



SYMPOSIUM

Metabolism and longevity: Is there a role for membrane fatty acids?

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Synopsis More than 100 years ago, Max Rubner combined the fact that both metabolic rate and longevity of mammals varies with body size to calculate that “life energy potential” (lifetime energy turnover per kilogram) was relatively constant. This calculation linked longevity to aerobic metabolism which in turn led to the “rate-of-living” and ultimately the “oxidative stress” theories of aging. However, the link between metabolic rate and longevity is imperfect. Although unknown in Rubner’s time, one aspect of body composition of mammals also varies with body size, namely the fatty acid composition of membranes. Fatty acids vary dramatically in their susceptibility to peroxidation and the products of lipid peroxidation are very powerful reactive molecules that damage other cellular molecules. The “membrane pacemaker” modification of the “oxidative stress” theory of aging proposes that fatty acid composition of membranes, via its influence on peroxidation of lipids, is an important determinant of lifespan (and a link between metabolism and longevity). The relationship between membrane fatty acid composition and longevity is discussed for (1) mammals of different body size, (2) birds of different body size, (3) mammals and birds that are exceptionally long-living for their size, (4) strains of mice that vary in longevity, (5) calorie-restriction extension of longevity in rodents, (6) differences in longevity between queen and worker honeybees, and (7) variation in longevity among humans. Most of these comparisons support an important role for membrane fatty acid composition in the determination of longevity. It is apparent that membrane composition is regulated for each species. Provided the diet is not deficient in polyunsaturated fat, it has minimal influence on a species’ membrane fatty acid composition and likely also on its maximum longevity. The exceptional longevity of *Homo sapiens* combined with the limited knowledge of the fatty acid composition of human tissues support the potential importance of mitochondrial membranes in determination of longevity.

Introduction: a connection between longevity and metabolic rate

Body size is of fundamental importance for understanding the life history of a species because so many aspects of the biology of an animal are related to its size. This is especially true for time-related parameters and a good case can be made that there is a “relativity of time” in biology related to body size. It has been long known that an animal’s speed of energy turnover (its metabolic rate) and its total time alive (its longevity) is related to its body size.

In a seminal step in the long search into what determines the distinctive maximum longevity of each mammalian species, Max Rubner (1908) combined

the metabolic rate and longevity of five different-sized mammals to calculate what he called “the life energy potential” for each of these species. The species he compared were guinea pigs, cats, dogs, cattle and horses and he calculated that these very different-sized mammals had a similar “life energy potential”. The average for his five species was ~800 kJ/kg. This was one of the earliest scientific and quantitative analyses of what might determine animal’s longevity and its conclusions agreed with the concept that things wear out with use and the faster they are used, the sooner they wear out. This concept was applied to animals as early as Aristotle (see Speakman 2005 for a short, enjoyable, historical perspective on the link between lifespan and metabolic intensity).

This perspective was supported by the finding that *Drosophila melanogaster* lived much longer when kept at low temperatures than when kept at high temperatures (Loeb and Northrup 1916) and, after Raymond Pearl published his 1928 book “The Rate of Living”, this idea was labeled the “rate-of-living” theory of aging (Pearl 1928).

When it was shown that free radicals were produced in living cells and that their levels were highest in the most metabolically active tissues (Commoner et al. 1954) it was also suggested that the long-known toxicity of oxygen was due to these free radicals (Gershman et al. 1954). Harman (1956) proposed that this production of free radicals from normal aerobic metabolism and the consequent damage constituted the physiological basis of aging. This was called the “free-radical” theory of aging. Later, after the enzyme superoxide dismutase (which converts the free radical superoxide to the non-radical hydrogen peroxide) was found to be both widely spread and highly conserved in organisms and also that some of the oxygen-derived reactive molecules that caused damage were not free radicals (e.g. hydrogen peroxide), the more generic term “reactive oxygen species” (ROS) was used in describing this theory of aging. The “free radical” theory of aging morphed into the “oxidative-stress” theory of aging. This is currently the most widely-accepted explanation for the aging process and a connection between the rate of aerobic metabolism of a species and its distinctive maximum longevity lies at the base of this theory.

