Human Lens Phospholipid Changes with Age and Cataract

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Purpose. To determine the phospholipid changes responsible for the increase in membrane lipid hydrocarbon chain order, or stiffness, with age and cataract in the human lens.

Methods. Clear human lenses were pooled into four groups, with donors ranging in age from 15 to 29, 30 to 49, 50 to 64, and 65 to 74 years. Whole human cataractous lenses were obtained from donors after extracapsular cataract extraction. Cataractous lenses were grouped into four classifications: mature, mixed cortical and nuclear, immature nuclear sclerotic, mature posterior subcapsular, and mature nuclear. Lipids were extracted and quantified gravimetrically. The relative phospholipid composition was determined by ^{31}P-nuclear magnetic resonance spectroscopy.

Results. The relative and absolute amount of sphingolipids, including dihydrosphingomyelin and sphingomyelin, increased with age, whereas glycerolipids, including phosphatidylcholine and two phosphatidylethanolamine-related phospholipids, decreased. These changes were exacerbated by the presence of cataract and were substantial, greater than the changes in lipid levels reported in any organ in association with any disease.

Conclusions. The changes in the amount of lipids with age and cataract support the idea that glycerolipids are selectively oxidized over lipids with fewer double bonds, such as sphingolipids. As a result of the elevation of sphingolipid levels with species, age, and cataract, lipid hydrocarbon chain order, or stiffness, increases. Increased membrane stiffness may increase light-scattering, reduce calcium pump activity, alter protein–lipid interactions, and perhaps slow fiber cell elongation. (*Invest Ophthalmol Vis Sci.* 2005;46:1682–1689) DOI:10.1167/iovs.04-1155

Changes in lens phospholipid composition with age and cataract are not new. Lipids were detected in the lens in 1825.[1] The large amount of myelin-like lipids (sphingolipids) in the human lens was noted in 1857,[2] and their increase with traumatic human cataracts was reported in 1914.[3] In 1881, the amount of cholesterol was found to be elevated in human cataractous lenses compared with clear lenses,[4] and in 1922, it was found to increase with age.[5] More detailed changes in human lens phospholipid content with age and cataract were reviewed in 1935 by Krause[6] and, more recently, were studied in 1965 by Feldman and Feldman,[7] Broekhuyse,[8] and others.[9] In the past decade, an unknown lipid that comprised approximately 50% of the phospholipids in the human lens[10] was identified by ^{31}P-nuclear magnetic resonance (^{31}P-NMR) spectroscopy. It was determined that this lipid was dihydrosphingomyelin, a highly stable saturated lipid.[11–13] Other human lens phospholipids were resolved by ^{31}P-NMR, and two phosphatidylethanolamine (PE)-related phospholipids and dihydrosphingomyelin, which had gone undetected in the human lens, were found to comprise approximately 80% of the phospholipids in three human lenses.[14] Because of these findings, lens phospholipid changes with age and cataract were reexamined in three pools of human lenses. Lens phospholipid compositional changes[14–17] are important because human lens membrane lipid composition is related to the membrane's organization,[18] structure,[19–23] and function.[13,24–27] Furthermore, species-related phospholipid differences support the idea that humans have adapted so that their lens membranes have a high sphingolipid content that confers resistance to oxidation, allowing these membranes to stay clear for a relatively longer time than is the case in many other species.[28] Age-related changes in human lens lipid composition may serve as a marker for oxidative stress and may reflect systemic oxidative insult, providing a window into the health of an individual.[28]

Methods

Clear lenses were obtained from human donors within eight hours after death, from the Kentucky Lions Eye Bank (Louisville, KY) and the University of Kentucky Lions Eye Bank (Lexington, KY), and then frozen in liquid nitrogen. Clear lenses from eyes of donors who had diabetes were excluded. All human lenses were collected with informed consent. With patients' permission, an author (VR) collected cataractous lenses after performing extracapsular cataract extractions in Udine and Rome, Italy. All experiments were performed in accordance with the Declaration of Helsinki. The research was approved by the University of Louisville's institutional review board. Lipid was extracted from human lenses by using a monophasic extraction protocol.[29]

To remove oxygen, all solvents were bubbled with argon gas. The extraction was performed in an argon atmosphere. Glass centrifuge tubes were used throughout the extraction. Pooled lenses (12–25) were put in a glass centrifuge tube containing 40 mL of methanol. Lenses were cut with a metal spatula and sonicated with a microprobe sonicator (Branson; Ultrasonics Co., Danbury, CT) three to four times for 15 seconds, with a 5-minute pause between sonication bursts to ensure that the samples were not heated. The solution was centrifuged at 5000 rpm for 1 hour and the supernatant decanted into another centrifuge tube, leaving a small amount of the upper layer, to avoid disrupting the pellet. The methanol in the supernatant was evaporated

