

Basal Metabolic Rate: History, Composition, Regulation, and Usefulness

A. J. Hulbert^{1,2,*}

P. L. Else^{1,3}

¹Metabolic Research Centre, University of Wollongong, Wollongong, New South Wales 2522, Australia; ²Department of Biological Sciences, University of Wollongong, Wollongong, New South Wales 2522, Australia; ³Department of Biomedical Sciences, University of Wollongong, Wollongong, New South Wales 2522, Australia

Accepted 10/31/03

ABSTRACT

The concept of basal metabolic rate (BMR) was developed to compare the metabolic rate of animals and initially was important in a clinical context as a means of determining thyroid status of humans. It was also important in defining the allometric relationship between body mass and metabolic rate of mammals. The BMR of mammals varies with body mass, with the same allometric exponent as field metabolic rate and with many physiological and biochemical rates. The membrane pacemaker theory proposes that the fatty acid composition of membrane bilayers is an important determinant of a species BMR. In both mammals and birds, membrane polyunsaturation decreases and monounsaturations increase with increasing body mass and a decrease in mass-specific BMR. The secretion and production of thyroid hormones in mammals are related to body mass, with the allometric exponent similar to BMR; yet there is no body size-related variation in either total or free concentrations of thyroid hormones in plasma of mammals. It is suggested that in different-sized mammals, the secretion/production of thyroid hormones is a result of BMR differences rather than their cause. BMR is a useful concept in some situations but not in others.

A Brief History of Basal Metabolic Rate: From Where Did BMR Come?

The first recognition by a human that breathing was necessary for life certainly precedes recorded history. The scientific study

of animal respiration blossomed with the emergence of physiology in the eighteenth century and coincided with the investigation of chemical combustion. In 1766, Karl Scheele discovered oxygen gas and named it fire air; 2 years later, Joseph Priestley independently isolated the same gas, calling it dephlogisticated air. Antoine Lavoisier, regarded as the founder of modern chemistry, was born 10 years after the birth of Priestley and was guillotined 10 years before Priestley's death. Lavoisier disproved the phlogiston theory and showed that air was a mixture of nitrogen and the gas he named oxygen in 1777. Lavoisier should be regarded as the father of the basal metabolic rate (BMR). With his wife as a major collaborator, Lavoisier showed that animal respiration is the combination of oxygen from air with carbon and hydrogen from the animal's body (which he recognized came from the food) to produce water, fixed air (carbon dioxide), and heat. He showed that the rate of oxygen consumption was influenced by (1) the consumption of food, (2) environmental temperature, and (3) the performance of muscular work. Lavoisier measured the minimal metabolic rate in a resting postabsorptive state, which was probably the first measurement of BMR (Blaxter 1989; Lutz 2002).

In the twentieth century, the measurement of metabolic rate became an important part of the examination of bioenergetics and growth. The rate of metabolism of animals can be assessed by measuring a number of variables, including consumption of oxygen, production of carbon dioxide, and heat produced, as well as the difference between food consumed and wastes excreted. Because metabolic rate varies in response to a wide range of factors, to facilitate scientific comparisons, it became necessary to define a set of conditions for its measurement. This is the reason for the origin of the concept of BMR, which was believed to represent the minimum energy cost of living. BMR is the metabolic rate of an adult animal at rest in a thermoneutral environment and a postabsorptive state. Although it can be determined by measuring a number of variables, it is most commonly measured as the rate of oxygen consumption.

BMR represents the minimal cost of living rather than the heat required to maintain body temperature. This is most obvious from the fact that it is only at the lower critical temperature that BMR represents the heat required to maintain body temperature. At ambient temperatures greater than the lower critical temperature for a particular species, the heat produced from BMR is greater than that required for maintenance of an animal's body temperature, and this excess heat must be re-

* Corresponding author; e-mail: hulbert@uow.edu.au.

moved from the body by vasomotor-mediated increases in the thermal conductance.

In 1895, A. Magnus-Levy showed that secretions from the thyroid gland stimulated the metabolic rate of humans. Until the development of radioimmunoassays in the 1960s for the measurement of blood thyroid hormone concentrations, the measurement of BMR was an important clinical measurement used to assess thyroid status of individual humans. This clinical context was a major influence on the development of strict conditions for the measurement of metabolic rate and the refinement of the BMR concept during the twentieth century. During this period, BMR was also increasingly used to compare metabolic activity among various mammals and birds. However, the detailed conditions prescribed for the correct measurement of BMR of humans were not easily translated to the measurement of BMR in animals. Indeed, as pointed out by Blaxter (1989), in practice it is often easier to define the precise conditions for measurement of an animal's BMR than to achieve them.

The concept of standard metabolic rate (SMR) was also developed to analyze the bioenergetics of ectotherms. It is related to BMR and includes the specification of the temperature at which metabolic rate is measured, which is important information when comparing the metabolic rate of ectothermic animals.

