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Explaining longevity of different animals: is membrane fatty acid composition the missing link?

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Abstract Saturated and monounsaturated fatty acids are very resistant to peroxidative damage, while the more polyunsaturated a fatty acid, the more susceptible it is to peroxidation. Furthermore, the products of lipid peroxidation can oxidatively damage other important molecules. Membrane fatty acid composition is correlated with the maximum lifespans of mammals and birds. Exceptionally long-living mammal species and birds have a more peroxidation-resistant membrane composition compared to shorter-living similar-sized mammals. Within species, there are also situations in which extended longevity is associated with peroxidation-resistant membrane composition. For example, caloric restriction is associated more peroxidation-resistant membrane composition; long-living queens have more peroxidation-resistant membranes than shorter-living worker honeybees. In humans, the offspring of nonagenarians have peroxidation-resistant erythrocyte membrane composition compared to controls. Membrane fatty acid composition is a little appreciated but important correlate of the rate of aging of animals and the determination of their longevity.

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Abbreviations

CR	Caloric restriction
AGE	Advanced glycosylation end-product
ALE	Advanced lipoxidation end-product
BMR	Basal metabolic rate
SFA	Saturated fatty acid
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
MLSP	Maximum life span potential
PI	Peroxidation index

Introduction

"Live fast-die young," a phrase often used to describe the early death of risk-taking humans, is also used to summarise one of the important early theories of aging, the rate-of-living theory. Max Rubner (1908) combined the mass-specific resting metabolic rate and maximum lifespan of mammal species to calculate their "lifetime energy potential," and showed that this was a relatively constant value (~800 kJ/kg) for five mammal species ranging in size from guinea pigs to horses. This was an important contribution suggesting that the pace of life and the length of life were

inversely related. Later, Raymond Pearl (1928) used this concept also to explain longevity variation within species and gave it the "rate of living" label. Specifically, he used the concept to explain why fruit flies live longer when maintained at lower temperatures. This link between the rate of aerobic metabolism of an animal and species longevity was important in the later development of the "free radical" theory of aging (Harman 1956). The "free radical" theory, nowadays also described as either the "oxidative stress" or "oxidative damage" theory, is currently the most accepted mechanistic explanation of aging and variation in longevity, with much evidence to support it. When it is used to explain much of the variation in maximum lifespan among different species, it still has at its base an implied "rate of living" perspective.

However, there are documented problems with the rate of living being a complete explanation for a species maximum lifespan. These include the following observations: (1) voluntary exercise and its associated increased metabolism does not reduce longevity (in rats and humans); (2) birds have a higher rate of living than similar-sized mammals yet generally are much longer-living; (3) within a species, there is no inverse correlation between rate of living and longevity of individuals (in mice and fruit-flies); (4) although calorie-restriction increases longevity, it does not do so by decreasing mass-specific metabolic rate; and (5) in both mammals and birds, although there is a significant inverse correlation between basal metabolic rate (BMR) and maximum lifespan, there is substantial variation in maximum longevity that cannot be explained by variation in rate of living (Fig. 1). A compilation of BMR and maximum lifespan data for 267 mammal and 108 bird species shows that, although there is a significant inverse relation between the two parameters, variation in BMR can explain only 26% of the variation in maximum longevity of mammals and 41% in birds. The relationships between body size, energy metabolism and lifespan have been analysed elsewhere [Speakman 2005; Furness and Speakman 2008 (this volume)]. It can be concluded that there must be other factors involved, apart from rate of living, to account fully for species differences in maximum lifespan. It is the purpose of this brief review to examine the evidence that the fatty acid composition of membranes may be such a factor.

