2012, 1:4
DOI: 10.4172/2167-0501.1000e119

Editorial Open Access

Sugars, the Crystalline Lens and the Development of Cataracts

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Editorial

The crystalline lens is the ocular structure which permits to focus the images on the retina. It contains high levels of proteins in a perfect structural organization that makes it transparent. The lens is an avascular structure that is surrounded by a basement membrane called capsule. Epithelial cells appear immediately below the capsule, and fibrillary cells or simply "fibers" form the rest of this ocular tissue. Since the embryonic development and so on, epithelial cells perform mitosis in equator area. The new fibers formed, lie concentrically on the previously developed fibers, forming a structure that resembles an onion.

The lens is transparent because it does not absorb and it disperses minimally the light passing through it. The amount of dispersed light from the lens is 5% and it is due to the fiber plasma membranes. As the volume occupied by these membranes is 0.05% of the total, it can be concluded that the cytoplasms of the fibers are virtually transparent. However, the cytosol of cells contains 35% of biomolecules, particularly soluble proteins: the crystallines.

The lens can suffer changes due to metabolic problems or simply due to aging. These modifications force the proteins to aggregate and precipitate, so that, transparency is gradually lost. This process is known as cataracts [1].

From a clinical perspective, cataracts can be defined as the deterioration of vision due to an alteration of transparency in the lens. From a biochemical point of view, any opacification producing the light scattering is a cataract. The aetiology of cataracts is diverse therefore it is very difficult to attribute its cause exclusively to a single factor. What is clear is that a failure in the metabolism of the lens is an important issue. This can has been clearly demonstrated in systemic diseases such as diabetes or galactosemia.

There is no doubt that the main location of the metabolism of the lens is its epithelium. The intricate system of GAP-junctions allows the epithelial cells to communicate with the internal cells. The synthesis of the structural components and maintenance of transport systems in the lens depends on a continuous source of ATP. This is a capital process in order to keep this structure perfectly transparent. Metabolic energy production depends almost entirely on glucose metabolism which is metabolized by three main routes: glycolysis, pentose phosphate shunt and the polyol pathway. Glucose can be uptake by two types of glucose transports in the lens GLUT1 and GLUT3 [2,3].

The glycolytic pathway of the lens does not differ from other tissues. Interestingly, one of the main regulatory enzymes of this pathway, hexokinase, is present at low levels and only two isoforms have been described, hexokinase I and II. The K_m of type I is lower than that of type II, however, hexokinase type II is more abundant than I. It is likely that the later is used when glucose levels rise [4].

Hexokinase concentration decreases as the individual ages. This may be one of the reasons why during aging lens is more disposed to pathologies such as cataracts, as the drop in ATP levels prevents the normal functioning of the lens in processes such as active control of electrolyte balance.

Some of the glucose is metabolized by the pentose phosphate shunt. This pathway does not generate large amounts of ATP, but is essential because it allows the synthesis of significant amounts of $NADPH+H^+$ by the first enzyme of this pathway, glucose 6-phosphate dehydrogenase. $NADPH+H^+$ is essential for glutathione reductase and also for the functioning polyol pathway. It has been shown that about 14% of the glucose is metabolized by this pathway. The activation of this pathway is triggered under conditions of oxidative stress since glutathione (GSH) must be available [5].

The third metabolic pathway for glucose is the polyol route, which is also known as the sorbitol pathway. This route was described by van Heyningen in 1959 after verifying the accumulation of polyols in the lens. Diets with high quantities of glucose, galactose, or xylose developed cataracts in experimental models [6].

The route of sorbitol is formed only by two enzymes, first aldose reductase, using $NADPH+H^+$ as a cofactor and second polyol dehydrogenase that uses NAD^+ as coenzyme. It is considered that about 1/3 of glucose entering the lens is metabolized through the sorbitol pathway [7].

Human aldose reductase has a K_m for glucose of 200 mM, and it is present mainly in the epithelia, where 70% of the activity of this enzyme has been located. This is important because it means that the concentration of sorbitol accumulates in a very small area of the lens so that the final effect is an increase of 50 times the concentration that would be expected if the distribution of the enzyme was homogeneous throughout the lens [8].

Polyol dehydrogenase (sorbitol dehydrogenase) is present in the lens of many species but has not been studied in depth as aldose reductase. Sorbitol dehydrogenase is distributed more evenly than aldose reductase. The polyol dehydrogenase is 50% in the lens epithelium and 50% in the cortex. Interestingly, unlike aldose reductase, polyol dehydrogenase cannot metabolize inositol, glycerol or dulcitol (galactitol) [9].