BMR and Body Size

In a theoretical treatise concerning homeothermic animals, Sarrus and Rameaux (1838) proposed what was called the surface law, which suggested that like heat loss, the heat production of different-sized species should be related to surface area rather than body mass. In the mid-nineteenth century, Regnault and Reiset showed that resting oxygen consumption rates of endothermic mammals and birds were 10–100 times those of ectothermic reptiles and amphibians; they also noted that the mass-specific rate of oxygen consumption was smaller in larger species (Lutz 2002). Max Rubner (1883) tested this proposition by measuring the heat production of dogs ranging in size from 3 to 31 kg and showed that the values were more similar when expressed relative to body surface area than if expressed per unit of body mass (Schmidt-Nielsen 1972, p. 90). This was regarded as confirmation of the surface law of metabolism. A. Krogh (1916) suggested that a more empirical approach should be used to examine the relationship between metabolic rate and body size. In 1932, two independent empirical studies showed that the BMRs of different-sized mammals and birds were proportional to the 0.73 power of body mass (Brody and Procter 1932; Kleiber 1932) rather than the $2/3$ power of body mass as suggested by the surface law.

During the 1930s, Francis Benedict measured and published the BMR of a huge variety of animals, and this culminated in his famous mouse-to-elephant curve relating BMR to body

mass. This extensive data set did not essentially alter the 0.73 value for power function of body mass to which mammalian BMR was related. Like many scientists, Benedict found this relationship perplexing, and in his famous 1938 *Vital Energetics* monograph, he had a section titled "Futility of Attempts to Discover a Unifying Principle in Metabolism." In his classic review, Hemmingsen (1960) showed that when expressed at a constant temperature, the SMR of different-sized multicellular ectotherms was related to essentially the same power function of body mass as endothermic mammals and birds but at a lower level of metabolic activity. In later years, largely for mathematical ease, these empirically derived allometric exponents were approximated to $3/4$ (Kleiber 1961).

The expression of this relationship between BMR and body mass as a relatively simple power function has seduced several scientists over the years into attempting to explain it by some underlying physical theory. None have been successful, with the most recent being the supply-side fractal theory proposed by West et al. (1997). This recent attempt has been strongly argued against by the late Peter Hochachka and colleagues (Darveau et al. 2002; Hochachka and Somero 2002), who point out that metabolic rate (especially BMR) is not determined by supply constraints. A recent exposition of this fractal theory explanation (West et al. 2002) that expands it to cells and mitochondria has ignored much empirical data on tissues and isolated cells (e.g., Porter and Brand 1995) that do not support the theory. This exposition has also proposed a theoretical reason for the minimum size of adult mammals based on flow limitations through tubes, yet it ignores the fact that all mammals, during development from a fertilized zygote, must of course operate at body sizes less than this proposed theoretical lower size limit.

Probably the best explanation to date for the metabolic rate–body size relationship (at least to us) is the one proposed by Hemmingsen (1960). He suggested the observed exponents (and they are often very different in different groups of animals) result from an evolutionary struggle between two competing tendencies: (1) the tendency for metabolic rate to increase in direct proportion to body mass (i.e., mass to the power of 1.0) as bigger individuals are made as copies of smaller individuals and (2) the tendency for metabolic rate to be limited by surface constraints (i.e., mass to the power of 0.67) during changes in animal body size over evolutionary time. As pointed out by Hemmingsen (1960), if a rhinoceros had the same mass-specific BMR as a mouse, it would need a surface temperature close to that of boiling water to rid itself of the heat generated from its BMR! Such surface constraints are not restricted to loss of internal heat through the body surface of endotherms (as was initially argued in the early theoretical development of the surface law by Sarrus and Rameaux [1838]) but include the surface limitations associated with the uptake and excretion of nutrients, respiratory gases, and metabolic wastes and thus equally apply to ectotherms as well as endotherms. Hemmingsen's

“evolutionary struggle” in those groups of animals that change body size over evolutionary time can be resolved in a number of ways: by changes in mass-specific metabolic rate, by changes in the size and structure of surfaces involved with nutrient uptake, waste removal, and exchange of respiratory gases, and by combinations of any of these changes. Thus, rather than proposing an explanation based on a physical theory, this empirical “evolutionary” explanation implies that the simplification of the relationship to a $3/4$ power of body mass is a cruel trick of nature played on susceptible scientists, and this value represents the dominance of surface constraints over the evolutionary inertia for mass-specific metabolism to increase in direct proportion to body size. Such an explanation suggests that the relationship between BMR (or SMR) and body mass will vary significantly between different groups of animals, depending on their evolutionary history. On a very broad scale, the allometric exponent relating BMR (or SMR) to body mass approximates $3/4$; however, several authors have shown that within groups of related species, the observed allometric exponents are quite variable, ranging from $<2/3$ to ~ 1 (e.g., see Hemmingsen 1960, Fig. 9; Withers 1992, Table 4-5; Peters 1983, App. IIIa, IIIb).

