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Membranes and the setting of energy demand

Abstract

In his classic 1961 book, *The Fire of Life*, Max Kleiber presented a critique of the theories advanced to explain the BMR-body size relationship. One of the theories he dismissed was that the chemical composition of animals varies with body size. Since this time, however, much has been learned about the make-up of BMR in different animals as well as the chemical composition of different-sized animals. Specifically, in recent years it has become obvious that mammal species and bird species do vary in chemical composition in a systematic manner associated with the body size of the species. Small mammal and bird species have cellular membranes that are predominantly polyunsaturated, and as mammal and bird species increase in size, their cellular membranes become progressively less polyunsaturated. Since Kleiber's time, it has also become obvious that a substantial amount of the energy turnover of BMR is associated with the activity of membrane processes, specifically the maintenance of trans-membrane gradients, such as the Na⁺ gradient across the plasmalemmal membrane and the H⁺ gradient across the mitochondrial inner membrane. The variation in both membrane composition and membrane processes associated with body size variation in metabolic rate has been combined in the 'membrane pacemaker' theory of metabolism. This theory proposes that: (1) membrane-associated activities are significant and dominant components of BMR; (2) when BMR varies among species, all the activities that constitute BMR vary in unison; (3) species with high mass-specific BMR have highly polyunsaturated membranes while those with low BMR have less polyunsaturation of their membranes; (4) highly polyunsaturated membranes have distinctive physical properties that cause the proteins in the membranes to have a high molecular activity, and this results in higher rates of metabolism of cells, tissues and, consequently, the whole animal. Evidence supporting this theory is both correlative and experimental. Manipulation of membrane composition changes the molecular activity of membrane proteins. These differences in membrane composition may also represent a link between metabolism and aging. They probably explain the lifespan-body size relationship in mammals and birds and also the mammal-bird difference in lifespan.

Keywords

Membranes, setting, energy, demand

Disciplines

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Review

Membranes and the setting of energy demand

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Summary

In his classic 1961 book, *The Fire of Life*, Max Kleiber presented a critique of the theories advanced to explain the BMR–body size relationship. One of the theories he dismissed was that the chemical composition of animals varies with body size. Since this time, however, much has been learned about the make-up of BMR in different animals as well as the chemical composition of different-sized animals. Specifically, in recent years it has become obvious that mammal species and bird species do vary in chemical composition in a systematic manner associated with the body size of the species. Small mammal and bird species have cellular membranes that are predominantly polyunsaturated, and as mammal and bird species increase in size, their cellular membranes become progressively less polyunsaturated. Since Kleiber's time, it has also become obvious that a substantial amount of the energy turnover of BMR is associated with the activity of membrane processes, specifically the maintenance of trans-membrane gradients, such as the Na⁺ gradient across the plasmalemmal membrane and the H⁺ gradient across the mitochondrial inner membrane. The variation in both membrane composition and membrane processes associated with body size variation in metabolic rate has

been combined in the 'membrane pacemaker' theory of metabolism. This theory proposes that: (1) membrane-associated activities are significant and dominant components of BMR; (2) when BMR varies among species, all the activities that constitute BMR vary in unison; (3) species with high mass-specific BMR have highly polyunsaturated membranes while those with low BMR have less polyunsaturation of their membranes; (4) highly polyunsaturated membranes have distinctive physical properties that cause the proteins in the membranes to have a high molecular activity, and this results in higher rates of metabolism of cells, tissues and, consequently, the whole animal. Evidence supporting this theory is both correlative and experimental. Manipulation of membrane composition changes the molecular activity of membrane proteins. These differences in membrane composition may also represent a link between metabolism and aging. They probably explain the lifespan–body size relationship in mammals and birds and also the mammal–bird difference in lifespan.

Key words: basal metabolic rate, lifespan, membrane lipid, sodium pump, docosahexaenoic acid.

