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Review

Size relationship of metabolic rate: Oxygen availability as the "missing link" between structure and function?

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Dedicated to Professor Wolfgang Hemminger on the occasion of his 65th anniversary.

Abstract

The fact that the specific (mass-related) metabolic rate of living beings decreases with increasing body size, has intrigued biologists for a long time. Several attempts have been made to explain the "allometric" (non-proportional) size relationship of metabolic rate, ranging from the thermoregulatory "surface law" and the fractal branching of supply systems up to the mutual interplay of biochemical reactions in varying degrees of physical exercise. Only a few conditions are known where the metabolic size allometry is temporarily suppressed so as to help the smallest animals with the highest size-related metabolic rates (hibernators, neonates) to withstand periods of reduced oxygen and food supply. Remarkably, a similar metabolic size relationship is known to calorimetrists in that the specific heat production of cell suspensions or tissue samples decreases with increasing cell density or tissue diameter. This is known as the "crowding effect" and is usually explained by impaired diffusion conditions with increasing sample size. Thus, what results as a passive consequence of supply conditions in calorimetry, seems to have been established as an active metabolic adaptation in biology. In fact, recent paleobiological and perinatological evidence suggests that an increasing oxygen availability is not only a prerequisite for improved metabolic performance, but has to be followed by an elevated oxygen consumption to avoid toxic side-effects. Hence, the overall validity of metabolic size allometry (with the few exceptions being confined to conditions of reduced supply) might result from an "escape from oxygen" which urges cells to consume the more oxygen, the better they are supplied, even though, in the smallest animals with the best supply conditions, the resulting substrate demand might be difficult to meet.

Keywords: Body size; Metabolic rate; Allometry; Crowding effect; Oxygen supply

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1. Introduction: historical origin and biological importance of scaling laws

In his landmark monograph "Scaling: Why is animal size so important" [1], published in 1984, the comparative physiologist Knut Schmidt-Nielsen offered a comprehensive review of the size relationship of physiological functions in animals. He thereby continued what, some 20 years earlier, had been begun by Max Kleiber in his famous work "The fire of life" [2], and what had been closely related to progress in calorimetry. Nowadays, a further 20 years on, size relationship still attracts a great deal of interest in comparative physiology [3–6], and once again, insights from biocalorimetry might help us to understand one of the most intriguing facts about scaling laws, namely, their universality among living beings of whatever provenience and complexity.

1.1. Mathematical fundamentals

From the beginning of the 20th century when direct and indirect calorimetric measurements were being performed on an increasing number of animals of every size, researchers sought to deduce a general rule, allowing prediction of the basal metabolic (heat production or oxygen consumption) rate of a particular species from its body mass. Based on several earlier, rather qualitative descriptions of "biological similarity", a comparatively simple quantitative equation was finally introduced by Huxley [7], relating metabolic rate (R_M) – or any other physiological parameter – to body mass (m) in the following manner:

$$R_M = am^b \tag{1}$$

In this formula, when b equals 1, a proportional ("isometric") relationship between metabolic rate and body mass is expressed. When, however, b differs from 1 (which is usually the case), the size relationship deviates from proportionality and is called "allometric".

From a methodological point of view, the power function has the advantage that, when expressed in logarithmic terms, it results in a linear equation

$$\log R_M = b(\log m) + \log a \tag{2}$$

with the exponent (b) being transformed into the slope of the line. Thus, whenever metabolic or any other data are plotted on log scales, the slope of the resulting regression line (to body mass) reflects the exponent of the underlying scaling law.