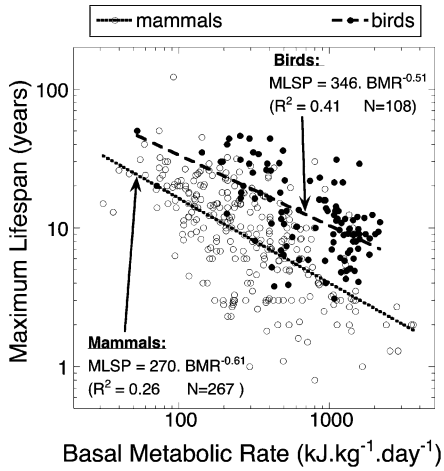

Fig. 1 The relationship between basal metabolic rate and maximum life span of birds and mammals (modified from Hulbert et al. 2007)

The membrane pacemaker theory of aging

The finding that membrane fatty acid composition varies in a systematic manner among species was important in the development of the membrane pacemaker theory. Thirty years ago, Gudbjarnason et al. (1978) reported that heart membrane fatty acid composition of different mammal species was correlated with heart rate (an indicator of the rate of living). Later, this systematic variation in membrane fatty acid composition was shown in other tissues of mammals and hence appears not to be restricted to heart membranes (Couture and Hulbert 1995). Furthermore, membrane composition was correlated with maximum lifespan in mammals (Pamplona et al. 1998). These findings led to a modification of the oxidative stress theory of aging: the membrane-pacemaker theory (Hulbert 2005; Hulbert et al. 2007). There are three basic reasons why membrane fatty acid composition can be argued to be an important factor in determining longevity: (1) membrane fatty acid composition varies systematically among species; (2) fatty acids differ dramatically in their susceptibility to peroxidation; and (3) many of the products of lipid peroxidation are themselves powerful reactive oxygen molecules (schematic provided in Fig. 2).

Not all atoms that make up fatty acid chains are equally susceptible to attack by free radicals. The bis-allylic hydrogens (i.e. those attached to single-bonded C atoms between double-bonded C atoms) are most prone to free radical attack. Consequently, fatty acid

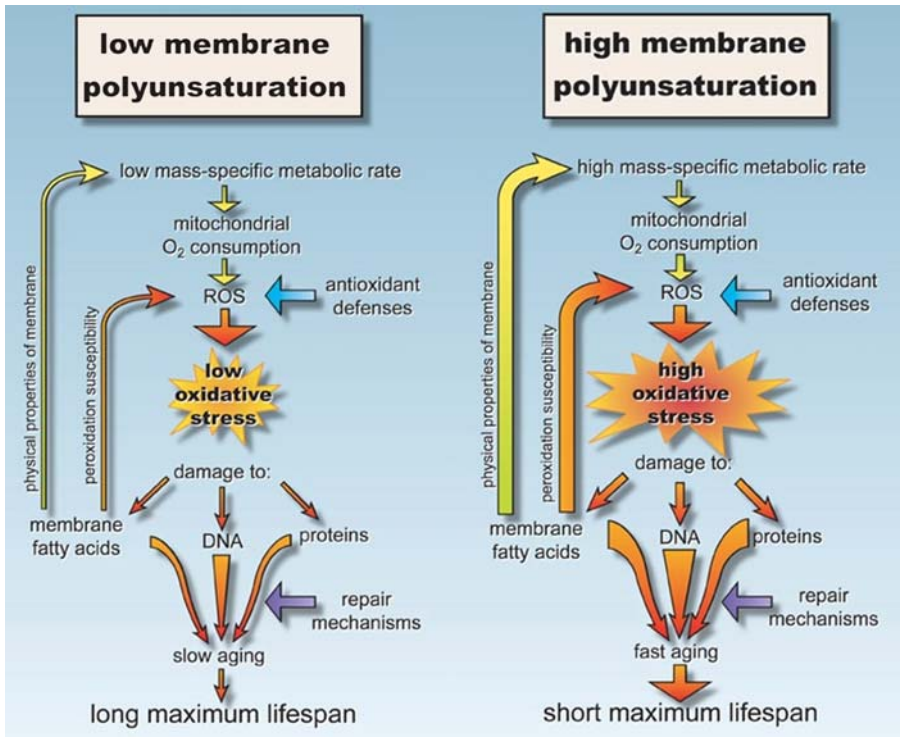

Fig. 2 Schematic diagram outlining the membrane pacemaker modification of the oxidative stress theory of aging, contrasting examples of low and high membrane polyunsaturation. Thickness of *arrows* represents relative intensity of the process (reproduced from Hulbert et al. 2007 with permission of Physiological Reviews)

