

## Hydrotropic Function of ATP in Age-Related Cataract and Presbyopia

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The etiology of age-related cataract and presbyopia is protein aggregation. Although the etiology of these two diseases is shared along with the organ involved, the crystalline lens, the functional mechanism of these diseases is different. Cataract is an opacification of the lens tissue resulting from interference with the passage of light traveling to the retina. Disturbances in the light occur when it encounters enlarged protein aggregates. Presbyopia results from a stiffening of the lens tissue reducing its flexibility, interfering with the tissues ability to change shape. This limitation of shape change diminishes the ability of the lens to accommodate in order to focus light on the retina. Stiffening of the lens tissue results from protein aggregation. Both diseases are age-related and affect visual function in nearly all humans living beyond midlife; however, both age-related cataractogenesis and presbyopiogenesis have their onset earlier than midlife, though at that time, effects on the visual function manifesting in symptoms and clinical signs, usually are not apparent.

To avoid protein aggregation, the maintenance of protein solubility has been postulated to be related to the maintenance of high concentrations of adenosine triphosphate (ATP) wherein ATP functions as a hydrotrope [1]. This hydrotropic function of ATP was demonstrated in cell and tissue homogenates. The high concentration of ATP (5 - 10 mM) reported in these homogenates was reminiscent of the unexpected and exceedingly high concentration of ATP we reported in the crystalline lens nearly 40 years ago [2] and this high concentration of ATP was not species specific [3,4]. Although ATP is traditionally thought to be the principal energy currency of cells, tissues, and organs, the millimolar amount (ca. 3 mM) contained in the crystalline lens as measured by <sup>31</sup>P magnetic resonance spectroscopy (<sup>31</sup>P MRS) is an order-of-magnitude greater than that required for cells, tissues, or organs to carry out all of the known functions of ATP combined. Further, these high concentrations were more puzzling, in that the lens is considered a metabolically quiescent organ. This observation coupled with an observation we made 30 years ago [5], where intact *ex vivo* lenses were incubated in supporting media with deuterium dioxide (heavy water), demonstrated specific ATP phosphate spectral line-width changes observed by <sup>31</sup>P MRS. In contrast to the alpha-group phosphate, the terminal group gamma-phosphate narrowed significantly, suggesting that ATP functions as a hydrotrope that interacts with the surrounding intracellular interstitial water. Such interaction can prevent aggregation of neighboring proteins by organizing the interstitial water, forming an interfacial rheologically dynamic water layer resulting in a space that can maintain separation between intracellular proteins as hypothesized by Greiner and Glonek [6]. Prevention of protein aggregation is especially important, since the crystalline lens has the highest protein content of any tissue in the body and has been characterized as a "bag of proteins".

Aging must be considered with regard to the relationship between protein aggregation and crystalline lens dysfunction in cataractogenesis and presbyopiogenesis. In the case of the age-related cataract, when protein aggregates exceed ½ the wavelength of light they preclude the normally undisturbed passage of light rays through the lens. This is especially important, since the age-related cataract typically affects the lens nucleus first, and is important, since the nucleus occupies the center of the lens through which the light rays must pass which is critical to good visual acuity. The increase in protein aggregation results in decreased visual acuity as well as increased rigidity of the lens tissue. The decline in visual acuity occurs after opacification of the lens tissue is first observed by biomicroscopic examination of

the lens. The appearance of lens opacification in age-related cataract usually manifests biomicroscopically after the 5<sup>th</sup> decade of life, with age-related cataractogenesis and presbyopiogenesis both being related to intralenticular protein aggregation.

With presbyopiogenesis, there is a loss of flexibility with increased protein aggregation in the lens tissue, such that the lens is less able to change shape during accommodation. During accommodation, the lens increases its antero-posterior dimension with a concomitant increase in refractive power. Such an increase permits focusing at near distances. During aging, there is decreased lens flexibility and increased difficulty focusing at near distances. This occurs by midlife even though by biomicroscopy, the lens appears transparent. This presbyopic process also is thought to be a result of increasing protein aggregation [7]. Protein aggregation is accompanied by an increase in rigidity or hardness of the lens tissue [8]. Although decreasing accommodative ability can be measured early in life, usually this results in a clinically significant presbyopigenic decline in the middle of the 5<sup>th</sup> decade of life.

Considering the above, we proposed a model describing the interaction of the ATP molecule with lens hydrophobic proteins and water [6]. The model proposes that the adenine moiety of ATP cloaks the hydrophobic segments of the intralenticular protein molecules. This allows for the triphosphate moiety connected to the adenine moiety via the ribose sugar to be projected into the surrounding interstitial water. Interaction of the phosphate groups of the triphosphate moiety with the water molecules results in the water molecules becoming organized and, thereby forming a layer. The water layer creates a rheologically dynamic interfacial space preventing aggregation of neighboring proteins. These relationships may explain how prevention of protein aggregation occurs, as well as how maintaining high concentrations of ATP may interdict or prevent both cataractogenesis and presbyopiogenesis.

Since the high concentration of ATP contributes a major portion to the <sup>31</sup>P spectral profile, the above findings, coupled with the potential for *in vivo* <sup>31</sup>P MRS studies using the integral curve to calculate the <sup>31</sup>P energy modulus [9], may allow nondestructive, noninvasive analysis of the metabolic health of the human lens during aging [10]. This is important, since the use of magnetic resonance offers a tool in which to conduct analyses and engender an understanding of the genesis of these two most common eye diseases. With increasing magnetic field capability, it is possible that <sup>31</sup>P MRS will permit quantification of intracellular metabolites, leading to the subsequent assessment of the metabolic status of tissues and organs.

In summary, ATP in high concentrations in the lens can function as a hydrotrope and, as such, maintain protein solubility, preventing protein aggregation. Protein aggregation is involved in disease processes and the maintenance of protein solubility appears fundamental to disease prevention. This is especially important, since there appears to be a constellation of diseases characterized by protein aggregation and in the case of the crystalline lens, protein aggregation in both cataractogenesis and presbyopiogenesis results in visual dysfunction.

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