Integrative and Comparative Biology, volume 50, number 5, pp. 793–807
doi:10.1093/icb/icq049

SYMPOSIUM

The Heat Dissipation Limit Theory and Evolution of Life Histories in Endotherms—Time to Dispose of the Disposable Soma Theory?

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From the symposium "Metabolism, Life History and Aging" presented at the annual meeting of the Society for Integrative and Comparative Biology, January 3–7, 2010, at Seattle, Washington.

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Synopsis A major factor influencing life-history strategies of endotherms is body size. Larger endotherms live longer, develop more slowly, breed later and less frequently, and have fewer offspring per attempt at breeding. The classical evolutionary explanation for this pattern is that smaller animals experience greater extrinsic mortality, which favors early reproduction at high intensity. This leads to a short lifespan and early senescence by three suggested mechanisms. First, detrimental late-acting mutations cannot be removed because of the low force of selection upon older animals (mutation accumulation). Second, genes that promote early reproduction will be favored in small animals, even if they have later detrimental effects (antagonistic pleiotropy). Third, small animals may be forced to reduce their investment in longevity assurance mechanisms (LAMs) in favor of investment in reproduction (the disposable soma theory, DST). The DST hinges on three premises: that LAMs exist, that such LAMs are energetically expensive and that the supply of energy is limited. By contrast, the heat dissipation limit (HDL) theory provides a different conceptual perspective on the evolution of life histories in relation to body size. We suggest that rather than being limited, energy supplies in the environment are often unlimited, particularly when animals are breeding, and that animals are instead constrained by their maximum capacity to dissipate body heat, generated as a by-product of their metabolism. Because heat loss is fundamentally a surface-based phenomenon, the low surface-to-volume ratio of larger animals generates significant problems for dissipating the body heat associated with reproductive effort, which then limits their current reproductive investment. We suggest that this is the primary reason why fecundity declines as animal size increases. Because large animals are constrained by their capacity for heat dissipation, they have low reproductive rates. Consequently, only those large animals living in habitats with low extrinsic mortality could survive leading to the familiar patterns of life-history trade-offs and their links to extrinsic mortality rates. The HDL theory provides a novel mechanism underpinning the evolution of life history and ageing in endotherms, and makes a number of testable predictions that directly contrast with the predictions arising from the DST.

Introduction

Large endothermic animals live longer than small ones (Holliday 2005; Speakman 2005a). Although there is a lot of interspecific variation in maximum longevity at any given body mass, and also some major differences among clades (Austad and Fischer 1991; Holmes et al. 2001; Brunet-Rossinni and Austad 2004; Furness and Speakman 2008), the impact of size is so dominant that there are no mammals the size of a house mouse (*Mus musculus*) that live as long as an elephant (*Loxodonta africanus*) with a maximum lifespan of 65 years [data from 'AnAge: The Animal Ageing and Longevity Database' (de Magalhães and Costa 2009)]. Similarly, there are no birds the size of a house sparrow (*Passer domesticus*) that live as long as does an ostrich (*Struthio camelus*) with a maximum lifespan of 50 years (AnAge Database). Bigger animals not only live longer but they also display a set of correlated life-history traits (Stearns 1983, 1989;

Advanced Access publication May 21, 2010
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Promislow and Harvey 1990; Promislow et al. 1992; Hendriks and Mulder 2008; Jeschke and Kokko 2009). Specifically, they mature more slowly and breed for the first time at a later age. Their reproductive rates are lower (longer intervals between reproductive events) and their productivity at each breeding event is also reduced (lower litter or clutch sizes). Larger animals also senesce more slowly (Ricklefs 1998). This set of correlated life-history traits has been called the fast-slow life-history continuum (Promislow and Harvey 1990; Oli 2004; Bielby et al. 2007; Jones et al. 2008; Jeschke and Kokko 2009). In endotherms, small means fast and large means slow.

We have previously suggested that studies of ageing should separate the variation in longevity that is due to the effect of body mass from the residual variation once body mass has been taken into account (Speakman et al. 2002; Speakman 2005a, 2005b). This article is about the effects of body mass on longevity and on correlated life-history traits. Like many other papers in this area, we take as an axiomatic position that interspecific variation in body mass exists, and we consider the consequences of this variation for life histories. In any given ecological context, these consequences will affect fitness and will feedback on whether selection favors evolution of a smaller or larger body size. Our concern is less with the process of selection on size but rather with the direct consequences of size for life-history traits. The article consists of four parts. We will first outline the classic evolutionary framework for explaining why animals age (Ljubuncic and Reznick 2009) and, in this context, why body mass is a key factor. This section focuses on the disposable soma theory (DST) (Kirkwood 1977; Kirkwood and Holliday 1979; Kirkwood 1993). In the second part, we will outline some problems with the DST as applied to endotherms. In the third part, we will propose a new, alternative explanation for how the association of body size and longevity might arise in endothermic animals, and provide some background for this new idea, which is called the 'heat dissipation limit' (HDL) theory (Król and Speakman 2003a; Król et al. 2007; Speakman and Król 2010). We conclude that the DST may be unnecessary for understanding ageing and the evolution of life history in endothermic organisms. We will then end the article by proposing several tests that might be made to assess whether the effect of body mass on longevity arises because of the processes suggested by these two alternative theories.