chains with no double bonds (i.e. saturates; SFA), or those with only a single double bond (i.e. monounsaturates; MUFA) are resistant to peroxidation, while those with multiple double bonds (polyunsaturates; PUFA) are prone to damage by free radicals. The more polyunsaturated the PUFA, the more susceptible it is to peroxidation (Halliwell and Gutteridge 1999). By combining the susceptibilities of individual fatty acid chains with the measured percent fatty acid composition of membrane lipids, it is possible to calculate a "peroxidation index" (PI) for the particular membrane (see Hulbert et al. 2007 for details). This single number gives an approximate indication of the susceptibility of a membrane to lipid peroxidation.

Many of the products of lipid peroxidation are themselves powerful reactive oxygen species that can further attack other PUFA molecules. This is why lipid peroxidation can be an autocatalytic, self-propagating process. The products of lipid peroxidation can also damage nearby proteins and nucleic acids, producing advanced lipoxidation end products (ALEs). In this respect, free radical attack on lipid membranes differs from attack on proteins and nucleic acids. Cells with peroxidation-susceptible membrane fatty acid composition (i.e. those with a high PI) will not only sustain substantial peroxidative damage to the membrane lipids themselves but will also exhibit substantial lipoxidative damage to cellular proteins and nucleic acids. Indeed, it has been suggested that mitochondrial superoxide production might be regarded as the "pilot light" of oxidative stress, while lipid peroxidation (via its reactive products) might be considered as the "full furnace" (Hulbert et al. 2007). As animals age, some of the products of lipid peroxidation accumulate as lipofuscin (also called "age pigment"). Granules of lipofuscin contain both end-products of lipid peroxidation and lipoxidatively damaged protein, and the accumulation of such age pigment in postmitotic cells is the most consistent and phylogenetically constant morphological feature of aging (Porta 2002).

The membrane pacemaker theory thus adds a feedback loop to the normal schematic of the oxidative stress theory of aging, and the strength of this feedback loop depends on membrane fatty acid composition (Fig. 2). Any successful theory of aging should provide insight into four paradigms: (1) species-specific variation in maximum life spans; (2) within-species variation in life spans (among strains and individuals); (3) mechanisms whereby physiological treatments alter lifespan and hence aging; and (4)

aging-associated changes in individuals during their lifetime. In the rest of this contribution I describe evidence linking membrane fatty acid composition with these paradigms, especially the differences in longevity among the endothermic vertebrates: mammals and birds.

Maximum life spans of mammals

The range of maximum life span potentials (MLSP) of different mammal species exceeds two orders of magnitude. Some very small mammals live for <1 year, while some humans have been recorded to live >120 years, and possibly *Homo sapiens* is the longest-living species of mammal. In mammals, maximum life span is inversely correlated with body mass (Hulbert et al. 2007). Small mammals also generally have membrane lipids that are more polyunsaturated than those of larger mammals (Couture and Hulbert 1995), and PIs calculated for liver mitochondrial membrane lipids isolated from mammals was inversely correlated with their MLSPs (Pamplona et al. 1998). An earlier test of the membrane pacemaker theory plotted PI of skeletal muscle phospholipids against MLSP for 11 mammal species, and the PI for liver mitochondrial phospholipids against MLSP for 9 mammal species. This analysis showed these two relationships to have similar slopes, such that every doubling of MLSP was associated with a 19% decrease in skeletal muscle PI and a 24% decrease in liver mitochondrial PI (Hulbert 2005). These two relationships have been re-examined here (Fig. 3) using enlarged data sets; the relationships are essentially the same as those previously reported.