That in endotherms there is some connection between the speed of metabolism and the length of life is illustrated in Fig. 1. Those endotherm species with a high mass-specific basal metabolic rate tend to have a short maximum lifespan. However, a couple of provisos are also obvious in this figure. Firstly, the relationship differs between mammals and birds. Secondly, there is considerable variation in the data, which suggests that it is not a very tight connection. For example, the dataset for mammals ($n = 267$) plotted in this figure shows statistically that variation in basal metabolic rate only explains about a quarter of the variation in maximum lifespan.

There are other reasons to suggest that the connection between metabolic rate and longevity is not a tight deterministic one. Both in rats and humans, it has been demonstrated that an elevated metabolic rate associated with substantial voluntary exercise throughout life does not shorten lifespan as would be predicted from a rate-of-living perspective (Holloszy et al. 1985; Lee et al. 1995). Similarly, within populations there is considerable

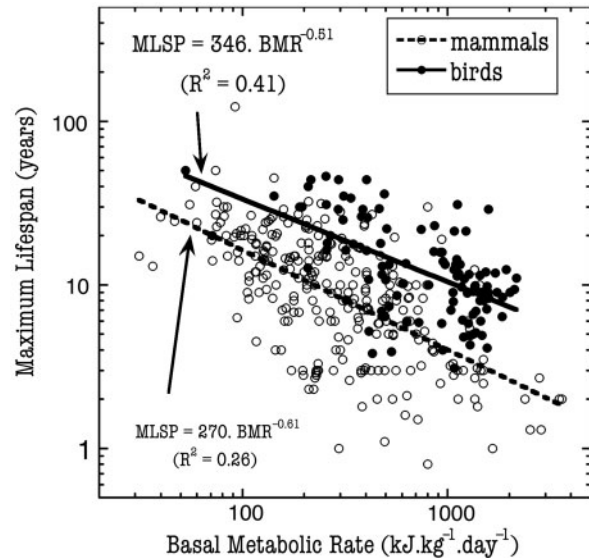


Fig. 1 The relationship between basal metabolic rate and maximum life span of birds and mammals (modified from Fig. 6 of Hulbert et al. 2007).

between-individual variation in both metabolic rate and longevity; however, there was no inverse relation observed between these two parameters in a captive population of mice (Speakman et al. 2000), nor in a laboratory population of *Drosophila melanogaster* (Hulbert et al. 2004). Dietary-restriction has been shown to extend longevity of rodents and many other species (Masoro 2002) and although it was originally thought that this effect might be due to a reduction in metabolic rate, this does not appear to be the case. Dietary restriction does not reduce the mass-specific metabolic rate of rats (McCarter et al. 1985) or *Drosophila melanogaster* (Hulbert et al. 2004).

Membrane fatty acid composition: a common link?

The early linkage by Rubner (1908), between the maximum longevity of mammalian species and the speed of their resting metabolism, centered around the fact that both metabolic rate and maximum lifespan varied with body size. The main processes that constituted the variation in resting metabolic rate were unknown in Rubner’s time. It has since become known that the variation in metabolic rate attributable to body size is partly due to the relative size of metabolically-active organs in differently sized mammals and partly to body-size-related differences in cellular metabolism. Furthermore, it is also now known that membrane-associated processes are major energy-consuming processes in cells and that

these membrane-associated processes also vary with body-size (see Hulbert and Else 2000, 2005 for reviews). Also unknown in Rubner's time was the fact that the fatty acid composition of cell membranes varied in a systematic manner with body size of mammals.

It is the purpose of this contribution to convince the reader that this systematic between-species variation in the fatty acid composition of membrane bilayers is a mechanistic link between the speed of metabolism and longevity, i.e., that (1) the fatty acid composition of membranes influences the speed of membrane-associated processes and consequently the cellular metabolic rate; and that (2) this variation in cellular metabolic rate, when combined with the relative size of the metabolically-active organs, determines the metabolic rate of the whole animal; that (3) the influence of membrane fatty acid composition on cellular metabolism is largely mediated by its influence on the physical properties of the membrane lipids surrounding membrane proteins, and that (4) the influence of membrane fatty acid composition on longevity is largely mediated by the chemical properties of these membrane fatty acids: namely, their differing susceptibilities to peroxidation and its consequences.