The classic evolutionary explanations for why we age and for the effect of body mass on longevity

Ageing is defined as the increase in risk of mortality as an animal gets older (Finch 1990; Carey 2003). Maximum longevity is only an epiphenomenon of the increase in age-related (intrinsic) risk of mortality (Finch 1990; Carey 2003). In theory, there is nothing to stop an individual animal from a species with a higher rate of ageing living to a greater maximum age than one from a species that ages at a lower rate. It is just very improbable. This is why many gerontologists suggest that we should avoid the use of maximum lifespan as a trait to represent the ageing of an entire species. Nevertheless, many studies have utilized maximum longevity to reflect interspecific differences in ageing, principally, because it is much easier information to collect, facilitated enormously by the curated AnAge Database. The alternative is to compile life-table data and to characterize the pattern of age-related increase in the risk of mortality by fitting either Gompertz or Weibull functions and derive appropriate parameters from the fitted curves (Wilson 1994; Abrams and Ludwig 1995; Mueller et al. 1995; Gavrilov and Gavrilova 2001; Ricklefs and Scheuerlein 2002). In practice, however, the maximum lifespan of a well-sampled species is highly correlated with age-specific increase in mortality, as estimated by the Weibull aging parameter ω (Fig. 1). We will therefore assume that maximum lifespan is a valid measure of the rate of ageing and that a species with a higher maximum longevity ages more slowly than one with a lower maximum longevity.

An evolutionary explanation for the age-related increase in risk of mortality was first proposed by Medawar (1952), who noted that the force of natural selection declines as animals get older because the numbers of individuals that are alive is progressively reduced by age-independent, chance mortality, called the extrinsic mortality risk. Adverse late-acting mutations, therefore, cannot be removed by selection, and these accumulate in the population leading to increased risk of mortality as an individual gets older (the 'mutation accumulation' [MA] hypothesis). High rates of extrinsic mortality would also favor the evolution of early maturation and high reproductive rates, and genes favoring these traits might themselves have negative late-acting effects (antagonistic pleiotropy [AP]) (Williams 1957). Both the MA and the AP theories predict that when extrinsic risks of mortality are high, this will favor rapid development, early high investment in reproduction

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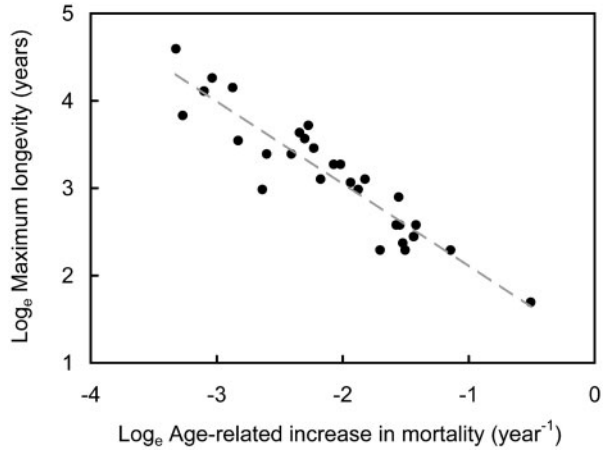

Fig. 1 Maximum longevity of 30 species of endotherms in relation to their age-related increase in mortality, estimated by the Weibull aging parameter ω. The negative correlation between the parameters is significant ($r = -0.45$, $P = 0.013$). Data for mammals (*Macaca mulatta*, *Pan troglodytes*, *Panthera leo*, *Martes zibellina*, *Callorhinus ursinus*, *Phoca hispida*, *Loxodonta africana*, *Equus burchelli*, *Hippopotamus amphibius*, *Cervus elaphus*, *Rangifer tarandus*, *Syncerus caffer*, *Ovis dalli dalli*, *Rupicapra rupicapra*, *Kobus kob thomasi*, *Damaliscus korrigum*, *Tamiasciurus hudsonicus*, and *Sylvilagus floridanus*) and birds (*Cygnus columbianus*, *Ficedula hypoleuca*, *Larus canus*, *Rissa tridactyla*, *Accipiter nisus*, *Eudyptula minor*, *Puffinus tenuirostris*, *Diomedia exulans*, *Parus major*, *Parus atricapillus*, *Turdoides squamiceps*, and *Passerina cyanea*) from Ricklefs (1998, Appendix A).

and a corresponding earlier action of 'late-acting' mutations, which would cause more rapid ageing and a shorter maximum longevity.

The DST (Kirkwood 1977; Kirkwood and Holliday 1979) emphasized that even if there is no AP, rapid high investment in early reproduction (driven by high levels of extrinsic mortality) would lead to increased rates of ageing. The DST extends the earlier genetic ideas by including strong physiological and ecological dimensions. This theory is built on three fundamental premises. The first is that animals do not just live longer by default until some late-acting mutation kills them, as is implied by the MA and AP ideas. To live a long time, an animal needs to have physiological mechanisms that maintain the somatic tissue for that period. These mechanisms are called longevity assurance mechanisms (LAMs). The second premise of the DST is that LAMs are energetically expensive. The third premise is that because the supply of energy in the environment is limited, animals face a trade-off in how they allocate this energy among competing processes. This fundamental idea that animals need to trade off their energy-demanding activities within a supply envelope defined by environmental resources dates back at least to the 1930s (Fisher 1930) and it has a long tradition in ecology (Lack 1954; Stearns 1976, 1977). Another process known to be energetically expensive is reproduction (Millar 1977, 1978; Innes and Millar 1981; Johnson et al. 2001a; Speakman 2008). Because resources are limited, and reproduction and LAMs are costly, the DST predicts that a life-history strategy that combines expensive reproduction with expensive LAMs is not energetically feasible. If a high rate of extrinsic mortality creates a selective pressure that favors rapid development and early high investment in reproduction, there will be an obligatory reduction in investment in LAMs and consequently an earlier increase in the age-related risk of mortality, thereby leading to a shortened lifespan. Conversely, a low rate of extrinsic mortality would not place such a premium on early investment in reproduction to the detriment of living longer, and animals in such a selective regime would delay breeding and adopt a strategy of relatively low investment in reproduction. Rather, they would allocate the released surplus energy to LAMs, and thus have a delay in the age-related increase in mortality and a greater maximum lifespan. The key to all three evolutionary hypotheses is variability in the extrinsic rate of mortality.