Although MLSP is related to body mass in mammals, there is variation around this general trend; some species are exceptionally long-living for their body size. Three such species are the naked mole-rat (*Heterocephalus glaber*), echidna (*Tachyglossus aculeatus*), and human (*Homo sapiens*). The body mass of adult naked mole-rats is ~35 g, which is similar to that of the common mouse (*Mus musculus*). Using the regression equation derived in Hulbert et al. (2007) for mammals as a whole, a 35-g mammal is predicted to have a MLSP of ~5 years, yet the documented MLSP for naked mole-rats is ~28 years (Buffenstein 2005). Adult echidnas weigh ~3 kg and consequently have a predicted MLSP of ~13 yr, yet their documented MLSP is ~50 yr (Carey and Judge 2000). Adult humans (~70 kg) have a predicted MLSP of ~26 years compared to an actual MLSP of ~120 years. These long-living mammals have actual MLSPs that are 4–6 times that predicted from their adult body mass. Although they are exceptionally long-living for their body mass, they are essentially the same as all other mammals with respect to the

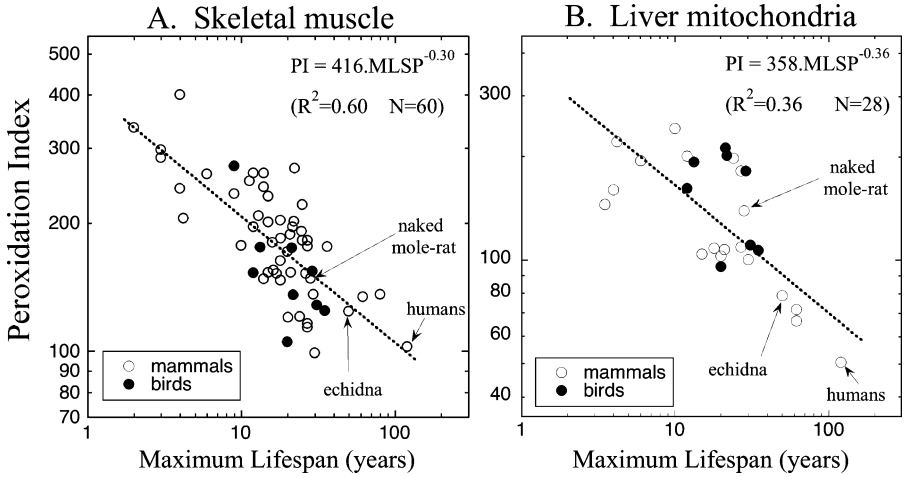

Fig. 3 Relationship between maximum life span of mammals and birds and peroxidation index of skeletal muscle phospholipids (**a**) and liver mitochondrial phospholipids (**b**). Skeletal muscle data combined from Valencak and Ruf (2007) and those cited in Hulbert (2005); liver mitochondrial data combined from Pamplona et al. (1998) and those cited in Hulbert (2005). Data for naked mole-rat from Hulbert et al. (2006b); echidna from A. Hulbert, L. Beard and G. Grigg, unpublished data. Equation in the top right-hand corner of each figure describes relationship between peroxidation index (PI) and maximum life span (MLSP)

relationship between their MLSP and the PI of their membrane lipids from both skeletal muscle and liver mitochondria (Fig. 3).

Birds compared to mammals

As with mammals, small species of birds generally have shorter MLSP than larger species (see Hulbert et al. 2007). In addition, birds are much longer-living than similar-sized mammals and have been suggested as good animal models for examining aging and the determinants of longevity (Holmes and Austad 1995). A recent compilation shows that, on average, birds have a MLSP twice that of similar sized mammal species (Hulbert et al. 2007). This is contrary to a strict interpretation of the rate of living theory, as birds have basal metabolic rates that average about 50% more than similar-sized mammals, and thus might be expected to have MLSPs two-thirds those of comparable mammals. This implies there is some other factor determining life span that generally differs between birds and mammals.

Birds of different body size show systematic variation among species in the fatty acid composition of their membrane lipids. Small bird species have more polyunsaturated membrane lipids than do larger birds in skeletal muscle (Hulbert et al. 2002), heart (Szabo et al. 2006), and liver mitochondria (Brand et al. 2003), as well as kidney (A.J. Hulbert, unpublished). Although the variation of membrane fatty acid composition with body mass of birds is similar to that in mammals, the membrane fatty acid composition of birds and mammals differs in one important respect. In birds, the balance between n-6 PUFA and n-3 PUFA is shifted more to n-6 PUFA than in similar-sized mammals. This appears to be important with respect to the relatively long lifespan of birds, since n-6 PUFA chains generally have fewer double bonds than equivalent n-3 PUFA, and consequently are less susceptible to peroxidative damage (see Hulbert et al. 2007). This means that membrane lipids from birds will generally have a lower PI value than equivalent membrane lipids from similar-sized mammals, but when PI data for membrane lipids from skeletal muscle and liver mitochondria of bird species is plotted against their MLSP (rather than body mass), there is no difference between birds and mammals (Fig. 3).