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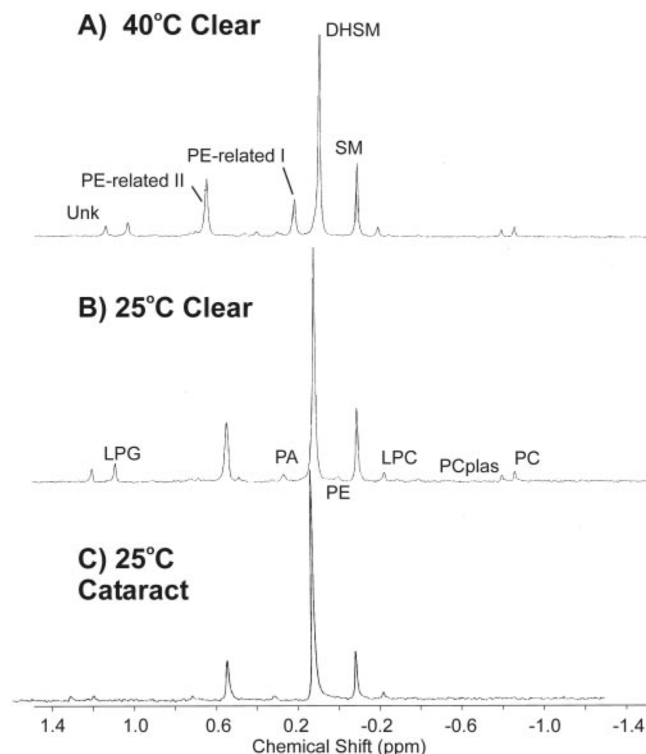

FIGURE 1. ^{31}P-NMR spectra of human lens lipids. Spectrum at (**A**) 40°C of clear lens lipids from donors with an average age of 69 ± 3 years; (**B**) 25°C of clear lens lipids from donors with an average age of 69 ± 3 years; and (**C**) 25°C of cataractous lens lipids from donors with an average age of 71 ± 10 years. Cataract types and definitions of abbreviations are shown in Table 1.

with a rotary evaporator (Buchi Rotavapor 011; Brinkman Instruments, Inc., Westbury, NY). Hexane and isopropanol (2:1 vol/vol, 10 mL) were added to the dry lipid film and gently sonicated with a microprobe for 15 seconds. The solution was transferred to a centrifuge tube and centrifuged at 5000 rpm for 1 hour. The lipid-containing supernatant was decanted into another tube, with care taken not to disturb the pellet, and the hexane and isopropanol were then evaporated with the rotary evaporator, lyophilized for 8 hours, and weighed.

Phospholipids extracted were identified and quantified by ^{31}P-NMR spectroscopy.[16] After solvent removal and addition of $CDCl_3$, the samples were heated at 50°C for 15 minutes and then allowed to return to room temperature before NMR spectral acquisition. To ensure narrower ^{31}P-NMR resonances, a 200-μL aliquot of cesium EDTA (Cs^+-EDTA) reagent[16] was added to 400 μL of each sample. Spectral data were then acquired (Inova-500 spectrometer; Varian, Lexington, MA). The following parameters were used: spectral width of 2024.7 Hz (sweep width, d¼ 10 ppm), 608 pulse, 4-K data points, 1.0-second delay time, and 0.711-second acquisition time at 40°C (or 25°C). Proton decoupling (500.16 MHz) was used. Spectra were processed with a line broadening of 3.0 Hz and phase correction. A computer running commercial software (GRAMS 386; Galactic Industries Corp., Salem, NH) was used for spectral deconvolution and curve fitting. The area of each band was used for the quantification of phospholipid composition.

RESULTS

^{31}P-NMR spectroscopy is ideal for determining the composition of human lens phospholipid because it is one of the few techniques that can resolve and quantify sphingomyelin and dihydrosphingomyelin, the major lipids of the lens. Our present results confirm results of our study of three human lenses[14] that showed the lens contains two PE-related phospholipids and dihydrosphingomyelin. The chemical shift of some of the phospholipids is sensitive to temperature. Spectra were measured at 25°C and 40°C, to resolve phospholipids such as the two PE-related phospholipids, which shifted downfield at higher temperatures, away from the large dihydrosphingomyelin peak (Fig. 1). Compositional studies of phospholipids in human lenses published before 1991 had relied on chromatographic separations, which could not resolve the two PE-related phospholipids and dihydrosphingomyelin, which comprise >70% of the clear human lens phospholipids, from sphingomyelin (Table 1).