During the development of mammals, there is a biphasic allometric relationship between body mass and metabolic rate (because these animals are growing, this is not, by definition, BMR). Until 20%–30% of adult body mass is reached, metabolic rate increases with an allometric exponent $>3/4$, and after this stage it increases with an allometric exponent ≤ 0.75 . In rats, cattle, and humans, the respective values are ~ 0.9 , 0.82 , and 1.04 followed by ~ 0.2 , 0.6 , and 0.6 , respectively (Brody [1945] 1974). In the macropod marsupial, *Macropus eugenii*, the initial allometric slope is 1.02 followed by 0.75 (Hulbert et al. 1991). A similar relationship has been described for the ontogeny of metabolism in an invertebrate, the isopod *Porcellio scaber* (Weiser 1984).

Although there has been considerable discussion over the evolutionary reasons (ultimate explanations) for the inverse allometric relationship between body size and mass-specific BMR, there is no argument that it exists. Until recently, there has been no underlying mechanistic reason (proximate explanation) for the relationship.

An intriguing finding has been that at least for mammals (where the data are most complete), BMR appears related to some other levels of metabolic activity with a relatively constant ratio irrespective of the size of the mammal species. If two parameters have the same allometric exponent with respect to body mass, then they have a constant stoichiometric relationship irrespective of body mass. For example, the field metabolic rate (FMR) of mammals (measured as CO_2 production by the doubly labeled water technique) is proportional to the 0.72 power of body mass (Nagy 1994). The relationship between FMR and body mass suggests that for mammals, on average, energy requirements of mammal species in the field are about

three times their BMR, irrespective of body size. In other words, the minimal cost of living in mammals (i.e., their BMR) averages about 30% of the normal energy turnover in the wild, irrespective of body size.

Similarly, within mammals, many physiological and biochemical rates vary with the same exponent as BMR (Topp et al. 1995). Some of these are illustrated in Figure 1, which shows that at the whole-animal level, the turnover of protein and various types of RNA exhibit essentially the same allometric slope as BMR and FMR. Similarly, ethane exhalation by mammals (which is a measure of the in vivo rate of peroxidation of omega-3 polyunsaturated fatty acids) varies with the same power of body mass as BMR. The fact that these biochemical and physiological rates vary with body mass to essentially the same power of body mass as BMR means that these processes constitute the same fraction of energy turnover in different-sized mammals. They have the same stoichiometric relationship with each other, even though the overall mass-specific BMR may vary dramatically (up to 100-fold). Similarly, although the resting oxygen consumption of isolated hepatocytes varies between mammals ranging in size from mice to horses, the relative proportions devoted to nonmitochondrial, mitochondrial proton leak, and mitochondrial ATP production are relatively constant (Porter and Brand 1995).

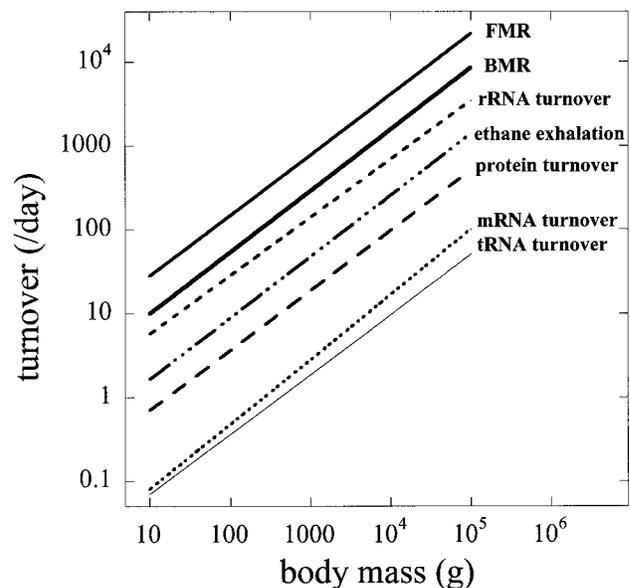


Figure 1. Relationships of field metabolic rate (FMR), basal metabolic rate (BMR), and a variety of biochemical turnover rates with body mass of mammals. The FMR relationship is from Nagy (1994); the BMR relationship is from Brody (1945); and the other relationships are from Topp et al. (1995). Units for FMR and BMR are kJ/d ; for rRNA turnover and ethane exhalation, units are nmol/d ; for protein turnover, unit is g/d ; and for mRNA and tRNA, turnover is expressed as $\mu\text{mol/d}$.

BMR of Endotherms and Ectotherms

It has been known for about a century and a half that the metabolic rate of endotherms is many times that of ectotherms. In an attempt to understand the basis of this difference, more than 20 years ago we began a series of experiments involving mammals and reptiles of similar body mass and body temperature (Else and Hulbert 1981). As with the body size variation in mammalian BMR, the sevenfold difference in BMR of these endothermic mammals and ectothermic reptiles is partly related to differences in the size of internal organs but more importantly is related to differences in cellular metabolism. For example, although the respiration rate of hepatocytes isolated from rats is about five times the respiration of lizard hepatocytes, the same relative proportions are devoted to non-mitochondrial processes, mitochondrial proton leak, and mitochondrial ATP production, and within the mitochondrial ATP production component, approximately the same proportion is devoted to maintenance of the transplasmalemmal Na^+ gradient by the sodium pump (Brand et al. 1991). This is illustrated in Figure 2. This severalfold difference in the rate of energy consumed for sodium pumping in the mammal compared with the reptile is associated with a similar difference in the relative "leakiness" of the mammalian cell compared with the reptilian cell (Else and Hulbert 1987).