An interesting observation from Fig. 3 is that the slope of the relationships between MLSP and PI is very similar for both skeletal muscle and liver mitochondrial phospholipids. For example, skeletal muscle phospholipid PI is proportional to the −0.30 power of MLSP, while for liver mitochondria it is proportional to the −0.36 power of MLSP. From these slopes, it is possible to calculate that every doubling of MLSP is associated with a 19% decrease in the PI of skeletal muscle phospholipids and a 22% decrease in the PI of liver mitochondrial phospholipids.

Longevity variation within species

Not only do different species have characteristic maximum life spans, there is, of course, considerable longevity variation within species. This longevity variation is manifest both between strains of a given species and between individuals within a species. This within-species variation can be either natural or experimentally induced.

An example of natural variation in longevity is that some wild-derived strains of mice (*Mus musculus*) have been shown to have longer life spans and more delayed maturation than genetically heterogenous laboratory mice kept under identical environmental conditions (Miller et al. 2002). In keeping with the membrane pacemaker theory, long-living wild-derived mice strains also have phospholipids (from both muscle and liver) with lower PIs than those of the laboratory mice strain (Hulbert et al. 2006a) (Fig. 4a). The fact that all strains were fed the same diet and kept under identical conditions indicates that such differences in membrane composition are under genetic control.

A classical example of experimentally induced longevity variation within species is that of the effects of calorie restriction (CR). This treatment is the most common manipulation in the study of aging and was first described for rats in 1935 (McCay et al. 1935). The degree of life span extension is linearly related to the amount of CR in both rats (Merry 2002) and mice (Weindruch et al. 1986), but the precise mechanism by which CR extends longevity is not known (Masoro 2002). A common finding is that lipid peroxidation is reduced during CR (Habib et al. 1990; Matsuo et al. 1993). In a seminal study, Laganiere and Yu (1987) showed changes in fatty acid composition of liver

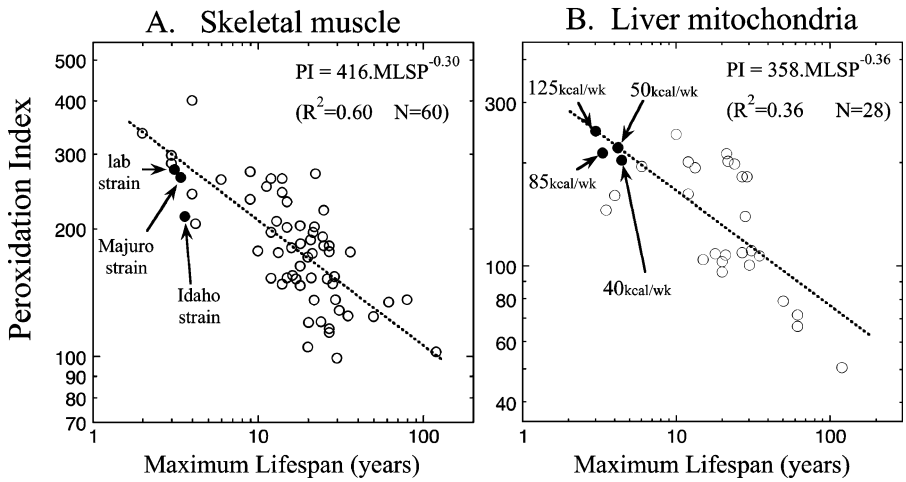

Fig. 4 Relationship between MLSP and PI of (**a**) skeletal muscle phospholipids of three strains of mice that differ in life span and (**b**) liver mitochondrial phospholipids of mice subjected to four different levels of caloric intake. Data points for mice are superimposed on general relationships for mammals and birds (*open circles*), which are the same data points for birds and mammals as plotted in Fig. 3. In **a**, the new fatty acid data points in this figure are for the mouse strains (*filled circles*) and are taken from Hulbert et al. 2006a while the life span data are from Miller et al. 2002. In **b** the new fatty acid data points for CR mice (*filled circles*) and are from Faulks et al. 2006 while the life span data are from Weindruch et al. (1986)