The first indication of a connection between membrane fatty acid composition and metabolic rate was the report by Gudbjarnason et al. (1978) that the docosahexaenoic acid content of cardiac phospholipids from mice, rats, rabbits, humans and whales was strongly correlated with their respective resting heart rates. As resting heart rate is a strong correlate of resting metabolic rate this suggested that membrane fatty acid composition might also vary with both resting metabolic rate and body mass of mammals. Later, it was shown that this was the case for a wide range of tissues and not restricted to the heart; that small mammal species had membrane lipids that were more polyunsaturated and less monounsaturated than those of large species (Couture and Hulbert 1995a) and furthermore; that the more polyunsaturated membranes of small mammals were also associated with "leakier" membranes and more active membrane pumps than in large species (Couture and Hulbert 1995b). It was proposed that highly polyunsaturated membranes were partly responsible (along with differences in organ size) for the high resting metabolic rate of small mammals. Similar correlations were observed in birds and this proposal was labeled the "membrane pace-maker" theory of metabolism. The evidence for such a link between membrane fatty acid composition and metabolic rate of different species has been discussed

elsewhere (Hulbert and Else 2000; Hulbert 2007) and the present contribution will concentrate on the potential connection between membrane fatty acid composition and longevity. It should be noted that variation in membrane composition is associated with variation in metabolic rate among species and that variation in metabolic rate within a species is not necessarily associated with differences in membrane fatty acid composition. For example, two recent studies show that differences in resting metabolic rate among mice are not associated with differences in membrane composition (Brzek et al. 2007; Haggerty et al. 2008).

Membrane peroxidation index and longevity: mammals, birds and bees

By definition, monounsaturated fatty acids have a single double-bonded carbon unit ($-C=C-$) per acyl chain while polyunsaturated fatty acid chains have "more" than one $-C=C-$ unit per acyl chain. Docosahexaenoic acid is the most polyunsaturated of the common fatty acids in mammalian membranes and has six such units along its 22-carbon hydrocarbon chain (it is commonly written as 22:6). In naturally occurring polyunsaturates, the $-C=C-$ units are all separated by a single bonded $-C-$ atom. The hydrogen atoms attached to each of these intermediate $-C-$ atoms are called *bis*-allylic hydrogens, and have the lowest C-H bond-energies of the fatty acid chain. This makes them the most susceptible to attack by ROS produced during aerobic metabolism (Halliwell and Gutteridge 2007).

This chemical difference between monounsaturates and polyunsaturates is important for the oxidative stress theory of aging because it means that polyunsaturates are susceptible to oxidative attack while monounsaturates are resistant to such oxidative damage. This is because polyunsaturates have *bis*-allylic hydrogen atoms but monounsaturates have none! Furthermore, the more polyunsaturated the fatty acid, the more *bis*-allylic hydrogens it has and consequently the more prone it is to oxidative attack by metabolism-produced free radicals. Docosahexaenoic acid (22:6), which has six double bonds and consequently five *bis*-allylic hydrogens per chain, is 320-times more susceptible to ROS attack than the common monounsaturated oleic acid (18:1) which has "no" *bis*-allylic hydrogens in its chain (Holman 1954). Thus, contrary to a common misconception, it is "not" just the presence of double-bonds in a mixture of fatty acids [(often quantified as the "double-bond index" (DBI) or "unsaturation index" (UI)] that will determine the

susceptibility of this mixture to oxidative damage, but rather the precise types of fatty acids present in the mixture and their relative abundance. Knowing the fatty acid composition of a membrane it is possible (by combining this composition with the relative susceptibility of individual fatty acids to peroxidation) to calculate its “peroxidation index”, or PI. This is a number that will approximately indicate the relative susceptibility of this membrane lipid mixture to peroxidative damage. The higher the number the more susceptible, the lower the value of PI, the more resistant to lipid peroxidation is the membrane bilayer. (For more details, and how to calculate PI, the interested reader is referred to Hulbert et al. 2007, p. 1181–2).