Composition of BMR and the Membrane Pacemaker Theory of Metabolism

The relative importance of various activities in BMR has been most studied in the laboratory rat, but as stated previously, from what is known of the relative composition of BMR in other species, it seems to be similar in most other higher vertebrates. In their review, Rolfe and Brown (1997) concluded that ~10% of the oxygen consumed during BMR is consumed by nonmitochondrial processes, ~20% is consumed by mitochondria to counteract the mitochondrial proton leak, and the remaining 70% is consumed for mitochondrial ATP production. At a whole-animal level, ATP production can be divided into 20%–25% for Na^+ , K^+ -ATPase activity, 20%–25% for protein synthesis, ~5% for Ca^{2+} -ATPase activity, ~7% for gluconeogenesis, ~2% for ureagenesis, ~5% for actinomyosin-ATPase activity, and ~6% for all other ATP-consuming processes. These estimates are averages over the entire animal, and the relative contribution of the different processes varies between tissues. For example, it is estimated that although Na^+ , K^+ -ATPase activity constitutes only ~10% of cellular energy turnover in the liver, it is responsible for ~60% in brain and kidney (Clausen et al. 1991). It can be seen from these estimates that membrane-associated activities constitute a significant portion of resting metabolic activity (and thus BMR) in higher animals.

From both the endotherm-ectotherm comparison and the body size-related variation in metabolic activity, it can be con-

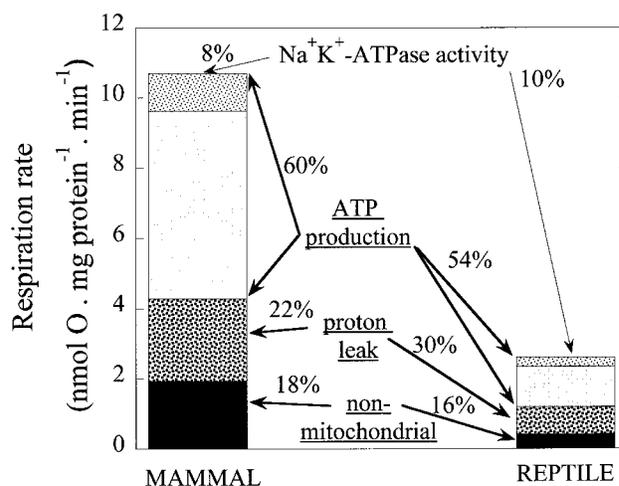


Figure 2. Absolute and relative composition of respiration rates (at 37°C) of hepatocytes isolated from the endothermic mammal *Rattus norvegicus* and the similar-sized ectothermic bearded dragon lizard *Amphibolurus* (= *Pogona*) *vitticeps* (data from Brand et al. 1991).

cluded that BMR has the same relative composition in animals that vary dramatically in their level of BMR. When BMR varies between species, a large number of processes seem to vary in unison. These conclusions led us to recently propose the membrane pacemaker theory as a mechanistic explanation of differences in BMR of higher vertebrates (Hulbert and Else 1999, 2000). This proposes that the lipid composition of membrane bilayers (specifically the degree of polyunsaturation/monounsaturations) influences the molecular activity of membrane proteins and consequently the metabolic rate of cells, tissues, and the whole organism. More detailed discussion of the effects of membrane lipid composition on molecular activity of membrane proteins is in Else et al. 2004 and others (e.g., Hulbert and Else 2000; Wu et al. 2001; Hulbert 2003). As can be seen in Figure 1, processes not directly associated with membranes (e.g., mRNA and tRNA turnover) also vary in proportion to overall variation in BMR.

The initial impetus to investigate the potential role of membrane composition in determining BMR was stimulated by the observation of Gudbjarnason et al. (1978) that the concentration of the highly polyunsaturated docosahexaenoic acid (DHA) in heart phospholipids (and thus heart membranes) was strongly correlated with heart rate in mammals ranging in size from mice to whales. We later showed that the higher metabolic rate of the rat compared with the lizard was also associated with a higher DHA content in their tissue phospholipids (Hulbert and Else 1989; Fig. 3). Similarly, the DHA content of tissue phospholipids was inversely related to body size in mammals ranging from mice to cattle (Couture and Hulbert 1995). In both comparisons, while the DHA content was greater in the species with the higher BMR, there was an