TABLE 1. Phospholipid Composition of Clear and Cataractous Lipids

Lipid	Clear (USA) 22 ± 4 y	Clear (USA) 41 ± 6 y	Clear (USA) 69 ± 3 y	Mature, Mixed Cataractous (Italy) 71 ± 10 y	Mature Posterior Subcapsular and Nuclear (Italy) 74 ± 11 y	Immature, Nuclear Sclerotic Cataractous (USA) 80 ± 6 y	Mature Nuclear Cataractous (Italy) 75 ± 7 y
Unk	3.8	2.3	2.6	0.0	0.0	1.0	1.5
LPG	2.8	1.7	3.4	0.0	0.0	1.2	1.5
PE-II	17	13	16	13	15	14	11
PA	3	1.3	1.3	1.9	0.0	1.1	1.2
PE-I	17	12	11	0.0	0.0	0.0	3.8
DHSM	38	50	43	63	66	63	57
PE	0.0	0.0	2.6	0.0	0.0	1.5	2.2
PS	5.7	1.4	0.0	0.0	0.0	0.7	0.0
SM	9.6	12	14	16	14	14	19
LPC	2.3	1.3	2.5	2.5	3.0	2.8	2.2
PCplas	1.6	1.0	1.3	0.6	0.0	0.0	0.0
PC	2.7	1.9	2.2	0.0	0.0	0.0	0.0

Data are the percentage of total phospholipid determined by ^{31}P-NMR. Data were obtained from pools of lenses collected in the United States and Italy. The average ages of the lenses used are given as the mean ± SD. Experimental error is ±10% of the value. PE-I, a PE-related phospholipid formerly assigned to phosphatidylethanolamine plasmalogen; PE-II, an unidentified band with possibly a PE headgroup; LPG, lysophosphatidylglycerol; PA, phosphatidic acid; DHSM, dihydrosphingomyelin; PE, phosphatidylethanolamine; SM, sphingomyelin; LPC, lysophosphatidylcholine; PC, phosphatidylcholine; Unk, an unidentified band.

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Table 2. Human Lens Data

Average Age* (y)	Age Range (y)	Classification	Extraction Yield (mg lipid/g lens)
22 ± 4	15–29	Clear (U.S.)	3.6
41 ± 6	30–49	Clear (U.S.)	18
57 ± 4	50–64	Clear (U.S.)	14
69 ± 3	65–74	Clear (U.S.)	24
60 ± 9	40–74	Clear (U.S.)	22
58 ± 9	48–72	Clear (U.S.)	18
74.6 ± 6	63–86	Clear (U.S.)	25
72 ± 2	65–80	Clear (U.S.)	22
Average, excluding youngest pool		Clear (U.S.)	20.5 ± 3.5†
75 ± 7	63–86	Mature nuclear cataracts (Italy)	14
71 ± 10	46–86	All were mature cataracts (Italy): 71% mixed, 17% subcapsular, 13% nuclear	12
73 ± 18	56–86	Mature mixed cataracts (Italy)	13
72 ± 2	65–80	Mature mixed cataracts (Italy)	15
74 ± 11	50–87	Posterior subcapsular and nuclear cataracts (Italy)	15
75.1 ± 0.5	65–85	Mature mixed cataracts (Italy)	13
70 ± 5	47–82	Mature mixed cataracts (Italy)	12
Average		All cataractous lens pools	13.3 ± 1.2†

Lipid extractions were performed once on the total pool of lenses with a monophasic protocol developed for extracting phospholipids from the lens.[29] The experimental variability of the extraction is ±1.6% of the yield value.

* ± SD.

† Averages were significantly different, $P < 0.01$, determined by Student's *t*-test.

Age-Related Changes in Human Lens Phospholipid Composition

Clear lenses were pooled into four groups: group 1, with donors ranging in age from 15 to 29 years (average, 22 ± 4; $n = 30$); group 2, ranging in age from 30 to 49 years (average, 41 ± 6; $n = 14$); group 3, ranging in age from 50 to 64 years (average, 57 ± 4 years; $n = 25$); and group 4, ranging in age from 65 to 74 years (average, 69 ± 3; $n = 26$). The major changes in the relative amount of lens phospholipid with age are for two PE-related phospholipids and sphingomyelin (Table 1). Because the phospholipid composition of only three pools of clear lenses was measured in this study, the age-related results should be interpreted cautiously; but, combined with previous studies, the changes with age are significant (see the Discussion section). The PE-related phospholipid I decreased with age from 17% at 22 years of age to 11% (Table 1). Previous studies have assigned this band to PE-plasmalogen.[10] Because the chemical shift of this band does not coincide exactly with that for PE-plasmalogen, we cautiously named this band PE-related phospholipid I. Sphingomyelin increased from 9.6% at 22 years of age to 14% at 69 years of age (Table 1).