Body mass may play a critical role in defining the extrinsic risk of mortality, simply because large body size buffers individuals from environmental perturbations that cause mortality (Ricklefs 2000; Hulbert et al. 2007; de Magalhães et al. 2007). Fasting endurance, for example, would be greater in a larger animal (Millar and Hickling 1990), so a catastrophic loss of all food supply would produce greater extrinsic risk of mortality for a small animal compared with a large one. Other extrinsic causes of mortality, such as disease and predation, may also be dependent upon body size. Larger animals may be protected from disease because they tend to live at lower densities, which may reduce transmission rates of vectors. Similarly, increased body size may also protect against risk of predation. Even if these general arguments seem rather weak and prone to many exceptions, there is direct empirical support for the suggestion that extrinsic risks of mortality decline in relation to body mass. Ricklefs (1998) accumulated life-table data for both mammals and birds, and fitted Weibull curves to the data on mortality. The advantage of using the Weibull model rather than the Gompertz model is that initial mortality rate from these fits (m_0) is presumed to be roughly equivalent to the extrinsic risk of mortality. In the data analyzed by Ricklefs, there is a strong negative relationship between m_0 and body mass

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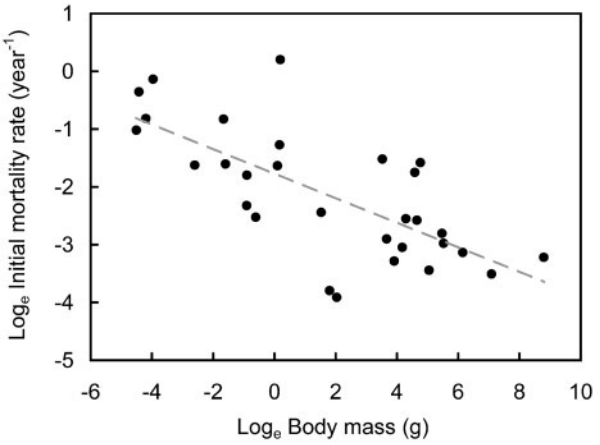

Fig. 2 Extrinsic mortality rate (estimated by the initial mortality rate m_0 from Weibull fits of survival curves in relation to age) of 30 species of endotherms in relation to their body mass. The negative correlation between the parameters is significant ($r = -0.71$, $P < 0.001$). Data from Ricklefs (1998, Appendix A); see Fig. 1 for the list of the species included.

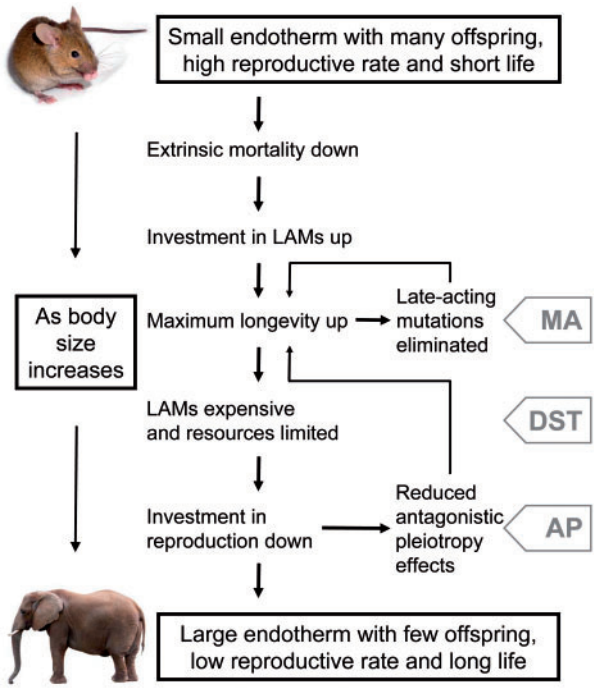

Fig. 3 A flow diagram showing how increased body size is currently believed to lead to reduced investment in reproduction and to increased longevity. Starting with a small endotherm at the top, increases in body size result in reduced extrinsic mortality. This leads to a situation in which investing in longevity assurance mechanisms (LAMs) evolves, causing an increase in maximum lifespan. This in turn allows late-acting mutations to be removed by selection (MA hypothesis), further increasing maximum lifespan. However, LAMs are energetically costly and must be traded off against reproduction (disposable soma theory, DST), causing a reduction in reproductive investment. This can bring further increases in lifespan by reduced AP effects. The end point of this process is a large endotherm with few offspring and a low reproductive rate, but a long lifespan. The images are from http://www.dreamstime.com/.

(Fig. 2) (Ricklefs 1998). Similar conclusions were reached by Holmes and Austad (1994, 1995). A flow diagram showing the main features of the current evolutionary hypotheses is shown in Fig. 3.

Some problems with the disposable soma explanation

The DST rests on three fundamental premises outlined above: animals need LAMs to protect their soma, LAMs are energetically expensive and resources are limited. With respect to the first two premises, a major problem with the DST is that while the existence of costly LAMs was postulated over 30 years ago, it is still unclear exactly what these LAMs are. Much work has implicated different cellular attributes in the resistance or susceptibility to ageing, including the fatty acid composition of membranes (Hulbert 2005; Hulbert et al. 2006; Hulbert 2007), telomere shortening (Haussmann et al. 2003; Haussmann and Mauck 2008; Salomons et al. 2009), oxidative damage (Van Remmen and Richardson 2001; Wiersma et al. 2004; Alonso-Alvarez et al. 2006; Andziak et al. 2006; Kregel and Zhang 2007; Costantini 2008; Cohen et al. 2008; Selman et al. 2008b, 2008c; Perez et al. 2009; Jang et al. 2009; Van Remmen and Jones 2009; Zhang et al. 2009), the generalized stress response (Gems and Partridge 2001; Gems and McElwee 2005; Benedetti et al. 2008; Gems and Doonan 2009), the insulin-like growth-factor/growth-hormone axis (Clancy et al. 2001; Bartke et al. 2001; Walker and Lithgow 2003; Bartke 2005; Selman et al. 2008a), and the sirtuin system (Howitz et al. 2003; Haigis and Guarente 2006; Dali-Youcef et al. 2007; Michan and Sinclair 2007; Bass et al. 2007; Guarente 2008; Finkel et al. 2009). Few experimental manipulations studying these effects have explicitly addressed whether the system in question involves significant energy costs to maintain. The articles that have dealt with this issue show that the expenditure of energy is either unchanged (Van Voorhies et al. 2003; Hulbert et al. 2004) or even reduced (Van Voorhies and Ward 1999; Van Voorhies 2003) by genetic manipulations that extend life. A rare example of a study showing a positive link between high energy expenditure (perhaps reflecting expensive LAMs) and longevity was our own study demonstrating that mice with higher levels of metabolism lived longer (Speakman et al. 2004). One of the most consistent experimental