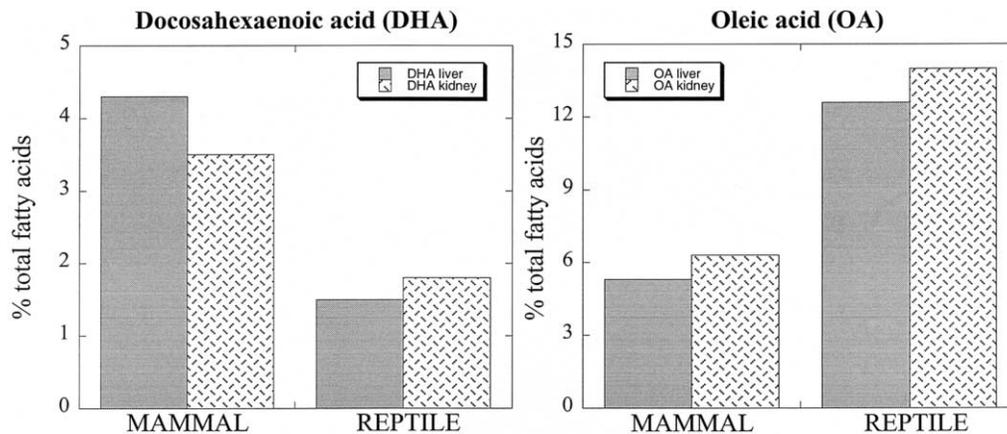


Figure 3. Relative composition of the polyunsaturate, docosahexaenoic acid (DHA) and the monounsaturate, oleic acid (OA) in liver and kidney phospholipids from the endothermic mammal *Rattus norvegicus* and the similar-sized ectothermic bearded dragon lizard *Amphibolurus* (= *Pogona vitticeps*) (data from Hulbert and Else 1989).

inverse relationship of BMR with the relative abundance of monounsaturated fatty acids such as oleic acid (OA) in the tissue phospholipids. In the mammal study, the only tissue that did not show a body size trend in fatty acid composition of its phospholipids was the brain, which had a high DHA content irrespective of body size.

The results for DHA and OA content of mammalian skeletal muscle phospholipids from a recent review (Hulbert et al. 2002b) are shown in Figure 4A. It can be seen that although the total unsaturated fatty acid content of phospholipids (and thus membranes) of mammalian skeletal muscle was relatively constant in mammals ranging from 7-g shrews to 370-kg cattle, there were declines in DHA content and increases in OA content with increasing body size. The DHA content of skeletal muscle phospholipids is proportional to the -0.40 power of body mass, which is a steeper relationship than the body mass–BMR relationship in mammals. In general, cellular composition does not seem to vary with body size in animals (Peters 1983), and thus this variation in the composition of membrane bilayers represents the greatest variation in cellular composition yet reported for mammals of different size.

In a recent study designed to test the membrane pacemaker theory, the fatty acid composition of skeletal muscle phospholipids of birds show a very similar relationship with body size (Hulbert et al. 2002a; Fig. 4B). In bird muscle, DHA content was related to the -0.28 power of body mass, which is very similar to the body size variation in BMR. As for mammals, this represents the greatest body size–related variation in cellular composition yet reported for birds.

The membrane pacemaker theory emphasizes the role of long-chain polyunsaturates in membranes in general and not only DHA. With respect to BMR, it proposes that membrane-associated processes are substantial contributors to BMR and that when BMR varies between animals, all the processes that

constitute BMR vary similarly. It proposes that the degree of polyunsaturation of membrane bilayers (especially but not only the DHA content of phospholipid membranes) importantly modulates the molecular activity of many membrane proteins (channels, pumps, receptors) and thus the metabolic activity of cells, tissues, and the whole organism.

Regulation of BMR and Thyroid Hormone Secretion Rate: Cause or Effect?

As described previously, it has been known for more than a century that thyroid hormones stimulate oxygen consumption and that the early development of the BMR concept was closely linked with its use as a measure of thyroid status of individual humans. An obvious question that arises from this observation is whether it is the rate of thyroid hormone secretion that determines BMR. A common method of assessment of the thyroid hormone secretion rate is to measure the rate of disposal of a small amount of exogenous radioiodine-labeled hormone. Because the blood levels of thyroid hormones remain relatively constant during such measurements, it can be assumed that the rate of disposal is equal to the rate of appearance of hormone in the blood. In the case of thyroxine (T₄), this is the rate of secretion from the thyroid gland, whereas in the case of triiodothyronine (T₃) it represents both the rate of secretion from the gland combined with the rate of peripheral production via the deiodination of T₄.

Tomasi (1991) has collated disposal rates of both T₄ and T₃ for a wide range of mammals and demonstrated that they are related to a power function of their body mass not dissimilar to that which describes the BMR–body mass relationship. These relationships are shown in Figure 5A. The secretion rate of T₄ in mammals is related to the 0.81 power of body mass, whereas