membranes during CR in rats, such that they become less susceptible to peroxidation. There have been a number of other reports of similar CR-induced changes in membrane composition (e.g. Cefalu et al. 2000; Lee et al. 1999; Pamplona et al. 2002). A recent study in mice has shown that changes in membrane composition are both proportional to the degree of CR and manifest within 1 month of onset of CR (Faulks et al. 2006). Figure 4b illustrates the changes in PI of liver mitochondrial membranes of these mice relative to the changes in maximum longevity previously reported by others in a different mice strain but using the same CR regime (Weindruch et al. 1986).

Some of the social insects provide another example of longevity variation within a species. For example, female honeybees (*Apis mellifera*) can be either workers or queens depending on the food they receive during the larval stage; while queens can live for years, workers generally live only for weeks (Winston 1987). Recent measurements show that queens, as well as larvae and newly emerged worker honeybees, have phospholipids high in peroxidation-resistant MUFA and low in peroxidation-prone PUFA (Haddad et al. 2007). Within the first week of adult life in the hive, the phospholipids of workers accumulate PUFA and exhibit an almost three-fold increase in PI. This increase is likely due to consumption of pollen by workers during this period; phospholipid composition is essentially unchanged throughout the remainder of the worker honeybees' life. These changes are manifest in all three body segments (head, thorax and abdomen) of workers and contrast with the situation in queens, which do not consume pollen and retain peroxidation-resistant phospholipid fatty acid composition during their adult life (Fig. 5). Assuming the same slope of the relationship between MLSP and PI of phospholipids of honey bees as observed in mammals and birds (see Fig. 3), an

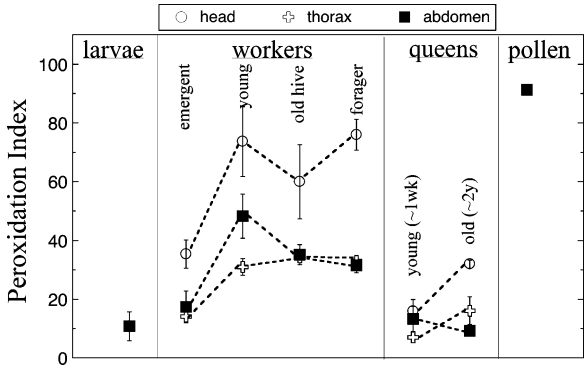

Fig. 5 Comparison of the PI of phospholipids from pollen and different life stages of the honey bee (*Apis mellifera*). Data are from Haddad et al. 2007. Larvae values are for whole larval phospholipids. Data for workers and queens are presented separately for head, thorax and abdomen. Pollen data are for pollen collected from the legs of forager worker bees. *Error bars* ± 1 SEM

approximately three-fold difference in phospholipid PI explains the order-of-magnitude difference in longevity of workers and queen honeybees.

Fatty acid composition as a longevity biomarker for humans?

As a species, *Homo sapiens* lives much longer than predicted from body mass. For our size, we have a predicted maximum longevity of only 'one score and six'. Associated with our exceptional longevity, we also have phospholipids with a particularly peroxidation-resistant fatty acid composition. Indeed in this respect, as a species we fit the relationship for mammals and birds in general (Fig. 3). There is considerable variation in the longevity of individual humans. Measurement of the fatty acid composition of human erythrocyte membrane lipids, as well as in vitro measurements on erythrocytes, has shown that centenarians have a reduced susceptibility to peroxidative membrane damage (Rabini et al. 2002). Part of longevity variation is genetic in origin. Studies of Danish twins suggests the heritability of longevity is 0.23 for females and 0.26 for males (Herskind et al. 1996); hence children of centenarians have been used as a model system for the study of the genetic basis of human aging (e.g. Atzmon et al. 2006). The fatty acid profile of erythrocyte membranes has been proposed as a potential biomarker of human longevity. A recent Italian study reported that the children of nonagenarians had erythrocyte membrane lipids with a PI of 64 (Fig. 6), which was significantly lower both than the value of 85 measured for a group of matched controls and the value of 83 for unmatched controls (Puca et al. 2008).