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manipulations that leads to extended life is caloric restriction (CR) (Weindruch and Walford 1982; Weindruch et al. 1986; Walford et al. 1987; Speakman and Hambly 2007). Animals under CR live longer and presumably activate LAMs that achieve this. The effects of CR on metabolic rate, however, are equivocal, with some studies suggesting that metabolic rate is reduced (Gonzalespacheco et al. 1993), others suggesting it remains unchanged (McCarter et al. 1985; Greenberg and Boozer 2000; Hulbert et al. 2004) and relatively few indicating it increases (Selman et al. 2005).

The impact of body mass on basal metabolic rate (BMR) across species, however, is unequivocal—larger animals have much lower levels of metabolism per gram of body tissue (Fig. 4) (Kleiber 1961; White and Seymour 2003; Brown et al. 2004; White and Seymour 2005; White et al. 2009). This pattern directly contradicts the DST, because it is difficult to imagine how the larger animals could possibly have many costly LAMs activated when their cellular metabolic rates (BMR per gram of body tissue) are so low. The average cellular metabolic intensity of an elephant, for example, is less than 1/30 that of a mouse.

With respect to the third premise that energy resources are limited, there is abundant evidence that many animals experience periods in their lives when energy resources are indeed limited. Probably the most conspicuous are the seasonal changes in primary productivity that lead to reductions in food supply at all trophic levels during winter, combined with a reduction in physical activity due to lower ambient temperatures in ectothermic animals. In endotherms, this leads to a whole suite of adaptations that cope with the lack of resources. These include hibernation, daily torpor, migration, reduction in body mass, moulting into a thick winter coat that retards heat loss, increasing thermogenic capacity, and many others (Melvin and Andrews 2009). Although it is obvious that energy supply can be limited in winter in higher latitudes, or during dry seasons in the tropics, the situation in summer (or in tropical wet seasons) is far less certain. Because of the much greater supply of energy, this is the time when most animals choose to breed. Hence, the very low supply of food and the evident limitation of resources during the non-breeding season is practically irrelevant for the potential trade-off between reproduction and LAMs. The key question is whether resources are limited during the breeding seasons. Several lines of evidence suggest that commonly they may not be limited.

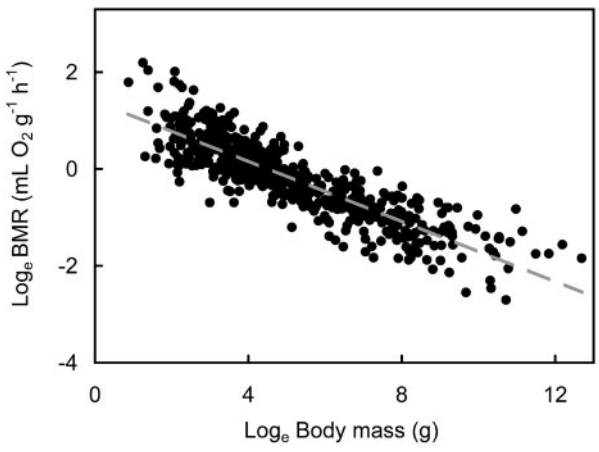

Fig. 4 Mass-specific basal metabolic rate (BMR expressed per gram of body tissue) of 619 species of mammals in relation to their body mass (data from White and Seymour 2003, Supplementary Table S1). The negative correlation between the parameters is significant ($r = -0.88$, $P < 0.001$). Despite expressing supposedly high-cost longevity assurance mechanisms (LAMs), larger animals have lower average cellular metabolic intensities than smaller animals.

First, almost all vertebrates have at the entrance to their alimentary tract a food-storage organ—in mammals it is the stomach, in birds it is the crop. These structures exist because animals are able to harvest food (energy) from their environment at a much faster rate than they can process and utilize it. The universal existence of these structures indicates that for almost all animals, the rate at which energy can be collected from the environment must at some phases of their lives be considerably greater than the rate at which it can be utilized. Second, if food is limited then supplementing the natural supplies with additional food should increases reproductive output. A review of 138 studies of food supplementation, including 129 studies of endotherms, revealed that the commonest responses were to advance the date of first breeding (33/39 studies) and to reduce the size of the home range (19/23 studies) (Boutin 1990). Advancing the first breeding date might be interpreted as moving forwards the transition from a time when food is limited to a time when it is not. Reducing home-range size may reflect the collection of a fixed amount of food defined by an intrinsically imposed limit. When food is supplemented, animals can collect this fixed quantity in a smaller home range than when there is no supplementation. In contrast to these responses, only nine of 21 studies reported increases in litter size or clutch size and, in all cases, these increases were quite modest. These modest increases might reflect reallocation of energy that previously had been used for foraging over the bigger home range. What is striking is that no animals responded by massively increasing

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their food intake and using this extra energy to generate enormously increased numbers of offspring. Third, many endotherms in winter moult and develop a thick coat that conserves energy by reducing heat loss when food is limited. During summer, they moult out of this winter coat into a thinner coat, which provides less insulative protection. If energy were a limited resource throughout the year, one wonders why they ever moult out of the winter coat into a summer coat that causes their energy demands to increase?