Following a series of earlier papers by other authors [8,9], it was left to Kleiber [2,10,11] to describe the allometric size relationship of basal metabolic rate (R_{BM}) in mammals in its final form ("Kleiber's rule")

$$\log R_{BM}\left[\frac{\text{kcal}}{\text{day}}\right] = 0.75(\log m\,[\text{kg}]) + \log 70 \tag{3}$$

corresponding to the power functions

$$R_{BM}\left[\frac{\text{kcal}}{\text{day}}\right] = 70m\,[\text{kg}]^{0.75} \tag{4}$$

and, as expressed in SI units,

$$R_{BM}\,[\text{W}] = 3.4m\,[\text{kg}]^{0.75} \tag{5}$$

This means that the metabolic rate greatly deviates from mass proportionality and that, in comparing a mouse with an elephant which is 100,000 times larger than a mouse, the basal metabolic rate of the elephant is only some 10,000 times higher than that of the mouse (Fig. 1(a)). When the "specific" (i.e., size-related) basal metabolic rate is calculated by dividing the above equation by body mass

$$R_{BM}\left[\frac{\text{W}}{\text{kg}}\right] = 3.4m\,[\text{kg}]^{-0.25} \tag{6}$$

it turns out to be roughly 10 times lower in the elephant than in the mouse, reflecting the decrease in metabolic activity with increasing body size ("law of metabolic reduction") (Fig. 1(b)).

1.2. Physiological consequences

As far as single organs are concerned, it has been found that, as a rule, these are more or less proportional ("isometric") to body mass with respect to their own size whereas the allometric size relationship of body metabolic rate is reflected in their functional properties. For instance, the heart mass (m_h) is proportional to body mass (m_b) to the power of 0.98

$$m_h\,[\text{kg}] = 0.0058m_b\,[\text{kg}]^{0.98} \tag{7}$$

whereas the heart rate (f_h, being an important determinant of cardiac output) scales to body mass according to the formula

$$f_h\,[\text{min}^{-1}] = 241m_b\,[\text{kg}]^{-0.25} \tag{8}$$

Analogously, the lung volume (V_l) is proportional to body mass to the power of 1.06

$$V_l\,[\text{ml}] = 53.5m_b\,[\text{kg}]^{1.06} \tag{9}$$

whereas the breathing rate (f_{resp}) obeys the equation

$$f_{resp}\,[\text{min}^{-1}] = 53.4m_b\,[\text{kg}]^{-0.26} \tag{10}$$

This means that, whereas heart mass amounts to roughly 5.5–6.0‰ of body mass and lung volume to 50–55 ml/kg body mass, the "theoretical" heart rate varies from 600 to 30/min, and

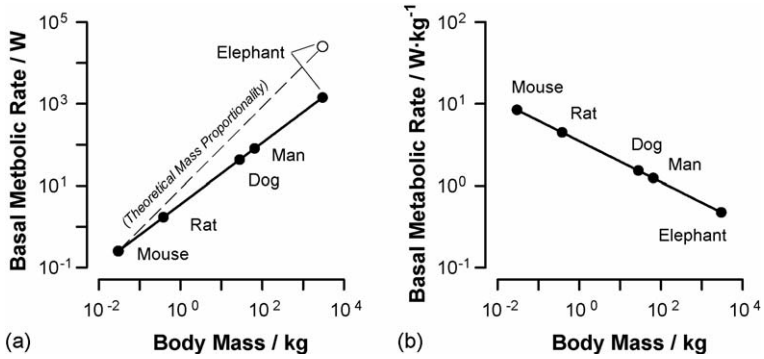

Fig. 1. Relationship between basal metabolic rate (BMR) and body size in mammals ("mouse-to-elephant curve"): starting from the mouse, the BMR of the elephant is lower than would be expected in the case of mass proportionality (a). This means that the "specific" BMR (per unit of body weight) decreases with increasing body size (b).

the breathing rate from 130 to 7/min, in a 30 g mouse and in a 3 ton elephant, respectively [1,12,13].

Remarkably, the allometric size relationship of metabolic rate holds true not only for the intact body and its organs, but also at the tissue, cellular, and even subcellular level (provided a common reference temperature is maintained). This was first shown by Krebs [14] who found the oxygen consumption rates in tissue slices from different organs to be higher in small than in large animals. A similar phenomenon was later observed in blood samples [15] where it seemed to reflect the higher red cell turnover rate in organisms of smaller size. And even in suspended mitochondria from different species [16], an increase in metabolic activity was found with decreasing body mass. Altogether, these findings suggest that the allometric size relationship is somehow "programmed" into cells although the factors that let them know whether they are in a small or large organism, are still unknown.