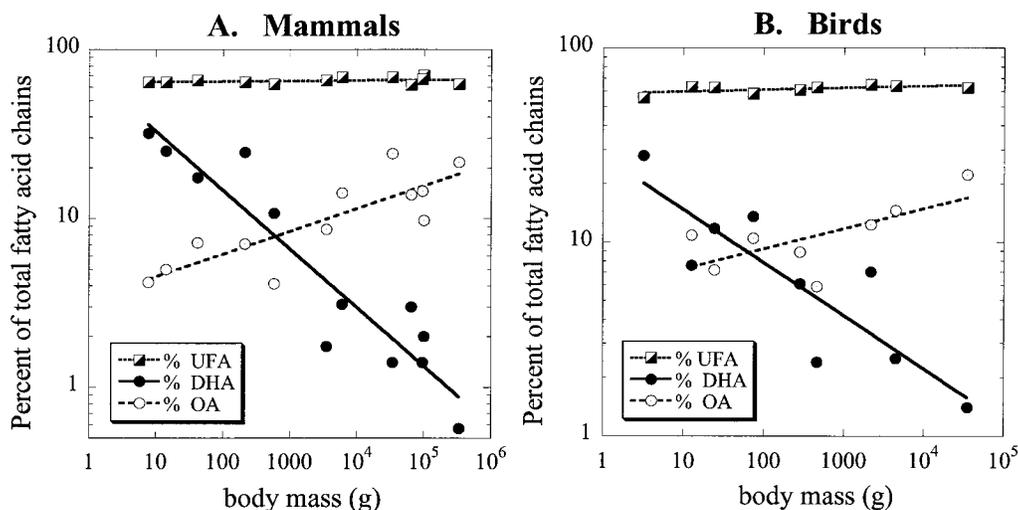


Figure 4. A, Relative concentration of total unsaturated fatty acids (*UFA*), the polyunsaturate, docosahexaenoic acid (*DHA*), and the mono-unsaturate, oleic acid (*OA*), in skeletal muscle phospholipids from different-sized mammals (data from Hulbert et al. 2002*b*). B, Relative concentration of total unsaturated fatty acids (*UFA*), the polyunsaturate, docosahexaenoic acid (*DHA*), and the monounsaturate, oleic acid (*OA*), in skeletal muscle phospholipids from different-sized birds (data from Hulbert et al. 2002*a*).

the secretion/production rate of T3 in mammals is proportional to the 0.74 power of body mass.

The fact that these parameters vary with approximately the same power of body mass says that there is a relatively constant stoichiometry between the consumption of oxygen and the disposal of these thyroid hormones. But what is cause and what is effect? Is the body size-related variation in BMR of mammals caused by the difference in thyroid hormone secretion/production rates, or is it vice versa? That is, are the differences in thyroid hormone secretion/production rates between different-sized mammals caused by differences in their BMRs? Assuming that there are no size-related differences in sensitivity to these hormones, then some insight might be obtained by examination of body-size differences in the plasma concentrations of these hormones. If the secretion/production of thyroid hormones in different-sized mammals is determining BMR, then we would expect that smaller mammals will have higher plasma levels of these hormones because this is the signal that cells will experience. As can be seen from Figure 5*B* and 5*C*, the plasma levels of both T4 and T3 (both “total” and “free” concentrations) do not vary with body mass in mammals and are not dissimilar to the range regarded as “euthyroid” in humans. This implies that differences in the secretion/production of thyroid hormones in different-sized mammals is an effect of, rather than the cause of, size-related differences in their BMRs. Another logical (but in our opinion, unlikely) possibility is that both BMR and thyroid secretion rate may vary in response to a third independent cause. In a similar manner, although the BMRs of endothermic and ectothermic vertebrate groups differ

manyfold, the “free” (unbound) levels of both T4 and T3 in their plasma is relatively similar (Hulbert 2000).

The thyroid hormone system can be viewed as a homeostatic system that maintains constant levels of these iodothyronines in the body. The relatively constant stoichiometry between energy turnover (oxygen consumption) and the metabolism (and thus removal) of the thyroid hormones is compensated by the secretion/production of equal amounts of these thyroid hormones. Such a view does not contradict the fact that changes in thyroid hormone concentration (as occurs after the acute injection of exogenous thyroid hormones) influence BMR but challenge the general perception of thyroid hormone secretion as a “regulator” of BMR. This different and provocative perspective concerning thyroid hormones and their effects, as well as other proposals (including that the BMR-stimulating effects of thyroid hormones are mediated by changes in the fatty acid composition of membranes), are discussed in more detail elsewhere (Hulbert 2000).

BMR: A Useful Concept?

The answer to this question must be both yes and no. It depends on the task at hand. To measure BMR is not particularly helpful if one is trying to precisely estimate the total food requirements of a species undergoing a particular activity. However, it is sometimes a useful concept if you are trying to estimate the increment in energy costs related to that activity. It has been particularly useful in comparing the rates of energy turnover in different-sized animals and thus examining the influence of body size on an animal’s physiology. We have found it partic-