Introduction

According to geometry, as objects of the same shape increase in size, their surface area will increase in proportion to the 2/3 power of their volume. In other words, if two objects have the same shape and density but one has twice the mass of the other, the surface area of the larger object will only be 59% greater and not double that of the smaller object. This relationship between relative surface area and size of similar shaped objects permeates biology and the understanding of animal function. For example, Sarrus and Rameaux (1839, cited by Kleiber, 1961) used this relationship to propose that if different-sized mammals are to maintain the same body temperature then the heat production (i.e. metabolic rate) of different mammals should be proportional to surface area and not body mass. This described the 'surface law' of metabolism, which Rubner (1883) experimentally tested

by comparing the heat production at 15°C of dogs ranging in body mass from 3 to 31 kg. He found that the heat production of his dogs was more constant when expressed per m² of body surface area than when expressed per kg body mass. Later Krogh (1916) suggested the use of a more empirical approach to examine the relationship between metabolic rate and body size of animals. Had Rubner used such an approach he would have found that heat production=142×mass^{0.61} (where heat production is in kcal day⁻¹ and mass in kg) was the relationship that best described his findings.

BMR and body size among mammal species

Since the metabolic rate of endothermic animals increases in

the cold, as well as during activity, during growth, and when processing a meal, a number of standard conditions were proposed to be necessary in order to validly compare the metabolic rate of individual animals. These conditions resulted in the concept of basal metabolic rate (BMR), which is the metabolic rate of a resting, fasted adult in a thermoneutral environment. In 1932, two North American groups independently published compilations of the BMRs of a range of endothermic vertebrates that varied greatly in body size (Kleiber, 1932; Brody and Procter, 1932). Considering that the precise mix of species differed between the two studies, these compilations gave remarkably similar equations describing the relationship between BMR and body mass. These were $BMR = 74.1 \times \text{mass}^{0.739}$ (see Kleiber, 1961) and $BMR = 70.5 \times \text{mass}^{0.734}$ (see Brody, 1945) (where BMR is in kcal day^{-1} and mass in kg).

Since these early studies, there have been many other such BMR compilations for various groups of animal species and most have obtained similar results. In some studies, the allometric exponent has been similar to that obtained by these early studies but the constant before the body mass term has differed (this constant is the BMR of an animal of unit mass). For example, Dawson and Hulbert (1970) found the BMR of marsupials could be described by $BMR = 48 \times \text{mass}^{0.737}$ (where BMR is in kcal day^{-1} and mass in kg). This equation means BMR changes with body mass in marsupials in the same relative manner as for placental mammals (i.e. BMR increases by ~67% for every doubling of body mass). However, it also shows that marsupials have a BMR that is ~65% that predicted for a similar-sized placental mammal (i.e. 48/74, using Kleiber's equation).

Withers (1992) presented a summary of the equations obtained by many of these studies. His compilation gives an average exponent of 0.72 (range: 0.55–0.76) for inter-specific studies on mammals specifically, and an average exponent of 0.76 (range: 0.50–0.98) for interspecific studies in general. While there is much variation in the reported allometric exponents describing the relationship between metabolism and body size, for convenience, $\text{kg}^{3/4}$ was suggested as the unit of metabolic body size. (Note that in the days before electronic calculators, a definite advantage of using the 3/4 power was that it could be easily and rapidly calculated with a slide rule!) Hemmingsen (1960) suggested that the observed exponents are the result of an evolutionary struggle between two influences. The first is the tendency for metabolism to increase in direct proportion to mass as species increase in size, such that they are just bigger copies of the smaller version (i.e. exponent=1.0). The second is due to surface limitations constraining the acquisition of nutrients/gases and elimination of wastes/heat (i.e. exponent=0.67). The fact that many exponents approximate 0.7 suggests that surface limitations are the more powerful of these two influences. Such an approach can also explain the variation of exponent values for different groups, as it depends on the evolutionary history of the group being examined. For the current authors, Hemmingsen has provided the best explanation of the allometry of BMR with body size.

Allometry is a powerful mathematical technique that is used to empirically analyse relative change between two variables and has a long history in studies of growth and development (see Thompson, 1961) as well as metabolism. An advantage of the early metabolism studies, which were almost exclusively limited to laboratory and domestic species, is that they provided a basis for comparing the BMR later measured for a wide range of different species. For example, the conclusion that fish-eating seals have relatively high BMR values (Hurley and Costa, 2001) can be made by comparing their measured BMR against that predicted from allometric equations such as those of Kleiber. Similarly, fish-eating sea birds have high BMR values by comparison with similar allometric relationships (Ellis, 1984).