1.3. Ecological consequences

As far as adaptation to the environment is concerned, the allometric size relationship of metabolic rate results in a lower tolerance to starvation in smaller animals, displaying a higher energy expenditure in relation to their body fat stores than larger species [1,2]. A similar "shortening of biological time" has also been found at the tissue level in that, under conditions of interrupted blood perfusion, the resulting breakdown in heat production occurs much faster in samples from smaller than from larger animals [17,18]. Moreover, not only the tolerance to starvation or hypoxia, but also the life span is known to be shorter in smaller than in larger animals. Based on the fact that the product of specific metabolic rate and life span is more or less constant among species, it has even been assumed that mammals or birds possess a given "quantity of life" which is expended the faster, the smaller the animal is [19,20]. Although this kind of "ageing theory" is commonly regarded as an overinterpretation of scaling laws, both the limited survival time and the shorter life span of small as compared to large species illustrate to what extent the life conditions of animals may be affected by their body size.

2. Theoretical approaches to metabolic size allometry

The striking observation that the metabolic rate of animals was not proportional to body size, gave rise to a long-lasting discussion on the mechanisms governing metabolic rate in animals. The main emphasis of this discussion was placed on the 0.75 (3/4) exponent of the allometric size relationship as reflected by Kleiber's rule. To explain this exponent, three different approaches were followed.

2.1. "Surface law" of heat exchange

Due to the fact that most of the early calorimetric measurements had been performed in mammals, i.e., in homeothermic animals, the earliest explanation of metabolic size relationship, first given by Rubner in 1883 [21], dealt with heat balance. Following this explanation, generally known as "surface rule" and still widely referred to in physiological textbooks, smaller animals lose more heat through their larger surface-to-volume ratio and, thus, need a higher heat production rate to keep their body temperature constant than larger ones. However, there are two main objections against this thermoregulatory explanation.

Firstly, it has been found that the allometric size relationship of metabolic rates does not only apply to mammals and birds, but also to poikilothermic vertebrates and even invertebrates which do not keep their body temperature constant and, therefore, have no thermoregulatory need to compensate for an increasing surface-to-volume ratio with decreasing size [22,23]. Hence, even though the allometric size relationship of metabolic rate might favor the balance between heat production and heat loss in homeothermic animals, it must have been a beneficial precondition rather than a consequence of thermoregulation [24].

Secondly, the power exponent of 3/4 found by Kleiber clearly deviates from the 2/3 mass proportionality which, for geometrical reasons, would be expected in the case of a "true" surface proportionality of metabolic rate. Obviously, it must be taken into consideration that the 3/4 exponent represents a statistical average of measurements [25,26] which, in the past, were not always performed under perfectly standardized con-

ditions. Accordingly, more recent investigations have revealed that in properly defined mammalian subgroups, a 2/3 exponent, as expected by Rubner's law, can actually be observed [27,28]. Nevertheless, in view of the overall validity of metabolic size allometry in both homeotherms and poikilotherms, this would only mean that in warm-blooded animals, a biological law might have been adapted to the requirements of thermoregulation which, however, must have more fundamental causes.

2.2. Fractal structure of supply systems

To explain these causes and the usual deviation from the 2/3 exponent to be expected in the case of pure surface proportionality, the mathematical concept of fractal geometry has been applied to biology [29].

One of the best known examples of fractal geometry is provided by the length of a coast line which, due to its irregularity, is the longer, the finer the applied scale is. Thus, rather than an absolute length, the increase in length with successive refinement of the scale can be determined. Remarkably, when these data are plotted on logarithmic scales, a linear relationship results where the slope of the line is a measure of the irregularity of the coast. In this case, the resulting exponent will amount to a "fractal" value between 1 and 2, indicating that the coast line, due to its irregularity, displays "partial area properties" [30,31].