Lipid peroxidation is initiated when a metabolism-derived free radical with an unpaired electron ($R\bullet$) and enough energy attacks one of these *bis*-allylic hydrogens on a polyunsaturated lipid molecule (LH). It removes the hydrogen (and a single electron) from the fatty acid chain and leaves the carbon with an unpaired electron. Consequently, the polyunsaturated fatty acid chain thus attacked becomes itself a reactive molecule, a lipid C-centred radical ($L\bullet$), which is capable of combining with an oxygen molecule to become a lipid peroxy radical ($LOO\bullet$). Lipid peroxy radicals can become a lipid hydroperoxide ($LOOH$) by removing another *bis*-allylic hydrogen from another polyunsaturated fatty acid chain and, thus, in turn produce another lipid-centered C-radical ($L\bullet$) which can continue the cycle of lipid peroxidation. In this way, ROS attack on a membrane lipid bilayer (that contains polyunsaturated fatty acids) differs from ROS attack on other cellular molecules such as proteins, carbohydrates and nucleic acids. Whereas ROS attack on these other types of molecules will damage the molecule and likely stop them from performing their function, ROS attack on membrane polyunsaturates will damage the molecule (by converting it to a lipid hydroperoxide) and will also produce another reactive molecule that will in turn continue the oxidative damage to other molecules. Lipid peroxidation is a self-propagating autocatalytic process that will continue to produce several potent ROS until terminated (by either antioxidants or the combining of two free radicals—“pair-bonding” is rather old—even unpaired electrons do it!). The products of lipid peroxidation, such as lipid hydroperoxides, can also undergo fragmentation to produce a broad range of reactive intermediates (called propagators) that can modify proteins and DNA to produce “advanced lipoxidation endproducts” (ALEs) that no longer

perform their respective functions. For more details see Hulbert et al. (2007).

Membrane lipid peroxidation should not be perceived solely as a “damage to membranes” scenario but also as a significant endogenous source of damage to other cellular macromolecules, such as proteins and DNA (including mutations). In this way membrane fatty acid composition, and especially the relative abundance of the different polyunsaturated fatty acids in membrane lipids, can have significant effects on the oxidative damage to many and varied cellular macromolecules and, thus, to cellular function. This adds a sort of positive feedback loop to the standard scheme that normally constitutes the “oxidative stress” theory of aging, which has been labeled the “membrane pacemaker” modification to the oxidative stress schema and is diagrammatically described in Fig. 2.

If this “membrane pacemaker” proposal is valid, then the membrane fatty acid composition (or more specifically the “peroxidation index” or PI calculated from this membrane composition) of mammalian species should be inversely related to the species maximum lifespan. The data for the membrane fatty acid composition of phospholipids (=membrane lipids) from a variety of mammalian tissues is increasing and this is especially true for the phospholipids of skeletal muscle (e.g. Valencak and Ruf 2007). As can be seen from Fig. 3A, the PI of skeletal-muscle phospholipids from a wide range of mammalian species is inversely related to the maximum longevity of these species. Similarly, if the more limited dataset of fatty acid composition of liver mitochondrial phospholipids from different mammalian species is plotted against the maximum longevity of the species, there is also a significant inverse relationship (Fig. 3B).

In general, birds live much longer than similarly sized mammals although their resting metabolic rate is not dissimilar. This is illustrated in Fig. 1 which shows that while the maximum longevity of bird species tends to be shorter in birds with a higher metabolic rate, as it is in mammals, in birds the relationship differs from that observed in mammals, Bird species have a longer maximum lifespan than that expected for a mammalian species with the same metabolic rate. Although birds also show a relationship between membrane fatty acid composition and body size (Hulbert et al. 2002), the relationship is not identical to that observed in mammals. Interestingly, when the peroxidation index for membrane lipids from various bird species is calculated and plotted against maximum longevity, the data points obey the same relationship observed for

