Medical Hypotheses 86 (2016) 132–134

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A decrease in the permeability of aquaporin zero as a possible cause for presbyopia ☆

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ARTICLE INFO

Article history:
Received 22 July 2015
Accepted 1 November 2015

ABSTRACT

The crystalline lens appears to be a simple organ with the sole role of focusing light upon the retina. However, numerous studies have underscored its dynamic nature with a host of compartmentalized physiological processes. As the individual ages, the normal lens develops two inescapable processes, presbyopia and cataracts. Yet, to date, there is no uniform explanation for presbyopia and many factors have been proposed as contributors including continuous enlargement of the lens, loss of power of the ciliary muscle and hardening of the lens fibers. Proposed explanations are incomplete and need experimental confirmation. This paper analyzes the possible causes for presbyopia and proposes a new one for it: a decrease in the permeability of aquaporin zero (AQP-0) also known as major intrinsic protein (MIP). Based on original findings of our laboratory, this paper proposes that a fluid flow exists inside the avascular lens. This fluid enters and leaves the lens during the accommodation process. We believe that for this to occur the lens utilizes the permeability of aquaporin zero which is abundant in the membrane of the fiber cells. Volume change due to fluid traversing the surface of the lens occurs during accommodation. We present the hypothesis that increasing the permeability of AQP-0 would facilitate accommodation. Therefore, defects in AQP-0 permeability may be a cause for presbyopia. We would also like to propose that it is possible to visualize and measure the fluid volume lost during un-accommodation and determine if the fluid is lost across the anterior, posterior or both surfaces. An age-related loss in lens water permeability could reduce fluid fluxes during the shape changes of accommodation potentially contributing to presbyopia.

At the macroscopic level, the ocular lens appears as a relatively simple structure with the sole role of focusing light upon the retina. However, numerous studies have underscored the dynamic nature of this organ with a host of compartmentalized physiological processes necessary for transparency. As the individual ages, the normal lens develops two inescapable processes, presbyopia and cataracts. Yet, to date, there is no uniform explanation for presbyopia and many factors have been proposed as contributors including continuous enlargement of the lens, loss of power of the ciliary muscle and hardening of the lens fibers. Proposed explanations are incomplete and need experimental confirmation. This publication analyzes the possible causes for presbyopia and proposes a new cause for it: a decrease in the permeability of aquaporin zero (AQP-0) also known as major intrinsic protein (MIP). Based on original findings of our laboratory, this paper proposes 2 interpretations related to electrolyte and fluid transport mechanisms by the lens – (1) that a fluid flow exists inside the avascular lens. This fluid enters and leaves the lens during the accommodation process. We believe that for this to occur the lens utilizes the permeability of aquaporin zero which is abundant in the membrane of the fiber cells. Volume change due to fluid traversing the surface of the lens occurs during accommodation. We present the hypothesis that increasing the permeability of AQP-0 would facilitate accommodation. Therefore, defects in AQP-0 permeability may be a cause for presbyopia. (2) We would like to propose that it is possible to visualize and measure the fluid volume lost during un-accommodation and determine if the fluid is lost across the anterior, posterior or both surfaces. An age-related loss in lens water permeability could reduce fluid fluxes during the shape changes of accommodation potentially contributing to presbyopia.

Presbyopia is the decline in the amplitude of accommodation that occurs with age from about 21 diopters in young men to age 45–50. Many factors have been proposed as contributors including continuous enlargement of the lens, loss of power of the ciliary

☆ Supported by NEI grant EY00160.