In analogy to this very simple example, it has been assumed that the deviation of metabolic size allometry from a "pure" surface proportionality results from the fractality of distributive networks (e.g., blood vessels) within the body [32,33]. A similar hypothesis was already put forward by Sernetz et al. some 20 years ago who compared the organism with a "bioreactor" [34,35]. Thus, although both the 3/4 exponent itself [27,28] and its deduction from fractal geometry [36–39] are still a matter of debate, this hypothesis clearly relates the metabolic rate of living beings to the supply conditions, in a similar way to what is seen in biocalorimetry (cf. below).

2.3. Metabolic preconditions of locomotion and exercise

A third theoretical approach to metabolic size allometry deals with the metabolic preconditions of locomotion and exercise [40]. Interestingly, when the metabolic costs of locomotion among living beings are compared, they turn out to depend on the mode of locomotion (flying, swimming, walking) rather than on the "type" of the moving animal, i.e., insects roughly fit the same allometric cost-to-size relationship as bats or birds [41,42]. Since the maximum metabolic rates to be attained during physical activity are in a fixed proportion to basal metabolic rates, animals have to be equipped with basal metabolic rates that allow them to reach the accordingly elevated metabolic rates during locomotion. Thus, from the point of view of exercise physiology, an increase in basal metabolic rate with decreasing body size is mandatory for small animals to be able to move. As far as the "correct formula" is concerned, it has been argued by Darveau et al. [43] and Hochachka et al. [44] that during rest and exercise, differing biochemical pathways with differing limiting steps are at work so that the net power exponent of the metabolic size relationship, as a result of those "allometric cascades", will vary depending on the animal's physical activity.

Altogether, these considerations point to the fact that metabolic size allometry is a multifactorial phenomenon for which several well-founded explanations can be given from different points of view. However, the question arises as to whether it is an inevitable precondition of life or may, at least temporarily, be dispensed with, to release small species from their metabolic constraints.

3. Exceptions from the overall metabolic size relationship

In view of the increasing specific metabolic rate with decreasing body mass, earlier authors had already postulated a lower size limit of mammals below which the metabolic requirements would be too high to be met, even by uninterrupted food consumption [45]. Although it is now assumed that some of the earlier investigations tended to overestimate the metabolic rates of very small mammals due to inappropriate measuring conditions, it has been confirmed that in the smallest homeotherms (e.g., in hummingbirds) an ultimate "packing density" of capillaries and mitochondria within tissues seems to be reached [46]. Against this background, it is not surprising that in some of the smallest species, at least temporary exceptions from the overall metabolic size relationship are to be found.

3.1. Suppression of metabolic size allometry in mammalian hibernators

This is true in a group of inhabitants of the temperate zones which escape the seasonal discrepancy between increased heat loss and scarcity of food by lowering their body temperatures to near ambient levels and spending the winter months at deeply reduced metabolic rates. Whereas mammalian hibernation has long been regarded as a "poikilothermic" state accompanied by a cold-induced metabolic reduction, it is now known that it consists of an endogenous metabolic reduction with subsequent lowering in body temperature [47,48], and that, whenever the species-specific minimal temperatures are reached, thermoregulation becomes reactivated to prevent the animal from detrimental cooling [49,50]. Remarkably, it has repeatedly been shown that, at their minimal body temperatures, all hibernators exhibit a more or less uniform minimal specific metabolic rate of roughly 0.1 W/kg [51–53] which equals the specific basal metabolic rate of the very largest mammals (such as elephants and whales) and might represent a lower limit of metabolic reduction among mammals [54,55] (Fig. 2(a)). This would also explain why smaller animals, as a reflection of their higher basal metabolic rates, display a higher tolerance to hypothermia than larger ones. The example of hibernators thus illustrates that, the smaller an animal is, the higher the relative benefit to be taken from a temporary suppression of metabolic size allometry [56].