Cataract-Related Differences in Human Lens Phospholipid Composition

Cataractous lenses obtained from the United States and Italy were classified into four groups: mature, mixed cataractous (Italy) ranging in age from 46 to 86 years (average, 71 ± 10 ; $n = 25$); immature, nuclear sclerotic cataractous (U.S.), ranging in age from 69 to 87 years (average, 80 ± 6.1; $n = 14$); mature posterior subcapsular and nuclear cataractous (Italy), ranging in age from 56 to 87 years (average, 74 ± 11; $n = 14$); and mature nuclear cataractous (Italy) ranging in age from 58 to 86 years (average, 75 ± 7 years; $n = 5$). Cataracts were grouped into three categories based on the visual assessment of the lenses before surgery. The two pools of nuclear cataracts with no cortical or subcapsular opacities were further subdivided into mature and immature groups. Mixed cataracts all had nuclear opacities and were grouped into lenses that also contained posterior subcapsular opacity or cortical opacity. With all cataract types, sphingolipid increased from 57% in clear lenses to 78% and both phosphatidylcholine and PE-related phospholipids decreased to undetectable levels, below 0.5% of the total cataractous lens lipid (Table 1).

Lipid Extraction Yields

Lipid extraction yields for pools of clear and cataractous lenses (Table 2) are plotted in Figure 2. An additional five pools of clear lenses and four pools of cataractous lenses that were not used for compositional analysis were used to measure the lipid extraction yields (Table 2). Approximately 15 lenses were used in each pool. The extraction protocol was not accurate enough to discern differences in extraction yields between types of cataracts. Table 2 provides age and other information about the lenses pooled. The extraction yield of lipid from cataractous lenses was 13.3 ± 1.2 mg lipid/g wet wt (±SD), 35% lower than clear lenses (Table 2, Fig. 2). The relative amount of lipid per lens or lens weight should be interpreted cautiously, as will be discussed.

Discussion

The changes observed in the phospholipid composition of the human lens with age and cataract were substantial, greater than that reported for any organ or disease. The cause of the changes may be due to lipid oxidation. Lens glycerolipids, including phosphatidylcholine and PE, are approximately three to four times more unsaturated than lens sphingolipid (Table 3), and consequently they can be selectively oxidized over

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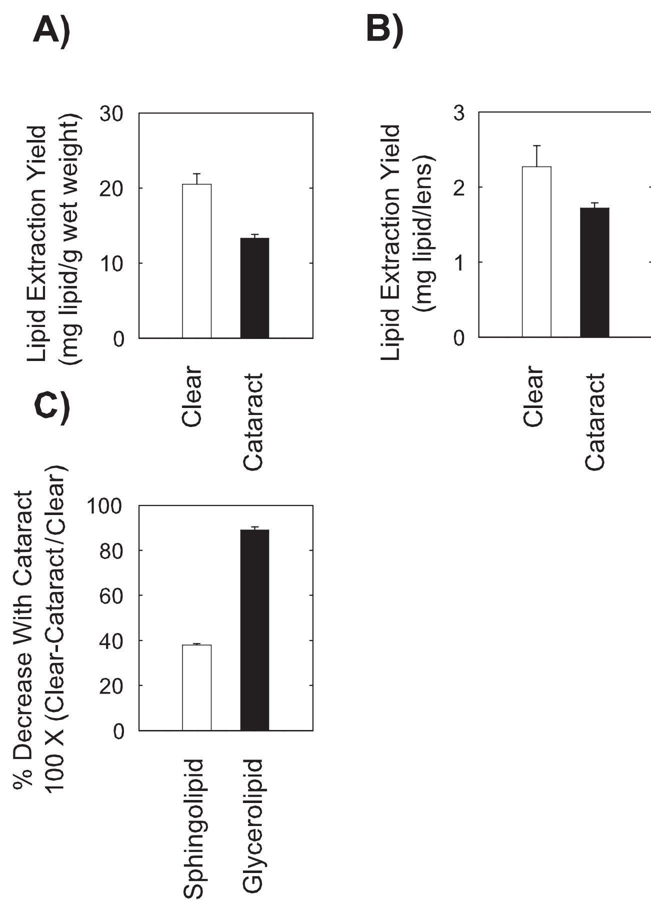