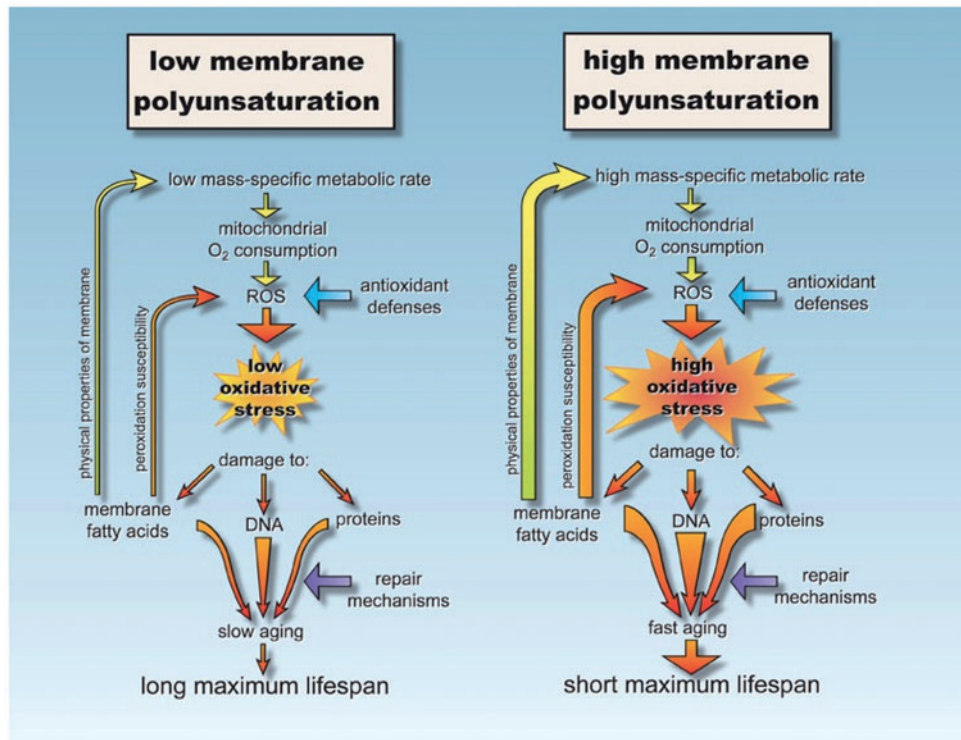


Fig. 2 Schematic diagram outlining the membrane-pacemaker modification of the oxidative-stress theory of aging. Two different examples are presented (low membrane polyunsaturation and high membrane polyunsaturation). The thickness of the arrows in each example represents the relative intensity of the process. (reproduced from Hulbert et al. *Physiol. Rev.* 2007, with permission from the Am. Physiol. Soc.).

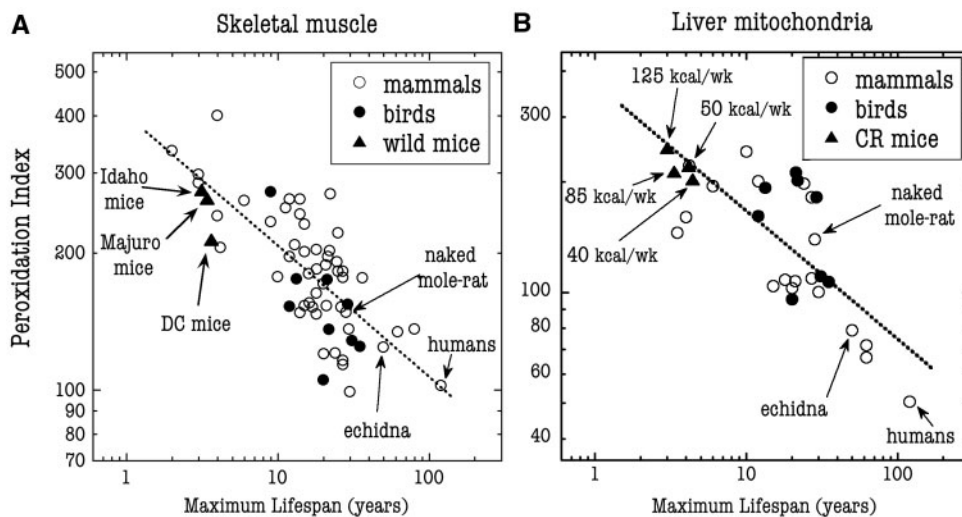


Fig. 3 The relationship between maximum life span of mammals and birds and the peroxidation index of skeletal muscle phospholipids (A) and liver mitochondrial phospholipids (B). The data points for skeletal muscle are combined from Valencak & Ruf (2007) and those cited by Hulbert (2005), while the data points for liver mitochondrial are combined from Pamplona et al. (1998) and those cited by Hulbert (2005). The data for the naked mole-rat are from Hulbert et al. (2006a) and those for the echidna from Hulbert et al. (2008). The data on peroxidation index of the mice strains (triangles) in A are from Hulbert et al. (2006b) and the data on life span are from Miller et al. (2002). The data on peroxidation index for the calorie-restricted mice (triangles) in B are from Faulks et al. (2006) while those on life span are from Weindruch et al. (1986).

mammals (Fig. 3). This suggests that membrane lipids of birds are less susceptible to peroxidative damage than membranes from similarly sized mammals but have essentially the same peroxidation susceptibility as mammalian species with the same maximum longevity.