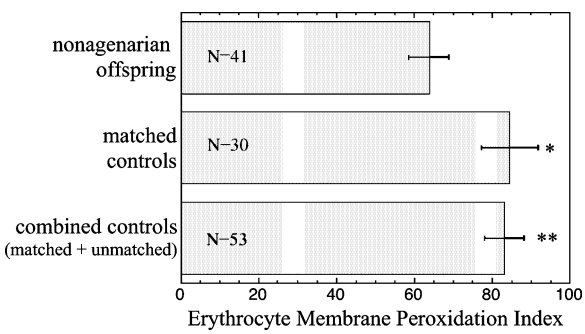

Fig. 6 Comparison of the PI of human erythrocyte membrane fatty acids. Data are taken from Puca et al. (2008). *Error bars*± 1 SEM; sample size shown in each bar. Both controls are significantly different (*P=0.02 and **P=0.009) from nonagenarian offspring

Another aspect of membrane lipid composition related to extended longevity?

So far, in this contribution I have concentrated on the fatty acid composition of phospholipids and the calculated relative susceptibilities membrane fatty acids of different compositions to peroxidative damage. However, there is a different aspect of membrane lipid composition that may also be relevant to aging. While in phospholipids an ester linkage joins acyl chains to the glycerol backbone, in plasmalogens (ether lipids) a vinyl-ether linkage is involved. Such vinyl-ether linkages may have antioxidant properties. Plasmalogens are very high in both central nervous system and the heart but their precise role is not clear. They have been implicated in age-related degenerative diseases and have been proposed to be important membrane antioxidants (Zoeller et al. 1988; Brosche and Platt 1998). The relative abundance of plasmalogens in species that differ in longevity has not been systematically examined, but a recent comparison of the exceptionally long-living naked mole-rat with the similar-sized but shorter-living mouse showed the naked mole-rat tissues to have much higher levels of plasmalogen than the mice tissues (Mitchell et al. 2007). It would be of interest to know if membrane plasmalogen levels are correlated with health or longevity within, as well as between, mammalian species.

Conclusions

The finding that the fatty acid composition of membranes varies in a systematic manner among species, coupled with the fact that fatty acid chains differ in their susceptibility to peroxidation, has provided a new window into understanding the mechanisms involved in aging and the determination of longevity. By knowing the fatty acid composition of lipids that constitute a membrane it is possible to calculate a peroxidation index for the membrane, which provides a indication of the susceptibility of the membrane to peroxidative damage. The maximum lifespan of mammals and birds is inversely correlated with this calculated peroxidation susceptibility. In a

diverse set of examples, variation in longevity within species has also been shown to be associated with differences in membrane fatty acid composition. These insights into the potential importance of membrane fatty acid composition for aging are expressed as the "membrane pacemaker" theory, a modification of the oxidative stress theory of aging. This new perspective emphasises that lipid peroxidation is a very important aspect of aging and that many of the products of lipid peroxidation can cause lipoxidative damage to other important cellular molecules (e.g. nucleic acids and proteins). Consequently, fatty acid composition of membranes may be an important aspect of general resistance to oxidative stress. The fatty acid composition of membranes may thus represent a missing link in our understanding of aging and the determination of longevity.

We know that membrane fatty acid composition is regulated, but have almost no idea of the regulatory mechanisms involved (for a brief discussion see Hulbert et al. 2005), nor how they differ between species. Moreover, I emphasise that the evidence cited in this review linking membrane composition to longevity is correlative. What is now needed are experiments to test if this link is actually causal. For example, the nematode *Caenorhabditis elegans* retains the FAT-1 gene, which produces a desaturase enzyme responsible for converting n-6 PUFA to the more peroxidation-prone n-3 PUFA. This enzyme is absent in higher animals. Use of RNAi to block this enzyme might result in a membrane composition with a reduced sensitivity to lipid peroxidation and consequently alter longevity. Such an experiment sorely needs to be done.

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