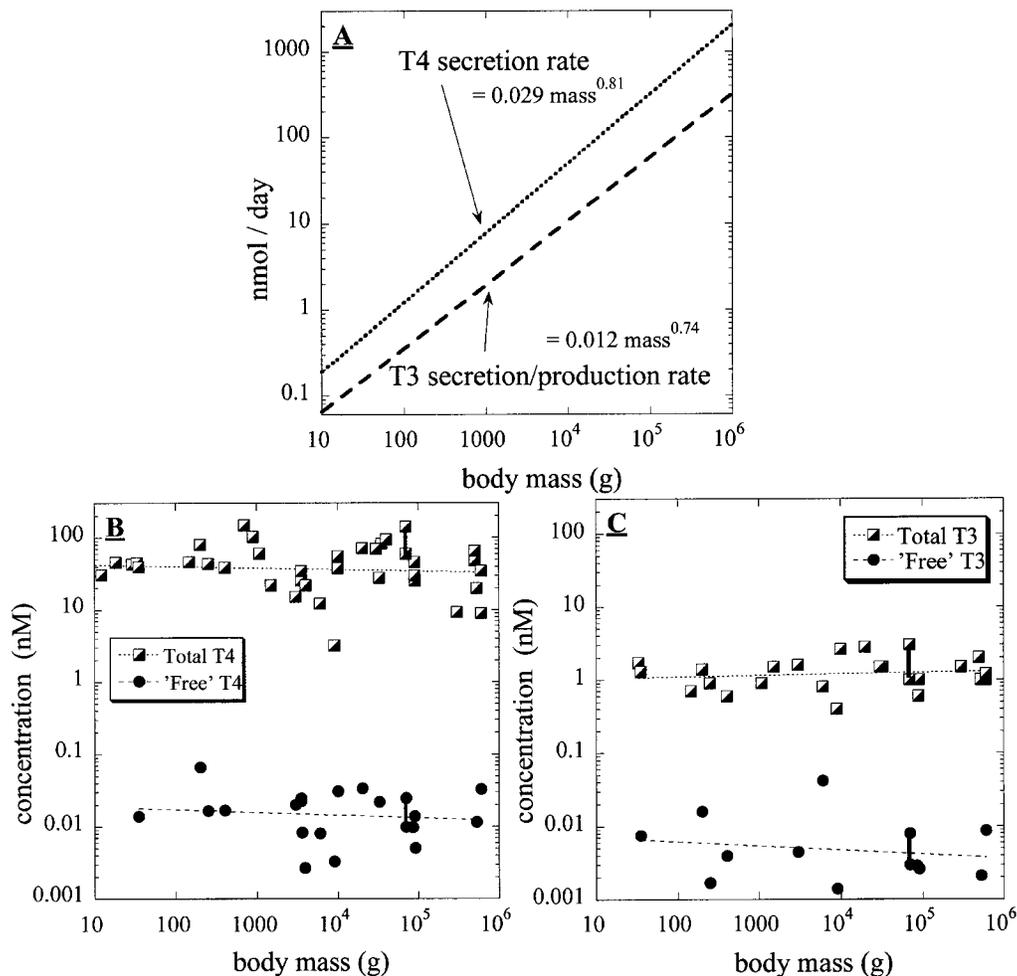


Figure 5. A, Relationship of thyroxine (T4) secretion rate and triiodothyronine (T3) secretion/production rate with body mass of mammals (redrawn from Tomasi 1991). B, Relationship of plasma concentration of total and “free” (unbound) thyroxine (T4) with body mass of mammals (data taken from Hulbert 2000). C, Relationship of plasma concentration of total and “free” (unbound) triiodothyronine (T3) with body mass of mammals (data taken from Hulbert 2000).

ularly useful in trying to dissect the underlying basis of the increase in metabolic rate associated with the evolution of endothermy in vertebrates. It has been fundamental in understanding the evolution of energy metabolism.

Perhaps the last words should be those of Brody ([1945] 1974, p. 59): “Basal metabolism is a convenient starting point for measuring the various heat increments as heat increments of: fever, feeding, lactating, gestating, working, keeping warm in cold weather, and so on.”

Acknowledgments

We are particularly indebted to enjoyable discussions over the years with colleagues and students, although obviously they cannot be held responsible for the views expressed here. For

some research reported here, we have been supported by grants from the University of Wollongong and the Australian Research Council.

Literature Cited

- Benedict F.G. 1938. *Vital Energetics*. Publication 503. Carnegie Institute, Washington, D.C.
- Blaxter K. 1989. *Energy Metabolism in Animals and Man*. Cambridge University Press, Cambridge.
- Brand M.D., P. Couture, P.L. Else, K.W. Withers, and A.J. Hulbert. 1991. Evolution of energy metabolism: proton permeability of the inner membrane of liver mitochondria is greater in a mammal than in a reptile. *Biochem J* 275:81–86.