Body size and metabolic rate during a mammal's lifetime

The change in body size during an animal's life can be immense, and developmental changes in structure and metabolism can be analysed relative to this change in body size by allometry. Fig. 1 shows such an analysis for metabolic rate of the rat. The rat zygote has a mass-specific rate of metabolism the same as that of the adult rat (Adolph, 1983). The zygote can be thought of as 'a chip off the old block' (i.e. it has a mass-specific metabolic rate that is the average for the cells of the adult rat). Following conception, the mass-specific metabolic rate increases 3–4 times and remains at approximately this level until after birth. Following birth, mass-specific metabolic rate of the rat slowly decreases until about 100 g body mass, after which it decreases more rapidly until the adult rate is achieved (Kleiber, 1961; Adolph, 1983). These stages in the life cycle of the rat are shown in Fig. 1 and have allometric exponents of 1.23, 0.87 and 0.31, respectively. This means that for a doubling of body size, during each of these stages of the rat's life cycle, metabolic rate increases by 135%, 83% and 24%, respectively.

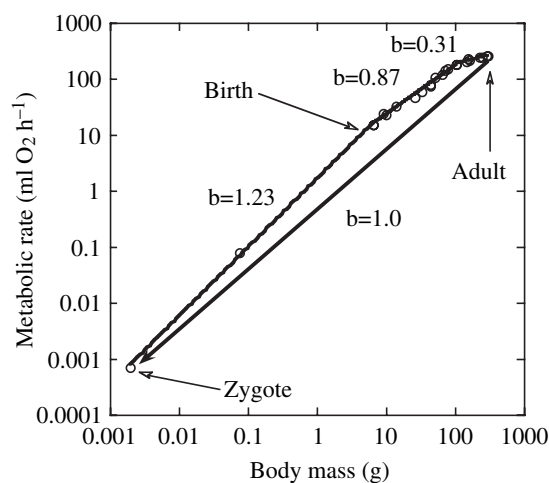


Fig. 1. Changes in the resting metabolic rate (at 37°C) of the rat during its life cycle. The value of the allometric exponent (b) is given for each section. Data are taken from Kleiber (1961).

The biphasic allometry of metabolic rate observed during postnatal growth in the rat has also been observed in a number of other mammals. For example, the metabolic rate of humans between birth and ~13 kg exhibits an allometric slope of 1.04, and after this size the allometric slope is 0.6 (Brody, 1945). Similarly, the metabolic rate of cattle between birth and 120 kg body mass can be described by an allometric relationship with an exponent of 0.82, and above this body mass the exponent is 0.6 (Brody, 1945).

Marsupials give birth to young that are very immature and much postnatal development takes place while the young are in the pouch. Indeed, pouch exit occurs at a stage of physiological development analogous to birth in placental mammals. In the tammar wallaby between 0.86 g and ~100 g body size, resting metabolic rate increases with an allometric slope of 1.02. Between ~100 g and adult body size (6–7 kg), resting metabolic rate increases with an allometric slope of 0.75. In this species, the total surface area of mitochondrial membranes follows the same developmental pattern, with biphasic allometric growth of some of the internal organs being the dominating influence on this pattern of development (Hulbert et al., 1991).

Thus during mammalian development several different allometric slopes describe the relationship between metabolic rate and body size.

What determines basal metabolic rate: energy supply or energy demand?

As described earlier, the metabolic rate of an individual mammal is highly variable and depends on whether the individual is physically active, processing a meal, or responding to a cold environment. At the level of the individual it is obvious that these natural and normal variations in metabolic rate are determined by the demand for energy to move, or heat to maintain body temperature, etc. Energy supply is adjusted to meet demand. The number of open capillaries within a tissue is modified according to demand, the pumping activity of the heart is modified according to demand and the physiological hunger drive to find food is modified to meet the individual's demand for energy. The homeostatic nature of the animal organism is that it changes over time in response to the demands placed upon it. The size of most organs of the body is not fixed but plastic, and they can change in size in response to the demand placed upon them. Tissue size is probably not a fixed genetic quantity but determined by the demand placed on the particular tissue.