The Importance of polyol pathway is remarkable in individuals having elevated levels of sugars in plasma and aqueous humour. In normal individuals, because the concentration of glucose is between 0.7 to 2.2 mM, aldose reductase will not work. Nevertheless, under pathological conditions such as diabetes, where glucose concentration is between 3 and 4.5 mM, aldose reductase has a chance. Also in galactosemia this pathway works and high levels of galactitol are

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Received April 25, 2012; **Accepted** May 03, 2012; **Published** May 04, 2012

Citation: Pintor J (2012) Sugars, the Crystalline Lens and the Development of Cataracts. Biochem Pharmacol 1:e119. doi:10.4172/2167-0501.1000e119

produced. The importance of this route is linked the activity of another enzyme, hexokinase, whose activity decreases with age. So, given that both enzymes have glucose as a substrate, the balance between the activities of both proteins is essential to know which will be the fate of glucose. The K_m of hexokinase lens is 100 μM, so that at high glucose concentrations, the enzyme is saturated. This fact makes the sorbitol pathway relevant, especially in those individuals with diabetes. Although the polyol dehydrogenase K_m for the sorbitol is low, this substance accumulates because its amount in the lens is low compared with that of the aldose reductase. It is considered that there is 30 times more aldose reductase than polyol dehydrogenase some animal models. However, in humans lens polyol dehydrogenase concentration is 80 times higher than that of aldose reductase. This fact is indicating that although it is probable the existence of cataracts due to the sorbitol pathway it is necessary to make a very careful study in experimental animals when extrapolating results to humans [4].

The addition or supplementation of glucose or galactose to laboratory animals such as New Zealand rabbits showed that significant morphological changes occurred in the lens. For example, it has been observed the appearance of vacuole-shaped structures in the lens after sugar supplementation. This effect was faster when the animals were fed with galactose (visible effects in 3 weeks) that when given glucose (visible effects at 3 months). The reason for all these differences is the route of polyols. Both glucose and galactose are metabolized by aldose reductase yielding respectively sorbitol and dulcitol (galactitol). Although both sugars are similarly processed, sorbitol to fructose can be transformed via the polyol dehydrogenase while dulcitol not a substrate for the second enzyme as previously indicated.

In conclusion, both substrates, glucose and galactose induce the accumulation of polyols, faster in the case of galactose, which ultimately produce a hyperosmotic effect which results in a water uptake, via aquaporins 1 (AQ1) and aquaporin 0 (AQ0, aka MIP), which tends to counteract the osmotic gradient produced [10].

In the last decade, RNA interference (RNAi), a new process of sequence specific post-transcriptional gene silencing, has emerged as a powerful tool for understanding gene function and it was initially studied in *Caenorhabditis elegans* [11]. RNAi is mediated by small interference RNA (siRNA) that is generated from long double strand RNA (dsRNA) of exogenous or endogenous origin [12]. These long dsRNA are cleaved by ribonuclease II (RNNase III) type protein Dicer. Dicer homologues can be found in Schizosaccharomyces pombe, *C. elegans*, Drosophila, plants and mammals, suggesting that small RNA-mediated regulation is evolutionary ancient and conserved and may have critical biological roles. SiRNA generated by Dicer is a short (21–23nucleotides) RNA duplex with 2 nucleotides overhang at each 3′ end. Each strand contains 5′phosphate group and 3′hydroxyl group.

SiRNA is incorporated into a nuclease complex called RISC (RNA induced silencing complex) that targets and cleaves mRNA that is complementary to siRNA. The initial RISC containing siRNA duplex is still inactive until it is transformed into an active form [13], which involves loss of one strand of the duplex by RNA helicase activity. RNAi can occur very quickly with proteins for many genes, being decreased within hours, and completely absents within 24 hrs [14].

The idea of using RNAi for therapeutic purposes has been tested extensively in recent years [15]. Where anti-sense directed therapeutics have failed, the enhanced delivery methods and potential gene therapy applications of RNAi are provoking excitement among investigators in multiple medical fields [15].

There are many targets that could be used to try to stop cataracts. However, the silencing of certain proteins could stop, in theory, cataract progression. Some target proteins may be investigated. For instance, silencing aldose reductase could be of interest, since it leads to the generation of polyols that trigger the initial osmotic shock that initiates cataracts.

Other interesting protein could be the glucose transporter GLUT1. This protein has a K_m greater than the other glucose transporter present in the lens, GLUT3. The latter is responsible for the massive influx of glucose in pathological situations such as diabetes.

A third possibility could be aquaporin AQ1, as it has a role in the entry of water from aqueous and vitreous humours and may be directly responsible for the entry of water when an over-concentration of polyols.

The reasons for choosing these three targets are, first, that play a dominant role in the development of cataracts. Second, the silencing is not going to completely abolish processes such as sugar metabolism, transport or water traffic. Aldose reductase uses glucose, but this is not the sugar substrate. Glucose can enter the other transporter, GLUT3, which always is saturated under physiological conditions, ensuring the entry of glucose. Regarding aquaporin addition to AQ1 there is another, the AQ0, also called MIP, which ensure the flow of water into the lens.

It is the time to start the use of new biochemical approaches to reverse or stop pathological conditions such as cataracts. The possibility open by the siRNA technology may change the lack of interest by the pharmaceutical companies in the development of compounds for the treatment of lens opacifications.

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