- Brody S. (1945) 1974. *Bioenergetics and Growth*. Hafner, New York.
- Brody S. and R.C. Procter. 1932. Relation between basal metabolism and mature body weight in different species of mammals and birds. University of Missouri Agricultural Experimental Station Research Bulletin.
- Clausen T.C., C.V. Hardeveld, and M.E. Everts. 1991. Significance of cation transport in control of energy metabolism and thermogenesis. *Physiol Rev* 71:733–775.
- Couture P. and A.J. Hulbert. 1995. Membrane fatty acid composition of tissues is related to body mass of mammals. *J Membr Biol* 148:27–39.
- Darveau C.A., R.K. Suarez, R.D. Andrews, and P.W. Hochachka. 2002. Allometric cascades as a unifying principle of body mass effects on metabolism. *Nature* 417:166–170.
- Else P.L. and A.J. Hulbert. 1981. Comparison of the “mammal machine” and the “reptile machine”: energy production. *Am J Physiol* 240:R3–R9.
- . 1987. Evolution of mammalian endothermic metabolism: “leaky” membranes as a source of heat. *Am J Physiol* 253:R1–R7.
- Else P.L., N. Turner, and A.J. Hulbert. 2004. The evolution of endothermy: role for membranes and molecular activity. *Physiol Biochem Zool* 77:950–958.
- Gudbjarnason S., B. Doell, G. Oskardottir, and J. Hallgrímsson. 1978. Modification of cardiac phospholipids and catecholamine stress tolerance. Pp. 297–310 in C. de Duve and O. Hayaishi, eds. *Tocopherol, Oxygen and Biomembranes*. Elsevier, Amsterdam.
- Hemmingsen A.M. 1960. Energy metabolism as related to body size and respiratory surfaces and its evolution. Report of Steno Memorial Hospital, Nordisk Insulin Laboratory 9:1–110.
- Hochachka P.W. and G.N. Somero. 2002. *Biochemical Adaptation: Mechanism and Process in Physiological Evolution*. Oxford University Press, Oxford.
- Hulbert A.J. 2000. Thyroid hormones and their effects: a new perspective. *Biol Rev* 75:519–631.
- . 2003. Life, death and membrane bilayers. *J Exp Biol* 206:2303–2311.
- Hulbert A.J. and P.L. Else. 1989. The evolution of endothermic metabolism: mitochondrial activity and changes in cellular composition. *Am J Physiol* 256:R1200–R1208.
- . 1999. Membranes as possible pacemakers of metabolism. *J Theor Biol* 199:257–274.
- . 2000. Mechanisms underlying the cost of living in animals. *Annu Rev Physiol* 62:207–235.
- Hulbert A.J., S. Faulks, W.A. Buttemer, and P.L. Else. 2002a. Acyl composition of muscle membranes varies with body size in birds. *J Exp Biol* 205:3561–3569.
- Hulbert A.J., W. Mantaj, and P.A. Janssens. 1991. Development of mammalian endothermic metabolism: quantitative changes in tissue mitochondria. *Am J Physiol* 261:R561–R568.
- Hulbert A.J., T. Rana, and P. Couture. 2002b. The acyl composition of mammalian phospholipids: an allometric analysis. *Comp Biochem Physiol B* 132:515–527.
- Kleiber M. 1932. Body size and metabolism. *Hilgardia* 6:315–353.
- . 1961. *The Fire of Life*. Wiley, New York.
- Krogh A. 1916. *The Respiratory Exchange of Animals and Man*. Longmans Green, London.
- Lutz P.L. 2002. *The Rise of Experimental Biology: An Illustrated History*. Humana, Totowa, N.J.
- Magnus-Levy A. 1895. Über den respiratorischen Gaswechsel unter dem Einfluss der Thyroidea sowie unter verschiedenen pathologischen Zuständen. *Berl Klin Wochenschr* 32:650.
- Nagy K.A. 1994. Field bioenergetics of mammals: what determines field metabolic rates? *Aust J Zool* 42:43–53.
- Peters R.H. 1983. *The Ecological Implications of Body Size*. Cambridge University Press, Cambridge.
- Porter R.K. and M.D. Brand. 1995. Causes of differences in respiration rate of hepatocytes from mammals of different body mass. *Am J Physiol* 269:R1213–R1224.
- Rolfe D.F.S. and G.C. Brown. 1997. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol Rev* 77:731–758.
- Rubner M. 1883. Über den Einfluss der Körpergrösse auf Stoff- und Kraftwechsel. *Z Biol* 19:535–562.
- Sarrus F. and J. Rameaux. 1838. Rapport sur une mémoire adressé à l’Académie royale de Médecine. *Bull Acad R Med Paris* 3:1094–1100 (cited in Brody [1945] 1974).
- Schmidt-Nielsen K. 1972. *How Animals Work*. Cambridge University Press, Cambridge.
- Tomasi T.E. 1991. Utilization rates of thyroid hormones in mammals. *Comp Biochem Physiol* 100A:503–516.
- Topp H., M. Vangala, K. Kritzler, and G. Schoch. 1995. Assessment of lipid peroxidation in rats of different body weight by determining expired ethane. *Biol Chem Hoppe-Seyler* 376:691–694.
- Weiser, W.A. 1984. A distinction must be made between the ontogeny and the phylogeny of metabolism in order to understand the mass exponent of energy metabolism. *Respir Physiol* 55:1–9.
- West G.B., J.H. Brown, and B.J. Enquist. 1997. A general model for the origin of allometric scaling laws in biology. *Science* 276:122–126.
- West G.B., W.H. Woodruff, and J.H. Brown. 2002. Allometric scaling of metabolic rate from molecules and mitochondria to cells and mammals. *Proc Natl Acad Sci USA* 99(suppl. 1):2473–2478.
- Withers P. 1992. *Comparative Animal Physiology*. Saunders, Fort Worth, Tex.
- Wu B.J., P.L. Else, L.H. Storlien, and A.J. Hulbert. 2001. Molecular activity of Na⁺,K⁺-ATPase from different sources is related to the packing of membrane lipids. *J Exp Biol* 204:4271–4280.