The last 20 years have seen important changes in the understanding of the control of metabolism at the biochemical level. Metabolic control analysis has shown the previous paradigm of metabolic activity being controlled by a few 'rate-limiting' enzymes at the beginning of metabolic pathways to be a flawed anthropomorphic engineering perspective based on how we construct our own machines, and not a true description of natural systems (Fell, 1997). Control of flux through metabolic pathways is normally distributed over many steps in

a pathway and needs to be empirically measured to determine where the balance of control lies. Analysis of the control of supply of and demand for a metabolite shows that better homeostasis is achieved when greater flux control is exerted by the demand reactions, i.e. towards the end of the metabolic pathways (see Fell, 1997). For example, top-down metabolic control analysis of the energy metabolism of rat hepatocytes showed that the flux control coefficient of NADH producers was in the range of 0.15 to 0.3, while that of NADH users ranged from 0.7 to 0.85 (Brown et al., 1990). This suggests that even at the subcellular level, energy demand is a more important determinant of energy flow in the normal situation than is energy supply (2–6 times more important in this particular case).

Constraints due to the surface area/volume relationship, as mammals change in body size over evolutionary time, coupled with the fact that different-sized mammals have similar body temperatures (~37°C), dramatically illustrate the need for a pacemaker that can modulate BMR. Hemmingsen (1960) presented one of the more memorable examples to explain this need. The first mammals were the size of mice, and if such a mammal evolved to the size of a rhinoceros without changing its mass-specific BMR, then the larger mammal would need a surface temperature more than 100°C just to rid itself of the heat produced by its basal metabolism! Such considerations are not limited to heat production but also apply to limits in obtaining the materials needed to run aerobic metabolism.

Finally, if energy supply were the major determinant of BMR, then restriction of supply by dietary calorie-restriction should decrease resting metabolic rate. This treatment is known to extend lifespan in a wide range of species. However although it extends lifespan it does not do this by decreasing mass-specific metabolic rate either in rodents (McCarter et al., 1985) or insects (Hulbert et al., 2004a,b). In rodents, while calorie restriction decreases the total metabolic rate, it also reduces body size and consequently there is no reduction in mass-specific rate of metabolism.

Composition of BMR

Most of the metabolic activity associated with basal metabolism is associated with the major internal organs. For example, in humans, the liver, kidney, heart, brain and lungs in total constitute only about 7% of body mass but are responsible for approximately 70% of resting heat production (see Schmidt-Nielsen, 1990). While some of these organs (e.g. lungs and heart) make up a relatively constant proportion of body mass in mammal species of different size, others such as liver, kidney, and especially brain, constitute a smaller proportion of the total body mass of larger mammal species. The allometric exponents for lung, heart, liver, kidney and brain mass in mammals are, respectively, 0.99, 0.98, 0.87, 0.85 and 0.70 (Brody, 1945). This allometric variation in organ size partly explains the allometric variation in BMR of mammals.

The remaining part of the explanation for the allometric variation in BMR in mammals lies in the fact that mass-specific

tissue metabolic rate declines as the mammal species increase in body size. For example, mass-specific tissue respiration varies with allometric exponents of -0.21 and -0.11 , respectively, for liver and kidney slices of mammals (Couture and Hulbert, 1995a) and -0.07 and -0.10 , respectively, for brain and lung slices (Krebs, 1950). The exponent relating liver slice respiration rate to body size in mammals (i.e. -0.21) is very similar to the -0.20 that describes the relationship between body mass and the respiration rate of isolated hepatocytes of mammals (Porter and Brand, 1995). When these tissue size and mass-specific respiration rates are combined, the allometric exponents for total tissue respiration for liver, kidney, brain and lungs are, respectively, 0.66 , 0.74 , 0.63 and 0.89 . The conclusion is that the allometric variation in BMR of mammals is partly due to allometric variation in relative organ size and partly to allometric variation in cellular metabolic activity. The allometric variation in tissue metabolic intensity of mammals is also mirrored in allometric variation in the total surface area of mitochondrial membranes in tissues of mammals (Else and Hulbert, 1985).