As can be seen in Fig. 1, there is considerable variation in maximum longevity that cannot be explained by resting metabolic rate. Some species are exceptionally long-lived. For example, three mammalian species of different body size; naked mole rats (*Heterocephalus glaber*), short-beaked echidnas (*Tachyglossus aculeatus*) and humans (*Homo sapiens*), all have documented maximum lifespans that are several times that predicted from their body size. Of interest is that measurement of the fatty acid composition of their membrane lipids show them to have a less-than-expected content of polyunsaturates and more-than-expected content of monounsaturates for their respective body sizes, but the PI calculated for these respective membrane compositions is the same-as-expected for the species' maximum longevity (Hulbert et al. 2006a, 2007, 2008). The data points for these three exceptionally long-living species are identified in Fig. 3. Similarly, petrels are long-living, while fowl are short-living for birds and these birds also have differing membrane fatty acid compositions (Buttemer et al. 2008).

Just as there is variation in maximum longevity among species, there is also well-documented variation within species. This within-species variation can be of either natural-origin or experimentally-induced. An example of natural origin is the finding that some wild-derived strains of mice, when kept in the same environment and fed the same food, have delayed maturation and a significantly longer lifespan than a genetically-heterogenous laboratory strain (Miller et al. 2002). Comparison of the membrane fatty acid composition of skeletal muscle from these strains shows the more longevous wild-derived mice to have membrane lipids that are more resistant to lipid peroxidation (i.e. they have a lower PI) than are those of the shorter-living laboratory mice (Hulbert et al. 2006b). These data points are plotted and identified in Fig. 3A.

Dietary calorie-restriction (CR) was the first experimental treatment shown to extend longevity. It was first demonstrated in rats (McCay et al. 1935) but has since been shown to be effective in many other species and although it is still not known how it prolongs longevity, a common finding is that it reduces oxidative damage to tissues (Masoro 2002). As explained above, one means of reducing oxidative stress is to lessen lipid

peroxidation. The rate of *in vivo* lipid peroxidation is reduced in rats during CR (Matsuo et al. 1993) and Laganier and Yu (1987) first demonstrated that CR in rats altered fatty acid composition of membrane lipids and made them more peroxidation-resistant. Several later studies have confirmed this finding (see Hulbert et al. 2007). More recently it has been shown that the same changes in membrane fatty acids occur in mice and that this is an early effect, evident within one of CR (Faulks et al. 2006). These results for the mice are plotted in Fig. 3B against the maximum lifespan of other mice subjected to the same CR paradigm.

Honeybees provide another example of variation in longevity within a species. Female honeybees can be either long-living queens (with longevity measured in years) or short-living workers (with a lifespan of only weeks), depending on what they are fed (Winston 1987). Long-living queens have very low levels of polyunsaturation in their membrane lipids (and thus a low PI) throughout their life. Larvae of workers and newly emerged workers have a membrane fatty acid composition similar to that of queens (with a low PI); however, after the first week of life in the hive, the PI of the membrane lipids is substantially increased due to an elevated content of polyunsaturates (Haddad et al. 2007). This is likely due to the consumption of pollen (which has high content of polyunsaturates) by workers during this first week. Queens are never allowed to consume pollen, being fed mouth-to-mouth by worker bees throughout their life. These findings are illustrated in Fig. 4 and suggest that the connection between

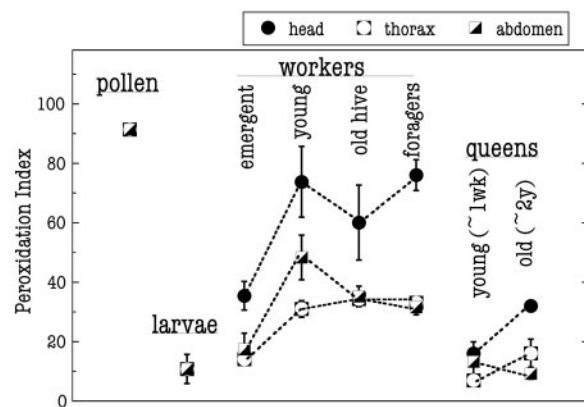


Fig. 4 A comparison of the peroxidation index (PI) of phospholipids from pollen and different life stages of the female honey bee (*Apis mellifera*). Data are from Haddad et al. 2007. Pollen values are for pollen collected from the legs of returning forager bees. Larval values are for whole larvae, while those for workers and queens are presented separately for head, thorax and abdomen. Error bars represent ± 1 SEM.