FIGURE 2. (**A**) Total lipid extraction yield of lens pools listed in Table 2. A monophasic extraction protocol was used that involved two extraction steps: a methanol extraction and a hexane-isopropanol extraction (2:1 vol/vol).[29] (**B**) Total lipid extraction yield of lens pools listed in Table 2 excluding the youngest pool of clear lenses and the clear lens pool, with an average age of 22 years. The latter pool had 6 mg lipid/lens, >2 SD above the average. Three additional pools of clear lenses for a total of 10 pools were averaged, but their wet weight was not determined and therefore the three additional pools were not included in Table 2. (**C**) Change in the two major phospholipid groups with cataract. Data were calculated from extraction yields and relative phospholipid composition data, with the assumption that the cholesterol-to-phospholipid molar ratio is 3:1 in human lenses. Averages in (**A**) and (**C**) were significantly different: $P < 0.01$ determined by Student's *t*-test. Error bars represent the standard error of the mean.

lipids with fewer double bonds, such as sphingolipids, because the rate constant for the propagation step of lipid oxidation sharply increases when the number of lipid double bonds is increased.[35] Oborina and Yappert[36] found that the oxidation of a polyunsaturated phosphatidylcholine is less when sphingomyelin is present than when saturated phosphatidylcholine is present in the membrane. For these reasons, we hypothesize that lens glycerolipids are selectively oxidized over more saturated sphingolipids. If this hypothesis were to be correct, lipid oxidation could be the event that causes the significant loss of unsaturated phospholipids, such as phosphatidylcholine, and the relative enrichment of dihydrosphingomyelin with age and cataract (Table 1, Fig. 3).

Broekhuyse[8] comprehensively measured the change in total human lens phospholipid with age. Using his data, and the relative data from Figure 3, we calculated that the amount of phosphatidylcholine (Fig. 4A) and PE-related phospholipid I (Fig. 4B) per wet weight of lens decreased linearly with age, as expected of unsaturated lipids that are susceptible to oxidation. Conversely, we calculated that the amount of sphingolipid (Fig. 4C) per wet weight of lens, a relatively unsaturated lipid, increased with age up to approximately 45 years. Because phospholipid and cholesterol synthesis do not change within the ages studied,[37] the relative (Fig. 3) and absolute (Fig. 4) changes between the sphingolipid (Figs. 3C, 4C) and glycerolipid with age must be due to degradation. Cholesterol synthesis has been shown to decrease in rat lenses 22 days after birth.[38] The data in Figure 4 support the idea that glycerolipids are selectively oxidized over lipids with fewer double bonds, such as sphingolipids. The plateau at 40 years of age for the absolute amount of sphingolipid (Fig. 4C) may result from the glycerolipids' reaching a critically low concentration, at which the sphingolipids become the target for oxidation and degradation, rather than the glycerolipids, which are usually the target but are depleted.

The total amount of lipid (cholesterol and phospholipids) relative to lens wet weight was 35% lower in cataractous lenses than age-matched control lenses (Fig. 2, Table 2). It would be unreasonable to expect that 35% of the lens membrane lipid would be missing in cataractous lenses, and comparisons between the amount of lipid in clear and cataractous lenses must be interpreted with caution because cataractous lenses could contain more water than clear lenses. This would make the apparent lipid content relative to lens weight lower in cataractous lenses. From the compositional data in Tables 1 and 2, we calculate that the absolute amount of sphingolipid decreased by 38% in cataractous lenses compared with clear lenses (Fig. 2C). In comparison, glycerolipids decreased by 89% with cataract (Fig. 2C). The changes in the amount of lipid with cataract are in agreement with age-related changes, supporting the idea that glycerolipids are selectively oxidized over lipids with fewer double bonds, such as sphingolipids.

The PE-related phospholipids account for approximately 30% of the human lens phospholipids (Table 1). Previous studies have assigned the PE-related phospholipid I band to PE-plasmalogen.[10] Plasmalogens are highly unsaturated and perhaps are oxidized in relatively older human lenses.[39] No studies before 1991 reported significant quantities of plasmalogens in human lenses.[9] In our study, PE-related phospholipid I decreased with age from 16% at 10 years of age to 2% at 80 years of age (Table 1, Fig. 3B). The results (Fig. 3B, filled circles), using pooled lipids, are in agreement with the age-related changes reported in three human lenses determined by ^{31}P-NMR (Fig. 3B, open squares). PE-related phospholipids were undetectable in three of four pools of cataractous lenses (Table 1, Fig. 3). Lens PE-related phospholipid I, decreases with cataract in hyperbaric oxygen animal models[40] and may be a marker of membrane integrity. Its loss is a marker of lipid oxidation.

Our data (Fig. 3D, filled circles; Table 1) show that the relative amount of sphingolipids (dihydrosphingomyelin and sphingomyelin) increased from 48% at 22 years of age to 57% at 69 years of age, in agreement with previous studies (Fig. 3D, open circles and squares).[14,16] With cataract, the relative amount of sphingolipid increased to 78% (Table 1, Fig. 3D). Sphingolipid may be essential in the lens. We hypothesize that humans have adapted so that their lens membranes have a high sphingolipid content to confer resistance to oxidation, allowing these membranes to stay clear for a relatively longer time than is the case in many other species.[28] However, an increase in sphingolipid content in the human lens with age and cataract may indicate deleterious phospholipid oxidation.