Over the last couple of decades, the relative contribution of different cellular activities to BMR of mammals has been estimated. The relative contributions of the processes varies between tissues. When this is taken into account, it is estimated that in the laboratory rat, about 15% of the oxygen consumption of BMR is consumed by non-mitochondrial processes, about 20% is consumed by mitochondria for the mitochondrial proton leak and the remaining 65% is consumed by mitochondria for production of ATP (Rolfe and Brown, 1997). The ATP produced by mitochondria are used for the following processes: Na^+ pump activity (20–25%), protein synthesis (20–25%), Ca^{2+} pump activity ($\sim 5\%$), actinomyosin-ATPase ($\sim 5\%$), gluconeogenesis ($\sim 7\%$), ureagenesis ($\sim 2\%$), with the remainder including nucleic acid synthesis (Rolfe and Brown, 1997). While the data is most complete for the rat, it appears that the relative contribution to BMR of these various activities does not vary with body size in mammals (see Hulbert and Else, 2000).

Although skeletal muscle activity is not a large contributor to basal metabolic rate (unlike maximal metabolic rate), there are conflicting estimates of the importance of mitochondrial proton leak in the respiratory rate of resting muscle. Measurements of proton leak in the isolated perfused rat hindlimb suggested that it was a substantial contributor to resting metabolic rate of muscle (Rolfe and Brand, 1996). However, more recent measurements demonstrate that muscle mitochondria are well coupled *in vivo* in mice (Marcinek et al., 2004) and thus suggest that the importance of proton leak in resting skeletal muscle has been overestimated.

Membrane processes and body size

It has been a surprise to many that membrane-associated activities constitute so much of the cost of living in mammals. Two such processes have been particularly examined in different-sized mammal species. These are mitochondrial

proton leak and the activity of the plasma membrane-bound Na^+/K^+ -ATPase. Together, these two membrane-associated processes are responsible for about half of the BMR of mammals.

Liver mitochondrial proton leak varies among different-sized mammal species with an allometric exponent of -0.13 (Porter and Brand, 1995; see Fig. 2A). It has been estimated that two-thirds of this body-sized-related variation is due to differences in membrane surface area while the remaining one-third is related to differences in the composition of the liver mitochondrial membrane (Porter et al., 1996).

The activity of the sodium pump (in maintaining the trans-plasmalemmal Na^+ gradient) also varies with body size of mammals. In liver and kidney slices the allometric exponents describing these relationships are, respectively, -0.14 and -0.13 (Couture and Hulbert, 1995a; see Fig. 2B). A separate study of both the number of sodium pumps and the enzymatic activity of Na^+/K^+ -ATPase in kidneys from different-sized