An alternative explanation to the DST for evolution of a fast-slow life-history continuum: the HDL theory

We suggest that an alternative contributory mechanism to the evolution of the fast-slow life-history continuum in endotherms, and the consequent effects of body size on longevity, stems from a physiological limitation faced by endothermic animals in the amount of energy they can allocate to reproduction. There is substantial evidence to suggest that such a limit exists. Studies which date back to the 1980s in both mammals and birds have attempted to diagnose the cause of this limitation. Several different theories have been posited which depend on the limit occurring at different stages between collecting energy from the environment and its ultimate expenditure by tissues of the animal in question. Experimental work in our and other laboratories has helped to clarify the importance of these different processes. The most recent data suggests that the limit depends on the capacity to dissipate body heat and the associated risk of hyperthermia (Speakman and Król 2010). Because heat loss is fundamentally a surface-based phenomenon, the low surface-to-volume ratio of larger animals generates significant problems for dissipating body heat associated with reproductive effort, which then limits their current reproductive investment. A fuller description of the HDL theory is presented below.

Starting from the prediction from the HDL theory that large animals by necessity must have low reproductive rates would explain the link between body size and extrinsic mortality (Fig. 2), because any large animals that had low reproductive rates combined with high extrinsic mortality rates would go extinct. The relationship in Fig. 2 may then arise not because large animals are intrinsically less prone to extrinsic mortality factors like starvation, disease and predation, but rather because any large animals showing such susceptibility would be eliminated. What we observe in Fig. 2 is probably, at least partly, the end-point of a protracted demographic selective process, eliminating those species that combine low reproductive rates with high extrinsic mortality.

This lower reproductive rate in larger animals would favor an increased lifespan because there would be reduced AP effects. That is, there would be no selection for genes that favor high investment in early reproduction because of the limit that dissipation of heat places on reproductive investment. Consequently, if these genes had later-acting negative effects (AP; Williams 1957), these effects would also not occur. Moreover, with extrinsic mortality reduced, this would also favor elimination of late-acting mutations and the evolution of LAMs. The key difference, however, between this idea and the DST is that in the DST, LAMs have to be costly and are traded off against reproduction. This trade-off causes the low reproductive rate. In the HDL theory, the low reproductive rate is a consequence of the limits to heat dissipation. Under this scenario, LAMs evolve only because there is a selective advantage to living longer due to the reduced extrinsic mortality. As in the other evolutionary theories, lowered extrinsic mortality is a key feature of this hypothesis. However, in this interpretation LAMs can be cheap. In fact, the HDL theory predicts that the cheaper LAMs are, the more likely they are to evolve because they do not then generate heat, which might interfere with capacity to reproduce. This framework is illustrated in Fig. 5.

The origin of the HDL theory lies in studies attempting to establish the factors limiting lactation performance. Lactation is widely agreed to be the most energy demanding part of the mammalian life cycle (Millar 1977, 1978; Gittleman and Thompson 1988; Hammond et al. 1994; Rogowitz 1996, 1998; Speakman 2008). During lactation, mammals (particularly small ones) greatly increase their food intake, thereby supporting milk production (König et al. 1988; Hammond and Diamond 1994; Speakman and McQueenie 1996). Energy intake increases rapidly at the start of lactation, but then reaches a maximum (Johnson et al. 2001a). Experimental manipulations that involve increasing litter size (Hammond and Diamond 1992; Johnson et al. 2001a), making lactating females simultaneously pregnant (Johnson et al. 2001b), artificially extending the period of lactation (Hammond et al. 1994; Laurien-Kehnen and Trillmich 2003) or forcing the mothers to exercise when lactating (Perrigo 1987) do not stimulate the females to increase their energy intake or their production of milk. Indeed, they will often kill their offspring rather than eat more

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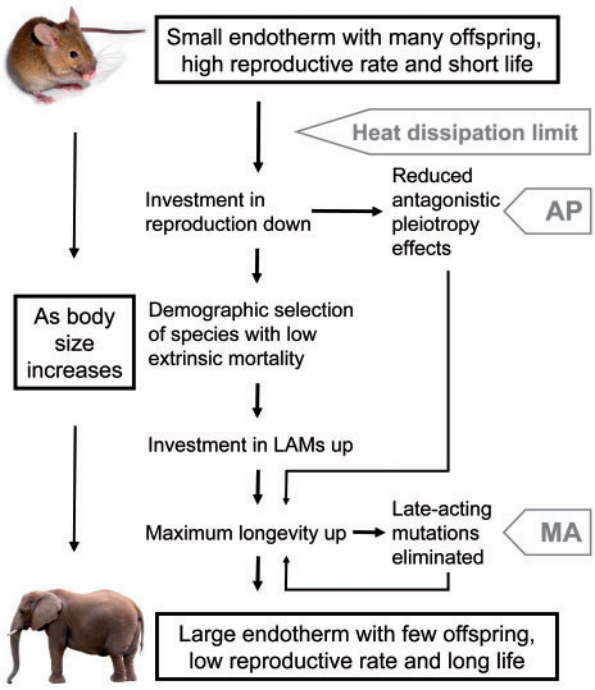

Fig. 5 Flow diagram showing how limits to the capacity to dissipate body heat, in relation to body size, may favor evolution of elevated lifespan in larger animals. By this model, as animals get larger they are constrained by the HDL to have low reproductive rates. By reduced AP, this will directly favor increased lifespan. The reduced reproductive rate leads to demographic selection of only those species with low rates of extrinsic mortality. This results in the evolution of LAMs, supporting the elevated lifespan. Longer-lived animals can also reduce the level of late-acting mutations because the force of selection is elevated (MA). Note that in this model, there is no need for the DST or LAMs that are energetically expensive. The images are from http://www.dreamstime.com/.

food. Interest in the cause of this limitation on energy intake at peak lactation spans at least the past 30 years, probably because the limit directly affects production of offspring and hence fitness.