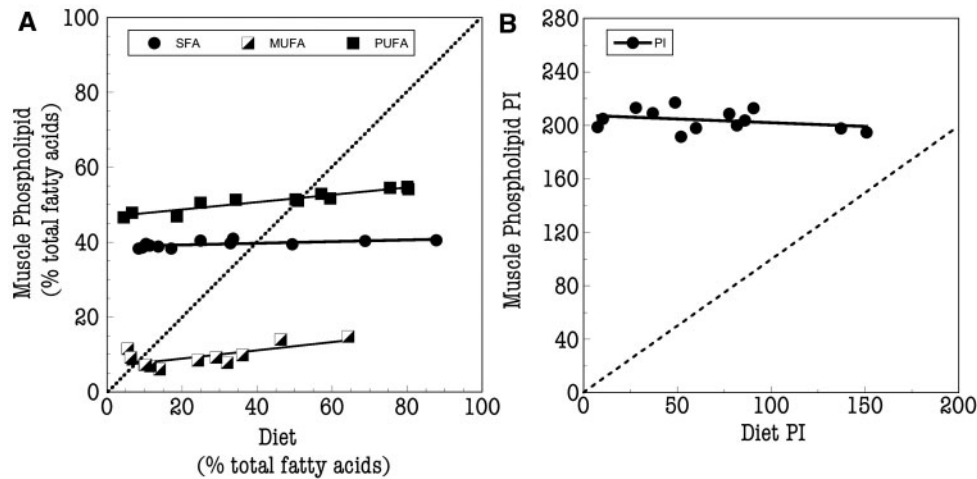


Fig. 5 The relationship between the fatty acid composition (A) and peroxidation index (B) of the diet and that of skeletal muscle phospholipids in the rat. Data are from Abbott et al. (2010). SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; PI = peroxidation index. Dashed line is the line of conformity (i.e. dietary values and those for muscle membrane composition are identical). Rats were fed the diets for 8 weeks; diets had 25% energy as fat. The diets were identical in every respect except for their fatty acid profile.

membrane fatty acid composition is not restricted to vertebrates.

Membrane fatty acid composition is regulated: diet has limited influence

Membrane fatty acid composition appears to be a genetically-regulated parameter, specific for each particular species, although we have minimal understanding of the mechanisms responsible. This is supported by the observation that strains of mice differing in longevity have different membrane fatty acid composition even though maintained throughout their entire life in the same environment and fed the same diet (Miller et al. 2002; Hulbert et al. 2006b). This statement needs to be made with the condition “provided they are supplied with an adequate diet”.

While animals are able to synthesize saturated and monounsaturated fatty acids from non-lipid sources, this is not the case for polyunsaturated fatty acids. Neither omega-3 nor omega-6 polyunsaturates can be synthesized by higher animals and thus are required pre-formed in the diet. They are not required in large amounts but both are essential nutrients. (In humans it is estimated that a combined intake of ~2.7% of the total energy intake is adequate) (ISSFAL 2004). As animals eat other organisms (which all have membranes and thus lipids) they generally consume enough fats. It is not often appreciated that even food that doesn't have obvious fat stores generally has enough lipids

to satisfy minimum essential requirements. For example, spinach is a good source of polyunsaturated fatty acids and even dried grass has fats.

Experimentally, we can vary the relative abundance of the different sorts of fatty acids in the diet and examine the effect of this dietary variation on membrane composition. This has been done recently in rats (Abbott et al. 2010) and the results for skeletal muscle phospholipids are presented in Fig. 5. What can be seen from this figure (Fig. 5A) is that, despite substantial variation in dietary fatty acid composition, the fatty acid composition of muscle membrane lipids (i.e. muscle phospholipids) is relatively constant. Furthermore, although there was significant variation in the PI calculated for dietary fats, there was little difference in the PI of membrane lipids of the rats fed the different diets (Fig. 5B). This is not restricted to muscle membrane lipids, as it is also observed for the membrane lipids of other tissues (SK Abbott, PL Else and AJ Hulbert, unpublished findings). In other words, membrane fatty acid composition is regulated and diet (as long as it has the minimum essential requirements) in general has limited influence on membrane composition. (This is not true for the balance between omega-3 polyunsaturates and omega-6 polyunsaturates because acyltransferase enzymes responsible for controlling membrane composition cannot differentiate between these two types of polyunsaturates but that need not concern us here and is discussed in more detail in Abbott et al. 2010).