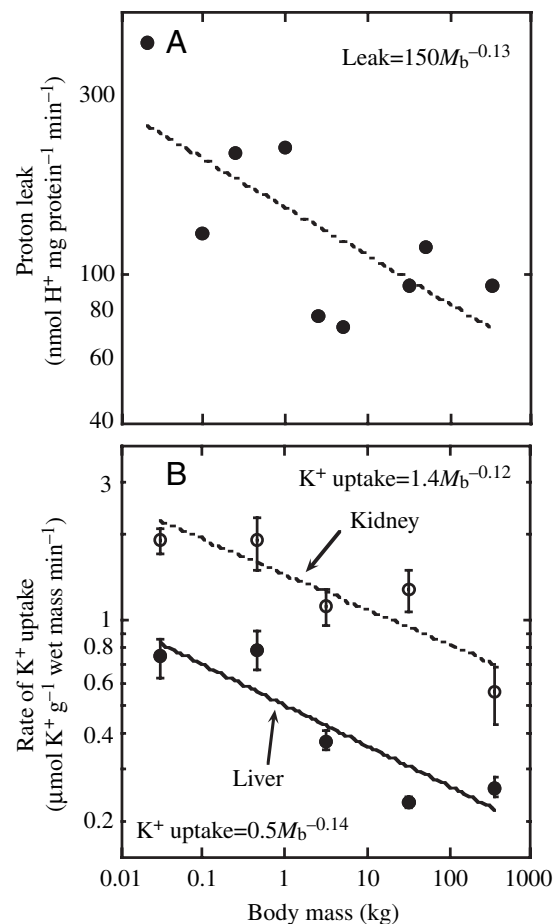


Fig. 2. (A) Allometric plot of the proton leak (at 170 mV and 37°C) in isolated liver mitochondria from mammal species differing in body mass (data are from table 1 in Porter et al., 1996). (B) Allometric plot of the activity of the Na^+ pump (at 37°C and expressed as K^+ uptake rate) in liver and kidney tissue slices from mammal species differing in body size. (Data from Couture and Hulbert, 1995a.) Values are means \pm S.E.M. The respective allometric equations are shown in each figure.

mammals shows that the tissue density of sodium pumps does not vary with body size in mammals, but enzyme activity does vary. When these two parameters are combined, the maximum enzymatic activity of individual sodium pumps can be calculated and it was shown that this decreased with body size in mammals with an allometric exponent of -0.10 (Turner et al., 2005). Combining all these results, it can be calculated that in mammals ranging in size from mice to cattle, the activity of the sodium pump in maintaining intracellular Na^+ homeostasis *in vitro* is $\sim 2\%$ of its maximal enzymatic activity.

The conclusion from the investigations of both of these membrane-associated processes were surprisingly similar. Both the plasma membrane and the mitochondrial membranes appear to vary in their leakiness with body size of the mammal species. In small species both of these membranes appear to be very leaky and their leakiness decreases with increasing body size. Not only does membrane leakiness decrease with increasing body size, but the activity of membrane-bound proteins also decreases as the body size of the mammal species increase. This suggests that membrane composition might vary with body mass.

Membrane composition and body size

Gudbjarnason et al. (1978) published a fascinating correlation between the heart rate of mammal species, ranging from whales to mice, and the relative content of the highly polyunsaturated docosahexaenoic acid (DHA) in their cardiac phospholipids. As heart rate is a strong correlate of mass-specific BMR of mammals, this represented the first suggestion that the composition of tissue membranes may vary with body mass in mammals. Intrigued by this finding, we further investigated whether membrane composition varied more generally with body mass in mammals (Couture and Hulbert, 1995b) and found this initial observation by Gudbjarnason represented a fundamental difference in the chemical composition of mammals related to body size.

No other aspect of the chemical composition of animal cells that has been investigated shows a systematic pattern relative to body mass. In a review of the acyl composition of mammalian phospholipids it

was found that there was a consistent pattern observed in heart, skeletal muscle, liver and kidney (Hulbert et al., 2002b). In phospholipids from all of these tissues, although the total percentage of unsaturated fatty acids did not vary significantly with body size, there was a statistically significant allometric decline in the unsaturation index of these phospholipids with increasing body size. This decline in the unsaturation index of the phospholipids (and thus membranes) in all four tissues was predominantly due to the fact that, as the mammal species increased in size, the DHA content of tissue phospholipids decreased. These relationships are presented in Fig. 3 and it can be seen that the allometric exponents describing DHA content ranged from -0.40 for skeletal muscle to -0.19 for liver. This pattern of decreasing DHA content of phospholipids and thus decreasing membrane polyunsaturation with increasing body size of mammal species is observed in subcellular membranes, reported for both mitochondrial membranes (Porter et al., 1996) and microsomal membranes (Turner et al., 2005) of different-sized mammal species. DHA is the most polyunsaturated of membrane fatty acyl chains, having six double bonds in each acyl chain. In skeletal muscle phospholipids, monounsaturated acyl chains increase in relative abundance with increasing body size while in other tissues it is the smaller, less polyunsaturated, acyl chains that increase in larger mammals (Hulbert et al., 2002b).