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http://dx.doi.org/10.1016/j.mehy.2015.11.002
0306-9877/

muscle and hardening of the lens fibers [1–3]. Advanced explanations are incomplete and need reliable experimental confirmation. Based on our published results indicating a fluid flow in and out of the lens during accommodation and un-accommodation respectively [4,5], we would like to propose the hypothesis that the loss of accommodation is due to a defect in fluid movement inside the lens. We believe that most lens fibers from the nucleus to the cortex contribute to the decrease in a volume of about 2.6% or 50 μl of fluid [4,6] that occurs when the lens becomes flatter for long distance vision. The pathway for this flow should be aquaporin zero (AQP-0). It is also known as major intrinsic protein (MIP), and is a member of the aquaporin family. AQP-0 is highly specific to the lens, where it is only expressed in the fiber cells. AQP-0 is a water pore of low permeability. At neutral pH, AQP-0 water permeability is approximately 40 times lower than that of AQP1. AQP-0 is a highly abundant membrane protein of the lens fiber cells where they are expressed in vast number. It is particularly enriched in its 11–13 nm thin junctions. Recent studies have demonstrated that AQP-0 water conductance can double under mildly acidic conditions, such as those found in the core of the lens [7]. Unlike all other aquaporins, AQP-0 is known to be present in single membranes as well as in membrane junctions between lens fiber cells. Based on these considerations we would like to propose the following hypothesis: as the individual ages and the lens grows, its cortex becomes less acidic, the AQP-0 losses permeability and as a consequence the flow that must occurs for accommodation is restricted. AQP-0 is know for its role in lens transparency and our hypothesis is not in contradiction whit the structure of AQP-0 [8,9].

One fact that the hypothesis should explain is, why in the normal emmetrope individual, the lens looses accommodation range at the expense of close distance. Why not at expense of distance vision? This is a question that current theories had ignored or provided incomplete explanations. Our hypothesis has a logical explanation. The forces involved in the outflow and inflow are different. To expel fluid the lens utilizes a mechanical force. The ciliary muscle relaxes and approximate to the sclera creating a tension via the zonulae that makes the lens flatter. To reabsorb fluid the ciliary muscle contracts relaxing the tension of the zonulae, which allows the negative pressure created during the outflow to act as a passive force to induce the inflow and reestablish the initial equilibrium. The mechanical force is more powerful that the force due to the pressure gradient between the fluid bathing the lens. Even when the AQP-0 permeability is reduced the mechanical force can overcome this higher resistance and elicit a normal outflow. The weaker difference in pressure elicits a smaller flow decreasing the lens volume. This process is continually repeated in time until the lens looses most of its accommodation range. In the in vivo lens the bathing fluid is the aqueous humor AH.

The hypothesis should be amenable to experimental confirmation. For that purpose a computer-driven stretching apparatus shown in Fig. 1 was built.

The complete apparatus (Fig. 1a) is composed of three major components: (1) a circular bath to which an upwardly pointing gliding rail was fastened to form the bathing chamber for the lens complex; (2) amount that fixed a digital camera in place and connected it to the gliding rail so that proper alignment can be made; and (3) a lens complex stretching device. Fig. 1b is a close-up of 8 servomotors, the arms of which were coordinated to simultaneously produce an evenly distributed stretching tension on a rubber diaphragm to which a central hole for containing the lens was cut. The arms of the motors did return to zero tension on the diaphragm at the end. Pictures were taken before stretching, after full stretching and within 50 and 200 ms after releasing the tension. Around the lens complex there is a special rubber washer. The 8 hooks of the servomotors are evenly attached to the rubber

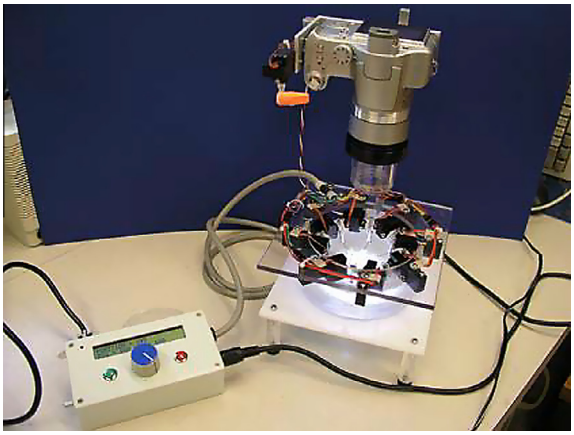

Fig. 1a. The figure shows the complete apparatus which is composed of a circular bath, a mount that fixed a digital camera and a lens stretching device.