The special case of human longevity: insights for animal longevity?

For our body size, we humans should expect to have a maximum lifespan of about 25 years. Yet, like the naked mole rat and the echidna, the maximum longevity of our species is about four times that predicted from body mass. Indeed, the largest extant land mammal, the elephant has a maximum longevity of about 80 years and until recently the most reliable record for the longest-living mammal was for a French woman who lived for 122 years (Carey and Judge 2000). This record was recently exceeded when a bowhead whale harvested by Eskimo hunters was found to contain harpoon fragments produced in the early 1880s and the whale was estimated to be at least 130 years old (George and Bockstoe 2008).

As noted earlier, these three exceptionally long-living mammalian species (naked mole rats, echidnas, humans) all have membrane fatty acid compositions that are relatively peroxidation-resistant for the size but what one would predict for the maximum lifespan (see Fig. 3). However, humans differ from the other two exceptionally long-living mammals. Both naked mole-rats and echidnas have basal metabolic rates that are ~40% lower-than-predicted for their body mass (O'Connor et al. 2002; Hulbert 1980). These reduced metabolic rates cannot “fully” explain the exceptional longevity of these species from a rate-of-living perspective (but can explain “part” of it) and they are compatible with their measured membrane fatty acid composition. Humans, however, have a basal metabolic that would be predicted for a typical mammal of their body mass. For both naked mole-rats and echidnas, the fatty acid composition of liver mitochondrial membranes is essentially the same as that measured for total liver phospholipids (Hulbert et al. 2006a, 2008). This is a common pattern among mammalian and avian species for which we have measured both mitochondrial and total tissue phospholipids (Brand et al. 2003; Hulbert et al. 2002; Porter et al. 1996). However, this may “not” be the case for humans. There is a limited dataset for fatty acid composition of tissues from normal healthy humans and I know of only one paper that reported the fatty acid composition of human mitochondrial phospholipids (Benga et al. 1978). This is for liver mitochondria and differs from the reported fatty acid composition of total phospholipids from liver (Burke et al. 2001; Elizondo et al. 2007; Sekine 1995). The PI value (=51) calculated for mitochondrial phospholipids from human liver is substantially less than the

average of 194 calculated from the three studies reporting the fatty acid composition of total phospholipid extracted from the livers of healthy humans. Furthermore, the study describing the mitochondrial phospholipids did not report the presence of any omega-3 polyunsaturates while all three studies of total liver phospholipids reported the presence of omega-3 polyunsaturates, the average value of the three studies being omega-3 polyunsaturates were 17% of total fatty acids. Care should be exerted in drawing too firm a conclusion from comparison of these studies as mitochondrial and total phospholipids from human liver were not measured in the samples and all measurements were made in different laboratories (with a large variation in total phospholipid composition from the different laboratories). However, there exists the suggestion that humans differ from other species so far measured in that we regulate the fatty acid composition of our mitochondrial membranes differently from other cellular membranes (especially excluding omega-3 fats?). In this light it is of interest that the amount of ethane exhaled by humans relative to oxygen consumption is calculated to be much lower than that for other species (Hulbert et al. 2007). This is of interest because ethane is an end-product of the peroxidative degradation of omega-3 polyunsaturated fatty acids.

The insight that the exceptionally long-living species, *Homo sapiens*, potentially provides for understanding the mechanisms determining animal longevity, is that the fatty acid composition of mitochondrial membranes may be much more important than the composition of other cellular membranes.

A final comment regarding humans is also worthwhile. Studies of 2872 Danish twin pairs born between 1870 and 1900 show that the heritability of longevity in humans is ~0.25 (Herskind et al. 1996). This means that the children of long-living parents likely have inherited biochemical characteristics that differ from the children of shorter-living parents, and are associated with longevity. It was recently reported that the children of nonagenarians have erythrocyte membrane fatty acid composition that is more peroxidation-resistant than that of matched controls (Puca et al. 2008b), an interesting finding. The recent review by Puca et al. (2008a) on human longevity has highlighted the importance of lipid metabolism in the slow aging of humans.

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