The only tissue that does not show the allometric variation in membrane composition is the brain. In this tissue membranes are very polyunsaturated (with high phospholipid DHA content), irrespective of the size of the mammal species. The possible reason for this has been discussed elsewhere

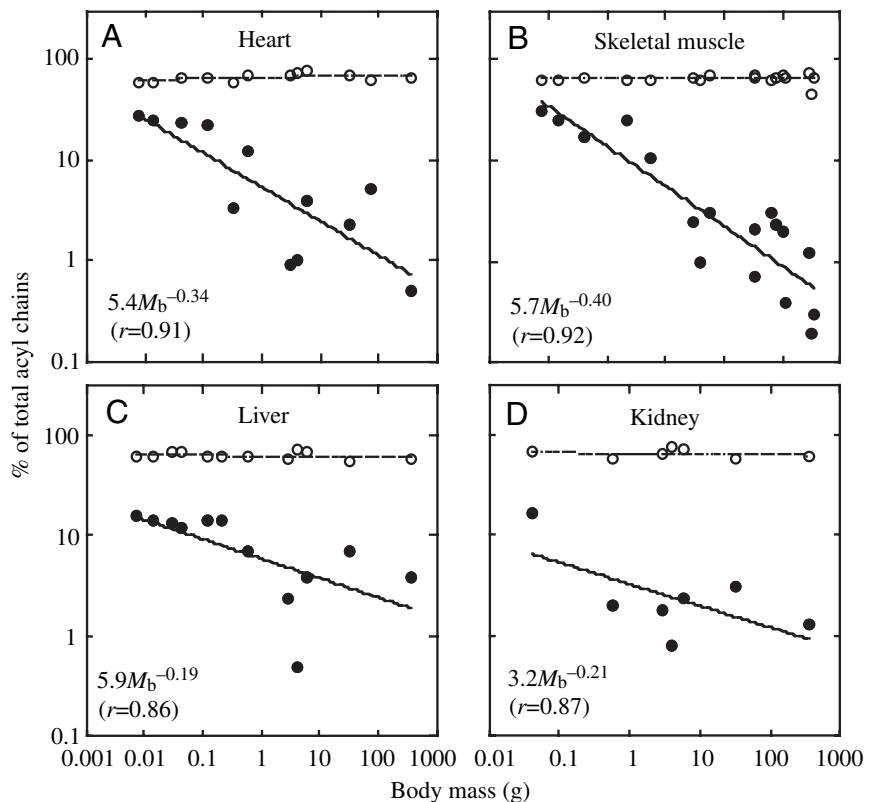


Fig. 3. Allometry of the fatty acyl composition in tissue phospholipids in mammals of different body mass. (A) Heart phospholipids, (B) skeletal muscle phospholipids, (C) liver phospholipids, (D) kidney phospholipids. Open circles represent the total percent of unsaturated acyl chains and filled circles the docosahexaenoic acid (DHA) content of the respective tissue phospholipids. All data are taken from Hulbert et al. (2002b). The allometric equation for the DHA data is shown in each panel.

(Hulbert and Else, 1999, 2000). This correlation of high DHA content with high metabolic activity is the basis of the membrane pacemaker theory.

Membrane pacemaker theory of metabolism

The membrane pacemaker theory of metabolism and evidence supporting it has been described in detail elsewhere (Hulbert and Else, 1999, 2000). It derives from both an examination of the allometric variation in mammalian BMR and the evolution of endothermic level of metabolism from an ectothermic metabolism, and can be summarised by a number of postulates. (1) Membrane-associated processes are both significant and dominant components of BMR; (2) when BMR varies among species, all the activities that makes up this metabolic rate vary in unison; (3) species with high mass-specific BMR have membranes that are predominantly polyunsaturated with especially high DHA content, while those species with very low mass-specific BMR have less polyunsaturated membranes, with a low DHA content; and (4) highly polyunsaturated membranes have physical properties that result in a high molecular activity of membrane-bound proteins, which results in high rates of membrane-associated activities and thus high rates of cellular metabolism, high metabolic rates of tissues and consequently the whole organism.