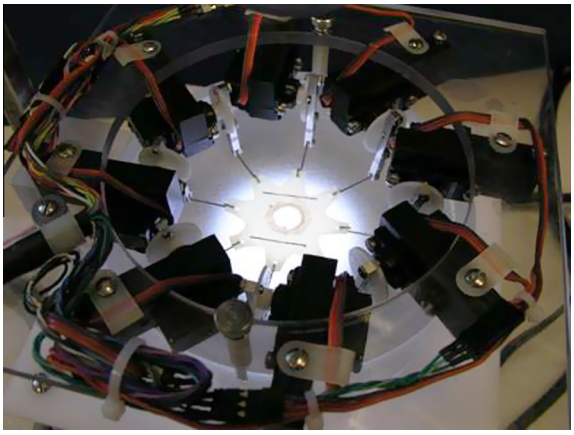

Fig. 1b. The figure shows up close the 8 servomotors which simultaneously produce an evenly distributed stretching tension on a rubber diaphragm connected to the lens.

washer. When the motors operate the tension is transmitted in a manner so that the lens maintains is circular shape (and not octagonal as in similar stretching devices) and the equator has the same dimension in every direction. The mounted lens is immersed in Ringer's during the experiment. When the motors operate to stretch the lens, the tension is distributed between the resistance of the rubber washer and the resistance of the lens to the stretching force. The length of the movement of the hooks is predetermined and constant. That length is distributed between the rubber washer and the lens equator. For example if the hooks separate 5 mm from the center of the lens, 4 mm may be accounted for by stretching of the washer and 1 mm by the lens equatorial diameter. We have demonstrated that the lens equatorial diameter increases is associated with a loss of about 3% of its volume [4]. Thus, facilitating the exit of fluid during stretching will result in a larger increase of the equatorial diameter and less increase in the radial length of the rubber washer. With this approach it is not necessary to measure forces or tensions. Maintaining all parameters constant, we can simply compare the equatorial length before and after an experimental maneuver designed to change the fluid permeability of the lens.

Mounting of the ciliary body-lens complex

The enucleated cow eyes were dissected to obtain the iris-ciliary body-zonulae-lens complex. For this, most of the cornea

was removed via a circular cut 1–2 mm anterior to the limbal region. The attachment between the sclera and the iris base was then isolated circumferentially. Afterward, the detached sclera was removed, leaving the underlining tissues exposed. To obtain the entire iris ciliary body lens complex, a circular cut around the equator of the retina isolated the anterior half of the eyeball, and the vitreous was removed. Total iridectomy was then performed. The whole ciliary-body ring (still attached to the lens via the zonulae) was divided into 4 sectors by making radial cuts (namely, sector of 11–1 o'clock, 1–5 o'clock, 5–7 o'clock and 7–11 o'clock). Vitreous still attached to the ciliary body was removed by gently rolling the lens on a gauze sponge. The stromal side of the ciliary body sectors was attached, with a minimal amount of cyanoacrylate glue. The purpose of the gluing was to hold the lens grossly in place so that it would not move significantly during an experiment; the solutions where the lens was immersed was kept at 35 ± 1 °C. This was accomplished with a heating probe and a temperature detector. The experiments will be done with the lens bathed in a solution with a pH from 4 to 9. It is expected that the pH of the lens would change accordingly.

Possible approach to test the hypothesis in an animal

We have demonstrated that pH can affect the amplitude of accommodation and speed of recovery of initial resting volume in the isolated cow lens, which, in the animal has limited accommodation if any. To test the hypothesis in an animal, one with a large range of accommodation should be selected such as the monkey. Then, under anesthesia using electrical stimulation to determine if perfusing the anterior chamber with solutions with acid to alkaline pHs affect the parameters of accommodation. Furthermore, AQP-0 could be the target for a therapeutic approach for preventing or delaying presbyopia as is proposed for other aquaporins [10].

Conflict of interest statement

None of the authors have any financial and/or personal relationships with other individuals or organizations that could inappropriately influence or bias this work.

This work resulted from academic inquiry and was supported by National Eye Institute Grants EY00160 and by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY.

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