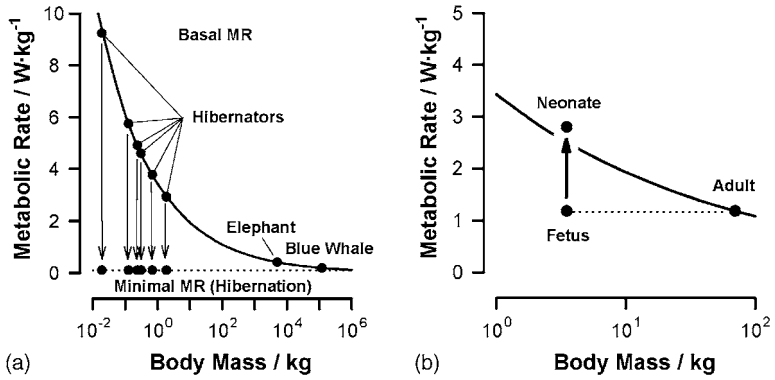

Fig. 2. Exceptions from overall metabolic size relationship: hibernating mammals are able to suppress the size allometry and to reduce their specific metabolic rates to a common minimal level that equals the specific basal metabolic rates of the largest mammals (a). Mammalian fetuses still exhibit an adult-like specific metabolic rate whereas the usual size allometry is activated only after birth (b).

3.2. Suppression of metabolic size allometry in mammalian fetuses

A similar exception is provided by the mammalian fetus which rather than exhibiting the metabolic rate to be expected from its own body size, is still at an adult-like metabolic level (the fetus "behaves like an organ of its mother") [57,58] (Fig. 2(b)). The fetal metabolic reduction which might be adaptive to the low intrauterine oxygen tension (if the fetal metabolic rate would be appropriate for the small body size, it would be probably too high to be met through the placenta) allows the immature being to grow at a high rate in spite of limited substrate supply. Moreover, the fetus can afford an "inappropriately" low metabolic rate as it is incubated at high ambient temperatures and does not need to compensate for an increased heat loss through its larger relative surface area. It is only after birth that the metabolic rate increases up to the level to be expected from body mass, as a result of the improved oxygen supply, and as a prerequisite of thermoregulation. However, some of the most immature mammalian neonates have been shown to retard the postnatal metabolic increase and to accept the lacking homeothermy in favor of an accelerated growth rate [59]. Thus, the perinatal period is another impressive example of how the size relationship may be subject to metabolic adaptations.

3.3. Oxyconformance in small newborn and adult mammals

Besides the temporary deviations from metabolic size allometry occurring in mammalian hibernators and fetuses, a more acute variability of metabolic rate has been observed in many small mammals, as a response to a lack of oxygen. For instance, it has long been known that some of the most immature mammalian neonates exhibit an unusually high hypoxia tolerance which is, at least partially, based on the ability to actively reduce their metabolic rate in response to an impaired oxygen supply [60,61]. Recent experimental evidence indicates that this kind of "hypoxic hypometabolism" may result from a "switching" between the (appropriately high) extrauterine and the (inappropriately low) intrauterine metabolic level [62,63]. A similar oxyconforming behavior has also been observed in adult mammals, with the relative benefit of metabolic reduction being the higher, the smaller the animal is [64]. Altogether, these examples show that a suppression of metabolic size allometry is by no means incompatible with life and may even be useful as a mechanism of metabolic adaptation.

4. Interrelationship between oxygen supply and metabolic rate

In view of the few exceptions discussed above, the question arises as to why these seem to be strictly limited to conditions of impaired oxygen and/or substrate supply. In fact, the overall metabolic size allometry is so universal that there is virtually no small animal normally living at low specific basal metabolic rate although this could be of considerable adaptive benefit (e.g., in terms of tolerance to starvation and longevity, cf. above). To answer this question, a hypothesis will be presented which starts from methodological observations in biocalorimetry and uses recent insights from paleobiology and perinatology to draw attention to the interrelationship between metabolic rate and oxygen supply.