Human lens lipid composition versus age curves, exhibiting a plateau at ~45 years (Figs. 3A, 3B, 4C), are remarkably similar to the curves of accommodative amplitude ver-

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Table 3. Human Lens Phospholipid Saturation

Sample	(*Cis* C═C)/Lipid (mole/mole)	Average Age (y)	Reference Source
Total Lens	0.46	72	Cotlier et al.[30]
Total Lens	0.83	73	Rosenfeld and Spector[31]
Total Lens	0.87	74	Rosenfeld and Spector[31]
Total Lens	0.73	68	Zigman et al.[32]
Total Lens Average	0.72 ± .16	72 ± 2	
Sphingolipid	0.29	?	Feldman et al.[33]
Sphingolipid	0.25	66	Tao and Cotlier[34]
Sphingolipid	0.20	72	Cotlier et al.[30]
Sphingolipid	0.27	64	Byrdwell and Borchman[15]
Sphingolipid	0.18	71	Rujoi M et al.[27]
Sphingolipid Average	0.25 ± .03	68 ± 3	
Dihydrosphingomyelin	0.28	64	Byrdwell and Borchman[15]
Dihydrosphingomyelin	0.18	70	Rujoi M et al.[27]
Sphingomyelin	0.22	64	Byrdwell and Borchman[15]
Sphingomyelin	0.17	70	Rujoi M et al.[27]
Phosphatidylcholine	1.7	64	Byrdwell and Borchman[15]
Phosphatidylcholine	1.3	70	Rujoi M et al.[27]
Phosphatidylcholine	0.66	?	Feldman et al.[33]
Phosphatidylethanolamine	0.84	?	Feldman et al.[33]

sus age[41,42] and human lens membrane cation passive permeability versus age.[43] Correlation does not necessarily indicate causation; however, scenarios can be envisioned in which lens membrane stiffness induced by phospholipid compositional changes directly or indirectly contribute to presbyopia and/or passive membrane permeability of cations.

Sphingolipid content may be the major factor influencing lens lipid hydrocarbon chain order, or stiffness. In every lens species examined, sphingolipids order lens membranes (Fig. 5). Lipid order is much higher in cataractous lenses (84%) than in clear lenses of the same age. This study allows the addition of cataractous lens sphingolipid composition to the data that shows a correlation between lens sphingolipid content and