In the 1980s, the dominant hypothesis was that the maximum food intake was limited by the capacity of the alimentary tract to process incoming energy. Hence, energy may be abundant in the environment and ingested rapidly into the alimentary tract, where it is stored in the stomach or crop, but the uptake capacity of the tract itself restricts the level of expenditure. This was called the 'central limitation' hypothesis (Drent and Daan 1980; Weiner 1989; Peterson et al. 1990; Weiner 1992; Koteja 1996b). The central limitation hypothesis predicts that maximum sustained energy expenditure should be independent of what the animal does because it is limited by the fixed intake of energy from the alimentary tract (Weiner 1992). Support for this idea was equivocal (Koteja 1996a), ultimately because the alimentary tract is extraordinarily flexible in structure and can change capacity in response to changing demands (Hammond and Wunder 1991; Hammond and Diamond 1992; Naya et al. 2008). In a key experiment, Hammond and colleagues found that lactating mice exposed to the cold were able to elevate their intake of food above the level that was apparently a limit when manipulations involved changing litter size, lactation duration or simultaneous exercise (Hammond et al. 1994). This effect was subsequently replicated in other strains of mice and in other species (Rogowitz 1996, 1998; Hammond and Kristan 2000; Johnson and Speakman 2001; Zhang and Wang 2007). Attention therefore shifted to metabolic capacity of the organs in which energy was being used. In lactation, the obvious candidate was the mammary tissue, and experiments were performed demonstrating that the mammary glands seemed to be operating at maximum capacity during peak lactation (Hammond et al. 1996). This became known as the 'peripheral limitation' hypothesis.

A fundamental prediction of the peripheral limitation hypothesis is that the mammary glands perform maximally at peak lactation independent of any other energetic challenges experienced by the female during lactation. In contrast, the total energy intake depends on combined energy demands due to all factors, including, for example, thermoregulation in the cold. Milk production should therefore be independent of ambient temperature. Directly contradicting this prediction, it was shown that during exposure to cold (8°C), mice not only elevated their intake of food but also produced more milk and had heavier offspring than they did at room temperature (21°C) (Johnson and Speakman 2001). Similarly, when mice were exposed to thermoneutral conditions (30°C), they ate less food, produced less milk and weaned smaller offspring (Król et al. 2003; Król and Speakman 2003a, 2003b). These observations of effects of ambient temperature on lactation are consistent with a HDL constraining total energy expenditure and reproductive output. Accordingly, when lactating animals were placed in the cold, they elevated intake of food not because of the increased demand for thermoregulation, but rather because the steeper gradient between body and ambient temperature increased their capacity to dissipate body heat. This allowed them to elevate highly exothermic processes such as milk production. Exposing mice to temperatures exceeding room temperature had the opposite effect of reducing their capacity to dissipate heat and forcing them to suppress milk production. Taken alone, the temperature manipulations during lactation support the HDL theory, but

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can also be potentially explained by thermal effects of the environment on the offsprings' capacity for growth and their demand for milk. To eliminate this possibility, the capacity of lactating mice to lose heat independently of effects on their offspring was manipulated by shaving fur from their dorsal surfaces (Król et al. 2007). Critically, shaved mice increased their food intake by 12.0% and their milk production by 15.2%, leading to elevated pup growth by 15.4%, strongly supporting the HDL theory. More recent attempts to replicate this effect in other strains of mice have not been successful (Zhao and Cao 2009), and the reasons for this difference among strains are unclear.

The role of heat as a factor constraining mammalian reproduction has in fact been known for some considerable time prior to our 'discovery'. It is well known that in larger domestic animals such as sheep, pigs, and cattle, reproduction is limited by heat production (Ominski et al. 2002; Renaudeau et al. 2003; Lacetera et al. 2003; Odongo et al. 2006) . The breakthrough in our studies was to find that the key factor limiting animals weighing 50–500 kg also constrains mice weighing 30–40 g, with a surface-to-volume ratio of 20–30-fold greater. The fact that this constraint occurs across such a large range of body masses suggests that the capacity for dissipation of heat is a fundamental unifying factor affecting all endotherms (Speakman and Król 2010). Although our work and that performed previously has focussed mainly on lactation, HDLs apply to any activity that generates sufficient body heat to impose a risk of detrimental hyperthermia. In mammals this will include lactation, in birds it is likely to be increased levels of physical activity associated with providing for their brood.

The HDL theory suggests that maximum capacity to lose heat is the key process that limits the expenditure of energy. Because heat loss is essentially a surface phenomenon, the HDL theory predicts that total daily energy expenditure should scale roughly in relation to the body's surface area (body mass$^{0.66}$). A more sophisticated model of heat loss, however, that takes into account changes in temperature and shape of the body (which are also not constant with size) indicated a scaling exponent of ~0.63 (Speakman and Król 2010). We have recently reviewed all the data on metabolic rates in the field (FMR) measured by the doubly-labelled water method in free-living endotherms, and found that the actual scaling of FMR with body mass was close to this theoretical expectation (Speakman and Król 2010). In fact, the relationship in terrestrial mammals had an exponent of 0.647, and that in birds was 0.658. Exponents derived from an analysis using phylogenetically independent contrast were 0.679 and 0.576, respectively. All four exponents did not differ significantly from the expectation of 0.63 predicted by the HDL theory.