4.1. Biocalorimetric insights

Whenever biological materials are studied by calorimetry, it can easily be seen that the specific metabolic rate decreases with increasing sample size. This was first described in cell suspensions where the heat production per single cell is inversely related to the cell density [65,66]. The so-called "crowding effect" has been tentatively explained by impaired diffusion of oxygen and substrates to the cells with increasing cell number, especially in unstirred cell suspensions [67]. A similar phenomenon has been observed in tissue slices where the heat output rate (at any particular time after the onset of measurement) is the lower, the larger the sample is [17,68] (Fig. 3). In this case, a theoretical model could be developed, based on the limited diffusion depth of oxygen and the differing metabolic activity in aerobic and anaerobic tissues [18,69]: whereas in very small samples the whole tissue is aerobic, resulting in a correspondingly high metabolic rate, in large samples, only a

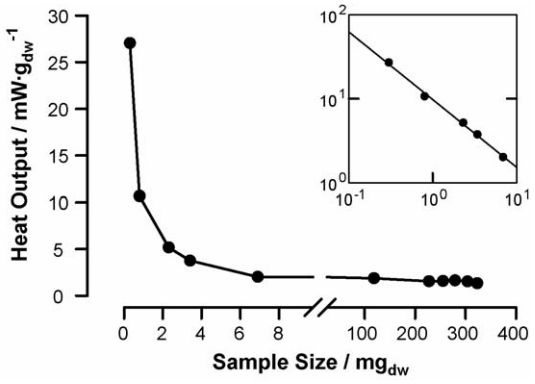

Fig. 3. "Crowding effect" of sample size on metabolic rate in tissue calorimetry: when the specific heat output rates of tissue slices are plotted against sample mass, an allometric size relationship (decrease with increasing sample mass) is found, similar to that known from intact animals. Data are from microcalorimetric measurements on rat liver samples, dw = dry weight.

small shell remains aerobic whereas the core becomes anaerobic and, thus, exhibits a greatly reduced heat production rate. Hence, the heat production per unit of volume will decrease with increasing sample size. When the specific heat output is plotted against sample size on logarithmic scales, a linear relationship is found, similar to the relationship between specific metabolic rate and body size in living organisms (Fig. 4). Although the reduction in heat production rate with increasing sample size or cell density, respectively, is a passive result of impaired diffusion to tissues and, thus, differs from the metabolic size relationship to be observed in living beings, it cannot be denied that the biological scaling laws seem to reproduce, on an active scale, what can be found in biocalorimetry, as a passive consequence of physical laws. However, it remains to be answered why in smaller beings, an increased specific metabolic rate seems to be a nearly unavoidable consequence. To understand this phenomenon, it is of interest to have a look at the changing role that has been attributed to oxygen during the past few years.

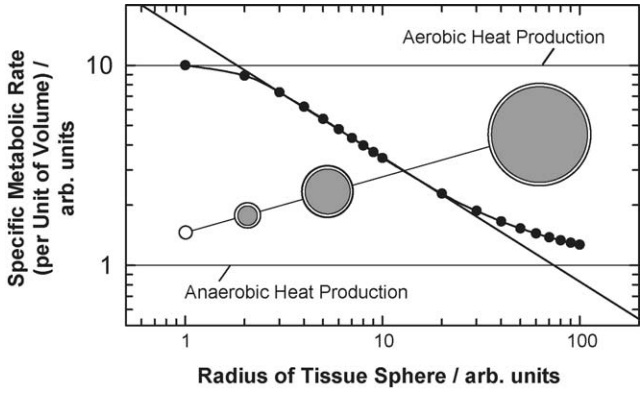

Fig. 4. Simplified model of the "crowding effect" in biocalorimetry: with increasing size, the aerobic shell of a spherical tissue sample becomes negligible in relation to its anaerobic core. Hence, the specific metabolic rate of the whole sample decreases from full aerobiosis ("10") to nearly complete anaerobiosis ("1"). When plotted on log scales, the data fit a typical allometric regression line.