This final postulate is based on a number of findings. These include recent modelling of the dynamic motion of DHA in membranes (Feller et al., 2002) as well as strong correlations between the physical properties of natural phospholipid mixtures as measured in monolayers and the measured molecular activity of Na^+/K^+ -ATPase from these membranes (Wu et al., 2001). A lot of the evidence supporting the membrane pacemaker theory is correlational. For example, in a comparison of Na^+/K^+ -ATPase enzyme from kidney, heart and brain of different-sized mammal and bird species, there was an 18-fold variation in the molecular activity of this enzyme. There was a significant positive correlation between the molecular activity of this membrane-bound enzyme and the relative DHA content of the surrounding membrane (Turner et al., 2003). Direct evidence that membrane lipid composition can determine metabolic activity comes from experiments where membrane lipid composition has been altered and predictable changes observed in both Na^+/K^+ -ATPase activity (Else and Wu, 1999; Wu et al., 2004) and mitochondrial membrane proton permeability (Stillwell et al., 1997). Changes in membrane lipid composition will be likely to influence other membrane-bound enzymes as well. The membrane pacemaker theory has significant implications for the effect of dietary fat type on membrane and cellular function and consequently for the aetiology of some disease states, which have been discussed in more detail elsewhere (Hulbert et al., 2005).

Birds compared to mammals

While thus far we have confined discussion of the allometry of metabolism to mammals, it has long been known that similar

relationships also apply to birds. The membrane pacemaker theory was based on comparison of endotherms and ectotherms and also allometric studies of metabolism in mammals. In order to test this theory of metabolism, we recently also examined body composition, tissue composition and metabolism in bird species ranging from 13 g zebra finches *Taeniopygia guttata* to 34 kg emus *Dromaius novaehollandiae*. These studies have shown very similar allometric relations, as previously observed for mammals.

The respiration rate of isolated hepatocytes decreases allometrically with increasing body size in birds and the relative proportions of hepatocyte respiration devoted to mitochondrial proton leak, mitochondrial ATP production, Na^+ pump activity and non-mitochondrial processes is constant with changes in bird body mass (Else et al., 2004). This is the same situation as in mammals.

Liver mitochondrial proton leakiness is allometrically related to body mass in birds as it is in mammals (Brand et al., 2003). Both skeletal muscle phospholipids (Hulbert et al., 2002a) and liver mitochondrial phospholipids (Brand et al., 2003) are more polyunsaturated in small birds compared to large birds. This allometric trend is overwhelmingly due to a decrease in the DHA content of avian phospholipids with increasing body mass, as it is in mammals. The molecular activity of Na^+/K^+ -ATPase is strongly correlated with the DHA content of the membrane surrounding the enzyme in both birds and mammals of different body size (Turner et al., 2003). One difference between birds and mammals is that the ratio of n-3/n-6 polyunsaturates is consistently less in bird phospholipids than in those from mammals of the same body size. As in mammals, these allometric trends in membrane fatty acyl composition are present in all tissues examined but brain, which is highly polyunsaturated irrespective of body size (A. J. Hulbert, N. Turner, M. Brand and P. Else, unpublished observations).

Body size and lifespan: membrane pacemaker theory of aging

Maximum lifespan is a species characteristic, and like BMR is allometrically related to body mass in both mammals and birds. Polyunsaturated acyl chains are susceptible to lipid peroxidation and monounsaturates are peroxidation-resistant. DHA is the most peroxidation-prone of polyunsaturated acyl chains. The allometric trends in membrane fatty acyl composition described above, as well as the difference between birds and mammals, may explain the differences in lifespan between small and large mammal species, as well as the lifespan differences between birds and mammals. Detailed analysis of this proposal is beyond the current contribution but has been discussed previously (Hulbert, 2003). Such a proposal has been called the 'membrane pacemaker' theory of aging and it is described in detail, and evidence regarding it is extensively reviewed elsewhere (Hulbert, 2005).

Membrane fatty acyl composition is the only known difference in chemical composition of cells known to be related

to body mass in both mammals and birds. It is an intriguing possibility that it may be both the causal explanation for the difference in pace of life allometrically related to body mass, and also causally related to the maximum duration of life in different-sized mammals and birds.

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