The much lower scaling exponent for FMR (0.576–0.679) compared with the exponent for BMR [generally presumed in the range 0.68–0.76 (Kleiber 1961; White and Seymour 2003; Brown et al. 2004; White and Seymour 2005)] means that a major prediction of the HDL theory is that the theoretical maximum scope for increasing metabolism (maximum capacity to dissipate heat divided by BMR) declines as animals get larger (Fig. 6). Actual scopes from the measurements of FMR in terrestrial mammals match this prediction. This empirical observation that FMR/BMR scope declines with body mass was first made by Degen and Kam (1995). The HDL theory predicts that larger animals will be under much greater constraint in their total energy budgets because they are unable to elevate their metabolism as high as do smaller animals due to the reduced capacity to dissipate heat; actual field data support this model.

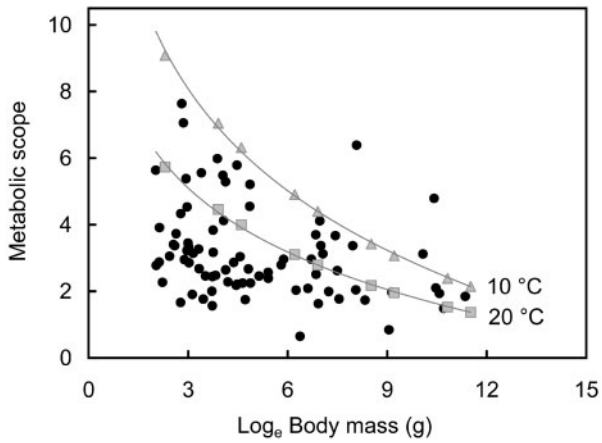

Fig. 6 Maximum metabolic scope predicted from the HDL theory (theoretical maximum capacity to dissipate heat divided by predicted BMR) at ambient temperatures of 10°C (triangles) and 20°C (squares) in relation to body mass. The actual metabolic scope (FMR divided by actual BMR) (circles) for 81 species of terrestrial mammals is also shown. The scope for increasing metabolism gets smaller as animals get larger. Most observed metabolic scopes fall within the boundary predicted by the model. Those outside the boundary probably reflect erroneous estimates of BMR. The predicted values of maximal capacity to dissipate heat and the FMR data are from Speakman and Król (2010; Appendix S1 and S2, respectively); the predicted BMRs are derived from the equation of White et al. (2009); the actual BMRs are from the same studies as the FMR data. Note that if the predicted BMRs are derived from the quadratic equation without temperature correction (Kolokotrones et al. 2010), the relationships between maximum metabolic scope and body mass at 10°C and 20°C are similar to those based on the equation of White et al. (2009) (Fig. S1, Supplementary material).

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The suggestion that a constraint on reproductive capacity in relation to body size might drive the evolution of life histories has been made elsewhere (Brown and Sibly 2006), in the context of the metabolic theory of ecology (Brown et al. 2004). The primary advance here is 2-fold. First, a mechanism causing this constraint has now been identified—the HDL capacity. Second, when combined with a view that energy supply in the environment is not limited during critical phases of reproduction, this leads to the revolutionary suggestion that animals do not trade off LAMs against reproduction within a total energy budget, as assumed by the DST. Instead, the evolution of LAMs is favored by the lowered reproductive rate and demographic selection of species with low extrinsic mortality. LAMs therefore, by this interpretation, do not need to be energetically expensive. If this model is correct, it means that we can effectively understand the evolution of life histories and ageing in endotherms without any need for the DST.

Six potential tests to separate between the DST and the HDL theory

Because the HDL theory refers to endotherms, these tests specifically concern comparisons involving mammals and birds. If a similar constraint on reproductive investment with body size were to be shown in ectotherms, the predictions would apply more widely. Hence, it is worth testing whether the predictions of the DST and HDL theory enumerated here also hold up in ectotherms.

Test 1: The DST requires that LAMs are energetically costly and that they trade off with reproduction. Because reproduction is already known to be an extremely expensive process involving increases in daily energy intake up to 9× BMR (Johnson and Speakman 2001; Johnson et al. 2001a), the energy costs of LAMs predicted by the DST must be large and easily detectable. They cannot be subtle effects below the detection threshold of existing equipment, otherwise they would have insufficient impact on reproductive performance. By contrast, the HDL theory predicts that the costs of LAMs will normally be trivially small (even undetectable). At present, there are many candidate LAMs and it is unclear which are true causal factors enhancing longevity and which are consequences of differences in lifespan. However, if there were a candidate LAM supposed to influence interspecific variation in longevity, it would be relatively easy to measure BMR (per gram of body tissue to express metabolic intensity) of the respective species that vary in the particular LAM. This comparison would also be valuably performed whenever environmental (e.g., nutritional) or genetic manipulations are made that increase lifespan. If the DST is correct, these manipulations will be activating expensive LAMs, and this will be reflected in increased metabolic intensity (BMR per gram of body tissue).

Test 2: The DST predicts that LAMs will be down-regulated when the animals reproduce. The HDL theory suggests that they will not be down-regulated, as they will not generate sufficient heat to interfere with reproduction. The consequence of down-regulation of the LAMs will cause significant changes in whatever the LAMs protect against. For example, if protection from oxidative stress is a LAM, the DST predicts that this protection will be switched off when animals reproduce, thereby leading to increased oxidative stress. There is some evidence to suggest down-regulation of oxidative protection during reproduction in birds (Wiersma et al. 2004), but only relative to altered energy demands; absolute levels of protection were unchanged.