4.2. Paleobiological insights

It is now generally accepted that the onset of aerobic metabolism was the result of the successive enrichment of the earth's atmosphere with oxygen which prompted the predecessors of mitochondria to invade other procaryotic cells ("endosymbiosis"), so as to use up the potentially "toxic" agent in a most useful way [70–73]. Interestingly, the intracellular oxygen tension in recent mammalian cells is as low as 3–5 mmHg so that they seem to have internalized the appropriate "paleo-atmosphere" [74]. This also explains why in some animals, considerable adaptations to limited oxygen supply (e.g., at high altitude) are possible as long as the low intracellular pO_2 is maintained by corresponding adaptations of the oxygen transport [75]. Recent evidence indicates that at these "critical" tensions, oxygen itself may exert a regulatory role on mitochondrial respiration, thus explaining the oxyconforming behavior observed in special adaptations [76]. Apparently, metabolic evolution has not only been driven by a tendency towards optimization in response to improved supply, but also by an "escape" from increasing oxygen in the animal's surroundings. This can also be seen in a second major event in metabolic evolution, namely, the transition from water to air breathing in vertebrates which resulted in a dramatically improved oxygen supply, and which was followed, with the transition from poikilothermy to homeothermy, by an increase in metabolic rate [24]. Obviously, the mutation underlying endothermy (probably an increased membrane leakiness with subsequently elevated membrane pump activity to prevent the cells from osmotic swelling) [77,78] not only required an appropriately high oxygen and substrate supply, but might also have helped to prevent the animals from being exposed to chronically elevated oxygen tensions.

4.3. Perinatological insights

Whereas in paleobiology, the toxic effects of a long-lasting exposure to elevated oxygen tensions remain somewhat speculative, the detrimental effects of excess oxygen can clearly be observed in clinical neonatology. As mentioned earlier, the oxygen tension in the fetal circulation amounts to 25–30 mmHg which, being similar to high altitude hypoxia, has been described as "Everest in utero" conditions [60]. Whereas this has long been interpreted as a sign of insufficiency of the placenta (as compared with the much more efficient lung), it is now increasingly being assumed that nature may have "deliberately" put immature organisms into a hypoxic compartment to prevent them from oxygen toxicity [79]. In fact, it is well known in clinical pediatrics that the exposure of premature babies to elevated oxygen concentrations may lead to severe retinal and pulmonary damage and eventually result in blindness and respiratory failure. More recently, it has been assumed that even a short-term application of pure oxygen in primary resuscitation or a long-term exposure to slightly supernormal oxygen levels during intensive care may suffice to exert adverse effect on retinal vascularization and pulmonary development in preterm neonates [80,81]. Obviously the immature organism lacks the detoxification systems necessary to cope with high extrauterine oxygen tensions,

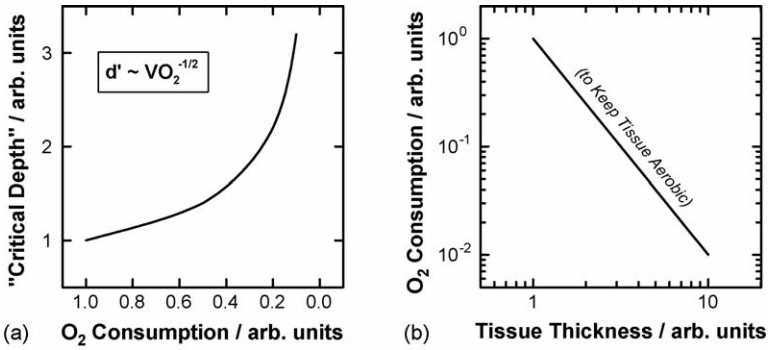

Fig. 5. Metabolic size relationship in oxygen supply to tissues: following Warburg's formula, the "critical depth" of tissue to be supplied with oxygen solely by diffusion increases with decreasing metabolic rate (a). When the decrease in metabolic rate necessary to maintain aerobiosis in spite of increasing tissue thickness is calculated, an allometric relationship results (b).

especially as long as the oxygen consumption rate – due to the retarded postnatal metabolic increase in immature mammals (cf. above) – is still not high enough to eliminate the excess oxygen in a "useful" way.