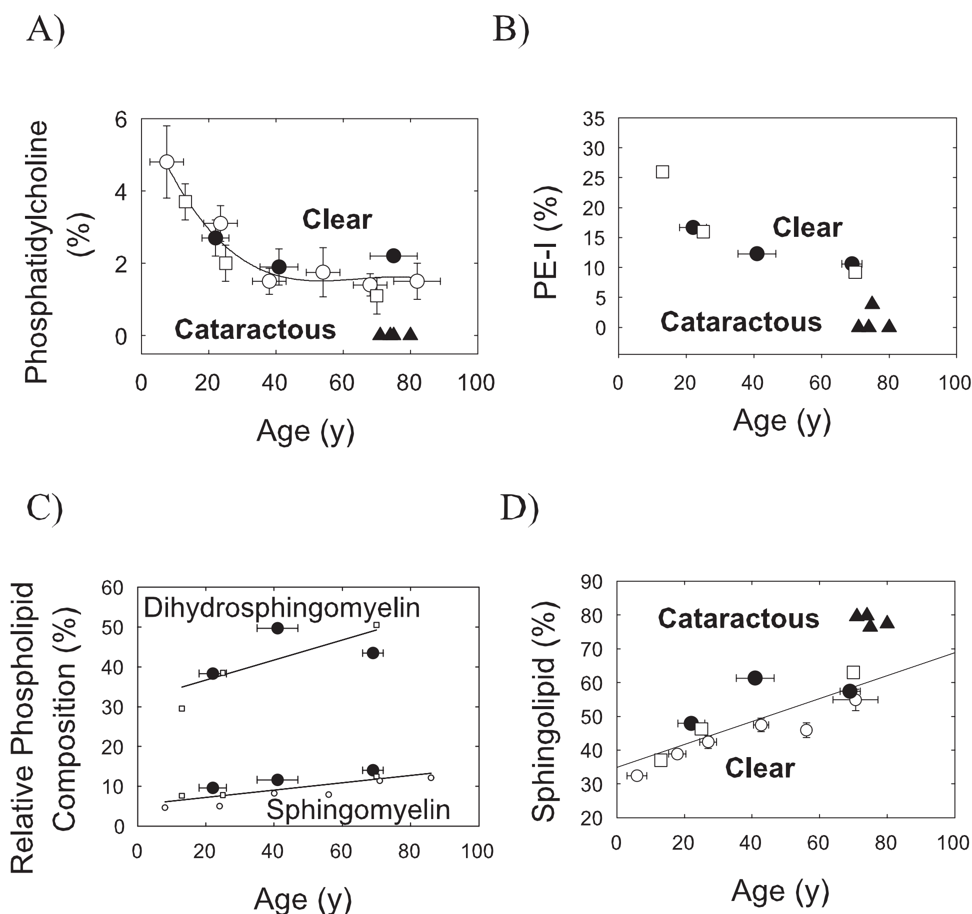

Figure 3. Changes in the relative levels of human lens phospholipids with age and cataract. Closed symbols were measured for this study. In cataractous lenses (▲), the amount of PE-I (**A**) and phosphatidylcholine (**B**) decreased and sphingolipid (**D**) increased, compared with amounts in clear lenses. (□) Data are from individual lenses[14]; (○, ●) data from pools of 5 to 15 lenses. Error bars for the relative amount of lipid are smaller than the symbol, unless indicated. (**A**, *curve*) The linear regression third-order curve fit to the data; $r^2 = 0.90$, $P < 0.005$. (**C**, **D**, *lines*) The first-order linear regression curve fit to the data. (**C**) $r^2 = 0.637$; (**D**) $r^2 = 0.675$; $P < 0.005$.

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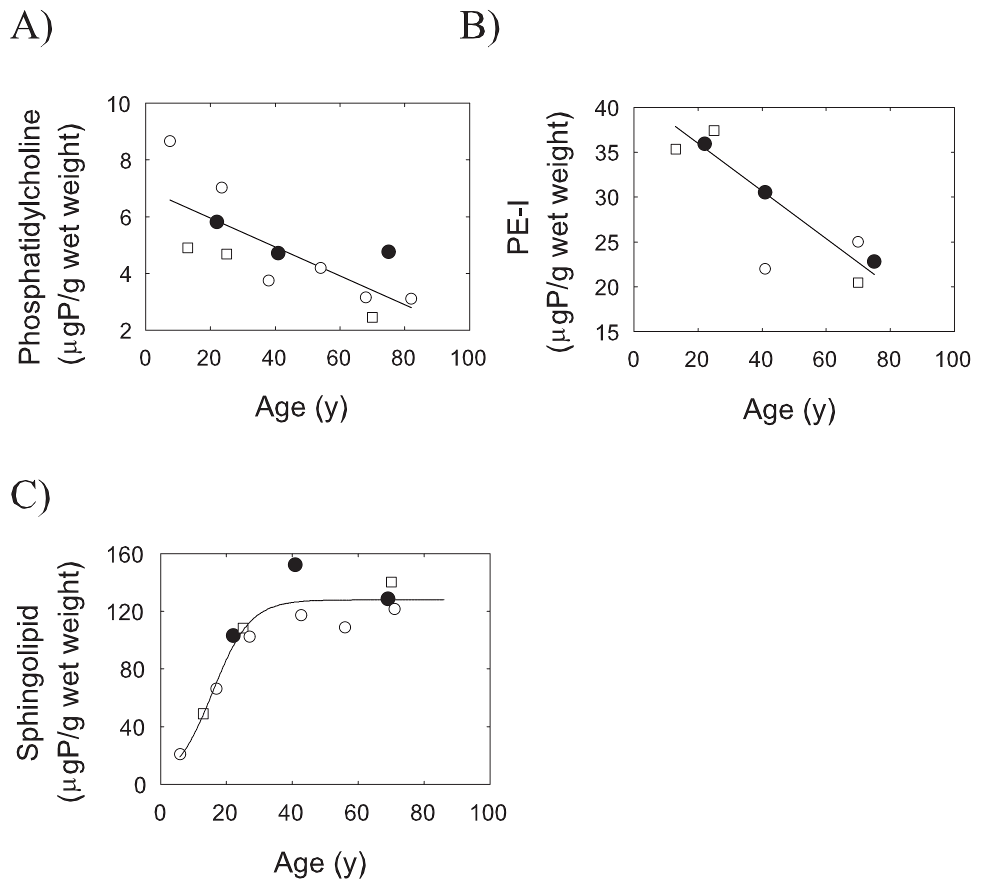