Test 3: The DST predicts that the LAMs are costly physiological factors that underpin a link between reproduction and longevity. In particular, it predicts that their down-regulation in reproduction leads to a shortened life. The HDL theory, in contrast, predicts that LAMs are not down-regulated when animals reproduce (or face other energetically demanding challenges) and hence predicts no negative relationship between reproductive activity and longevity. Many studies have been performed in ecological settings in which animals are forced to work harder during reproduction (e.g., enlargement of clutches or litters) and it is often shown that working harder does shorten life (Reznick 1985; Partridge and Harvey 1988; Stearns 1989; Reznick 1992; Daan et al. 1996). In this context, however, ecological factors may cause the elevated mortality, so a positive result is not necessarily because one or more physiological LAMs has been down-regulated. Ideally then, tests of lifespan between reproductive and non-breeding animals should be performed in abstraction from the ecological context, to reveal if any of the effect is due to physiological mechanisms (i.e., LAMs). Preliminary data from zoo animals suggest that there is no detectable cost of reproduction on survival outside of the ecological context (Ricklefs and Cadena 2007), but this study was not experimental. Data from humans, which are also generally outside of an ecological context, are controversial and probably reflect the cross-sectional nature of the data. Some studies have supported a negative effect of reproduction on longevity (Westendorp

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and Kirkwood 1998; Lycett et al. 2000), but others have failed to find such a link (Le Bourg 2007). Some analyses indicate an effect of early but not of later reproduction on mortality in late life (Henretta 2007) but yet others find a negative effect of late reproduction but not of earlier reproduction (Gagnon et al. 2009). Experimental data for endotherms are lacking.

Test 4: The DST predicts that environmentally (e.g., nutritional manipulations such as CR) or genetically manipulating LAMs to extend life will have a detrimental effect on reproductive performance. The HDL theory predicts no such effects unless the manipulation or gene coincidentally affects the animal's capacity to dissipate heat, or it generates significant amounts of heat that it interferes with reproductive performance. For example, the uncoupling protein 1 (UCP1) is a mitochondrial uncoupler that results in significant heat production. If it were argued that UCP1 dissipates the proton gradient and thus reduces production of free radicals by mitochondria, and thereby reduces oxidative-mediated damage to macromolecules, it could be suggested that elevated UCP1 levels is a LAM. Overexpression of UCP1, however, would significantly increase heat production by virtue of its uncoupling activity, and this heat might directly reduce reproductive performance by restricting heat production from reproductive activities, like milk production. UCP1 (and other uncoupling protein) levels are normally chronically reduced during lactation, thereby avoiding this competition (Trayhurn et al. 1982; Trayhurn 1985; Trayhurn and Richard 1985; Pedraza et al. 2001; Xiao et al. 2004). Genetic manipulation of UCP1 levels that subsequently affect reproduction therefore would not refute the HDL theory, since UCP1 also affects heat production. Numerous genetic models of extended lifespan in mice are available, in which direct effects on heat production or dissipation are not anticipated, and comparisons of reproductive performance of these genetic models with that of wild-types could be made to test this predication. Supporting the HDL, CR inhibits reproduction while it is being administered, but there appears to be no long-term negative impact on reproductive performance (Johnston et al. 2006).

Test 5: If there is a decrease in extrinsic mortality due to some factor unrelated to body size, the DST predicts that this change will lead to an increase in selection for LAMs and a consequent decrease in reproductive performance. In contrast, the HDL theory predicts that LAMs will be positively selected but they will have no impact on reproduction because they are cost free. Conflicting data exist regarding this prediction. One pertinent factor influencing extrinsic mortality independently of body size is flight (Holmes and Austad 1994; Holmes et al. 2001). Bats and birds both live significantly longer than terrestrial mammals of equivalent size, presumably because of the reduced extrinsic mortality (Ricklefs 1998). In bats, there is a parallel reduction in reproductive rate (Austad and Fischer 1991) as predicted by the DST, but in birds this is less clear and more systematic analysis is required (Ricklefs and Scheuerlein 2003).

Test 6: The HDL theory predicts that if the capacity to dissipate heat is increased, a species of animal thus affected would have greater capacity to expend energy. This should lead to a greater capacity for reproduction. Because this is not traded off against LAMs, the elevated reproductive effort should not have a negative impact on longevity. By contrast, the DST would predict such a trade-off. Aquatic mammals are an example of a taxon on which such a test of this prediction might be performed; they have been shown to have greater FMR, consistent with the HDL theory (Speakman and Król 2010), but effects on reproductive performance and longevity have not been not assessed. Similarly, the HDL theory predicts that animals living in cooler climates should have greater reproductive performance without any negative impacts on longevity.

Conclusions

Our work on the factors that limit reproductive performance in rodents has revealed a reproductive constraint, the HDL, which is related to body mass. The convergence of the HDL on the curve relating BMR to body size restricts large animals to having low reproductive output. This in turn may be a contributory factor to reduced extrinsic mortality in larger endothermic animals by demographic selection, and ultimately may positively select for LAMs and extended lifespan. This theoretical approach makes a number of predictions about the relationship between reproduction and LAMs that are readily amenable to testing. In particular, the HDL model predicts that LAMs will not be costly or traded off with reproduction for limited resources. These predictions contrast with those from the DST. The HDL theory may be an important mechanism underpinning the evolution of life history and of ageing in endotherms.

Acknowledgments

We thank James Harper and Anne Bronikowski for the invitation to speak at the symposium, which

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stimulated this review. We are grateful to many past and present students, postdoctoral fellows, and colleagues for their direct and indirect inputs into the ideas in this article; Don Thomas, Henk Visser, Steve Austad, Simon Verhulst, Serge Daan, Murray Humphries, Colin Selman, Kim Hammond, Shelly Buffenstein, Tony Hulbert, Martin Brand, Zhijun Zhao, Dehua Wang, and Craig White all made useful contributions. We also thank João Pedro de Magalhães, Harold Heatwole, and an anonymous reviewer for their extensive and invaluable comments on earlier drafts of the article.

Funding

Biotechnology and Biological Sciences Research Council (grant BB/C504794/1 to J.R.S. and E.K.); and the Natural Environment Research Council (grant NE/C004159/1 to J.R.S.). J.R.S was funded to attend the SICB meeting by the Ellison Medical Foundation (grant AG-CW-0299-09).

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