Hydrotropic function of intralentiuclar ATP.

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Commentary

Nearly 4 decades ago, ATP was measured for the first time in an intact *ex vivo* living organ, the crystalline lens, using ^{31}P nuclear magnetic resonance [1]. At that time and during decades to follow, the millimolar concentrations of this metabolite, known to function principally as the energy currency of intracellular metabolism, was unexplainably and excessively high. In contrast, only micromolar concentrations are required and necessary for intracellular energy metabolism and any of the other known functions of ATP, combined. This elevated millimolar concentration of intralenticular ATP was reported in 14 different mammalian species [1-3], including avian and reptilian species [3]. Not until the report of Patel et al. [4], however, was there evidence for the requirement of millimolar concentrations for ATP, where it functions as a hydrotrope, preventing protein aggregation in both cellular and tissue homogenate preparations.

The report by Greiner and Glonek (Hydrotropic function of ATP in the crystalline lens. Exp. Eye Res. https://doi.org/10.1016/j.exer.2019.107862) coupled with their previous report [5] of the relationship of intralenticular ATP and perturbations in its phosphate groups when incubated in deuterium oxide (D_2O), and the findings of Patel et al., allowed an explanation for the millimolar concentrations found in the lens [1]. Moreover, consideration of these observations led to the formation of a hypothesis to explain the intracellular function of ATP as a rheologically dynamic interface with intracellular waters.

The relationship between the ATP concentration and its reduction with aging is discussed in humans as well as the relationship between ATP reduction and cataractogenesis in both humans and *ex vivo* animal models.

ATP is an amphiphilic molecule and, as such, can form nonpolar bonds to hydrophobic regions on intralenticular fiber cell protein molecules. This renders these hydrophobic regions on lens proteins hydrophilic, and the bonding orients the ATP molecule, such that its charged triphosphate moieties extend into the intracellular water. From sophisticated ^{31}P magnetic resonance spectroscopy (MRS) experiments, where intact *ex vivo* lenses are incubated in D_2O, Glonek and Greiner [5] reported evidence to support the conclusion that the ATP phosphate side-chain groups interacted with intracellular interstitial water. These interactions are dependent on the facile mobility of the terminal phosphate group of the ATP side chain. Greiner and Glonek describe a detailed novel model that more precisely explains this interaction and proposes how protein aggregation can be prevented.

The observations and hypothesis presented by Greiner and Glonek are important, since they are made in a living organ system, the lens, which can not only be manipulated in studies during time-course experiments but which have implications for *in vivo* ^{31}P MRS studies, using a ^{31}P spectral modulus for quantitative evaluations [6]. Since the nuclear magnetic resonance sensitivity of an element for analysis is dependent on its magnetic susceptibility along with its concentration in the tissue or organ system under study, phosphorus is low in contrast relative to proton (^1H), which is the nucleus of choice for current magnetic resonance imaging analysis.

Use of the ^{31}P spectral modulus, however, permits analyses even under conditions of low signal-to-noise, because the ^{31}P spectrum can be conveniently divided into low- and high-energy phosphate bands upon examination of the spectral integral. Practical detection of phosphorus *in vivo* requires the use of the ^{31}P spectral modulus and the employment of surface coil technologies combined with high magnetic field MRS instrumentation.

The ability of ATP to function as a hydrotrope maintaining protein solubility in order to prevent protein aggregation appears to be fundamental to disease prevention. The implications of this work are enormous in the sense that abnormalities in protein aggregation are involved in numerous disease processes both in the eye (e.g., cataractogenesis, presbyopiogenesis, corneal diseases, and retinal degenerative diseases) and in the rest of the body (e.g., heart muscle, skeletal muscle in Duchenne's dystrophy, renal diseases, Alzheimer's disease).

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