FIGURE 4. Total phospholipid was calculated from the relative amounts of phospholipid plotted in Figure 3 and the total phospholipid data extrapolated from Broekhuyse,[8] where P is phospholipid phosphorus. See Figure 3 for the symbol key. (**A**, **B**, *lines*) The linear regression first-order curve fit to the data. (**A**) $r^2 = 0.573$; $P < 0.005$; (**B**) $r^2 = 0.918$; $P < 0.005$. (**C**, *line*) The third-order linear regression curve fit to the data $r^2 = 0.907$; $P < 0.005$.

lipid order (Fig. 5). Lipid hydrocarbon chain conformational order was measured from the infrared CH_2 symmetric stretching band frequency to estimate the *trans* to *gauche* rotomer ratio.[22] Lipids having hydrocarbon chains with ordered conformations are stiffer and less mobile than lipids that are disordered. Lipids in the disordered state may be defined as having all *gauche* rotomers. Those in the ordered state may be defined as having all *trans* rotomers. Except for the camel lens nucleus, lipid order and sphingolipid content were linearly related (Fig. 5). This study confirms that the sphingolipid content of cataractous lens lipids is 79% as predicted by an order of 84%.

Our studies suggest that as a result of increased sphingolipid content in cataractous lenses compared with age-matched clear lenses, light-scattering increases.[44] Lipids scatter 2 to 95 times more light in vitro than do crystallin proteins, indicating that they may contribute to the light-scattering intensity of the lens in vivo.[44] Because lipids with ordered hydrocarbon chains have higher polarizabilities, they scatter 2.5 times more light than lipids with disordered

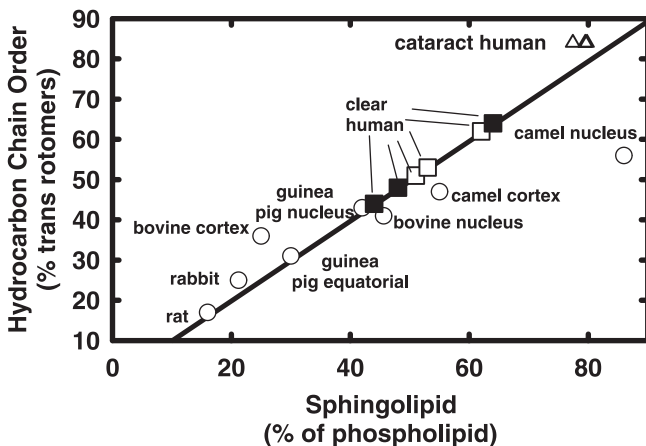

FIGURE 5. The relationship between lens sphingolipid content and hydrocarbon chain order. Hydrocarbon chain order reflects the structural stiffness of the membrane lipid hydrocarbon chain region. (□) Clear human lens cortex; (■) clear human lens nucleus; (△) cataractous human lenses. All the data except the cataractous lens lipid data are from Borchman et al.[28] Cataractous lipid order is from Paterson et al.[23]

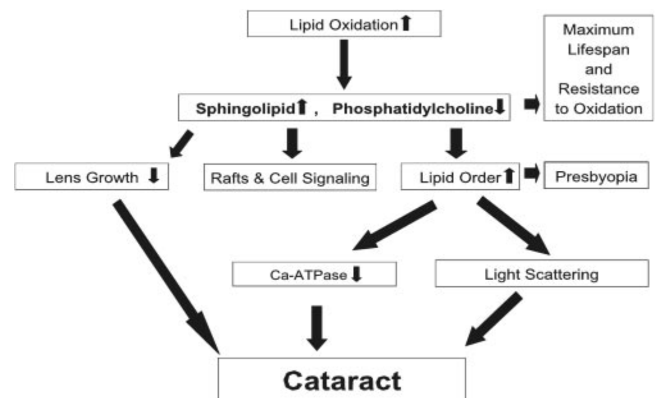

FIGURE 6. Schematic of relationships between lipid compositional changes and their possible contribution to cataract, presbyopia, and lifespan.

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hydrocarbon chains.[44] One would expect an increase in hydrocarbon chain order from 60% in clear human lenses to 80% in cataractous lenses to cause a 20% increase in light-scattering from the lipid component of the lens membrane. An increase in lipid hydrocarbon chain order may also contribute to cataractogenesis indirectly by reducing the activity of the sarco/endoplasmic reticulum isoform of the calcium pump.[25] Reduced pump activity could cause an increase in lens calcium levels. Calcium is elevated in all cataracts,[45–50] and maintenance of the calcium homeostasis is essential to lens clarity. The higher sphingolipid content of cataractous lenses may also change protein–lipid interaction[51,52] and slow fiber cell elongation[14]—two factors that could contribute to cataract (Fig. 6).[13,14] Lens lipid alterations with age and cataract may be a model for aging in other tissues.

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