5. Conclusions

Summarizing these considerations, it becomes evident that under in vitro conditions (i.e., in biocalorimetry), due to the limited depth of oxygen diffusion, large tissue samples remain partially anaerobic and, thus, exhibit lower specific heat production rates than smaller samples. Even though this is a passive result of physical laws, it seems that (following the fractal geometry of supply systems) also under in vivo conditions, the mean size of the ultimate "tissue units" being supplied by the finest branches of capillaries increases with increasing body size. Hence, in the case of unchanged specific metabolic rate, there would be a risk of impaired oxygen supply to tissues with increasing body size. However, as has been demonstrated by Warburg [82], the penetration depth of oxygen into tissues by diffusion is inversely related to the height of metabolic rate (Fig. 5(a)) so that a decreasing metabolic rate is able to compensate for the impaired supply conditions with increasing size. In fact, when the decrease in metabolic rate necessary to maintain aerobiosis in spite of increasing tissue thickness is calculated, a typical allometric size relationship results (Fig. 5(b)). Thus, it seems highly probable that the "law of metabolic reduction" reflects an active adaptation of living organisms to the same diffusion constraints which, in biocalorimetry, impair the oxygen supply to tissue samples of increasing size.

Whereas, from this point of view, the *decrease* in metabolic rate with increasing body size appears to be a precondition of maintained oxygen supply, the question remains as to why the *increase* in metabolic rate with decreasing size is apparently so essential that exceptions are limited to rare conditions of impaired energy supply (such as during fetal life or in hibernation). As mentioned above, it would be easy to imagine small animals which live at "inappropriately" low metabolic rates and profit from the reduced energetic needs. However, the overall building plan of aerobic organisms, dating back to the "endosymbiotic" invasion of mitochondria into other procaryotic cells, apparently includes the maintenance of a low pO_2 within cells, to avoid toxic side-effects of excess oxygen. This can only be achieved by an increase in specific metabolic rate with decreasing size since, otherwise, in view of the smaller "tissue units", a relative hyperoxia would result in smaller as compared to larger beings. This does not mean that the metabolic rate of recent adult mammals varies with oxygen supply—which, obviously, is not the case. However, it does mean that on a phylogenetic or ontogenetic scale, every increase in pO_2 might have prompted mitochondria to enhance their metabolic activity and/or to enlarge their distance from capillaries, so as to bring the oxygen tension in their immediate surroundings back to a tolerable level. Remarkably, this is exactly what has been found in a recent comparative study on microcalorimetric and ultrastructural changes in rat myocardium after birth [83].

If the limited tolerance to starvation and the shorter life span of small as compared to large beings are referred to, the overall increase in metabolic rate with decreasing body size might appear to be an unnecessary wasting of energy. If, however, the paleobiological escape from oxygen and the deleterious effects of oxygen on immature tissues are taken into consideration, the allometric body size relationship of metabolic rate might turn out to prevent the intracellular pO_2 from increasing beyond a detrimental level. This would mean that any elevation in metabolic rate occurring during phylogeny and ontogeny has not only to be looked upon as a favourable consequence of optimized oxygen supply, but also as a necessary response to impending tissue hyperoxia. Moreover, this would mean that exceptions from metabolic size allometry should be limited to conditions where tissue hyperoxia (due to "inapproriately" low metabolic rates) is largely avoided. This is true both for the intrauterine conditions where the low metabolic rate is accompanied by a very limited oxygen supply, as well as for mammalian hibernation, where breathing and circulation are correspondingly lowered so as to preserve tissues from "unused" oxygen [84,85].

Independent of the discussion about the "true" exponent of the allometric power function, one of the main unsolved problems with regard to metabolic size allometry is its striking universality among beings of whatever complexity and provenience. Bearing in mind that in every calorimetric experiment, the heat production rate is governed by the diffusion conditions, it seems not fully unreasonable to assume that also during metabolic evolution, the metabolic rate has adapted to the sup-

ply conditions so as to maintain the delicate balance between a "too low" and a "too high" oxygen tension within living cells. Given a uniform construction plan of living beings, this would necessarily result in a narrow determination of metabolic rate, depending on body size. In more general terms, oxygen could act as a signal that keeps the cells informed as to whether they are in a small or in a large organism, and, thus, turn out to be the "missing link" between structure and function.

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