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On the complex relationship between energy expenditure and longevity: Reconciling the contradictory empirical results with a simple theoretical model

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ABSTRACT

The relationship between energy expenditure and longevity has been a central theme in aging studies. Empirical studies have yielded controversial results, which cannot be reconciled by existing theories. In this paper, we present a simple theoretical model based on first principles of energy conservation and allometric scaling laws. The model takes into considerations the energy tradeoffs between life history traits and the efficiency of the energy utilization, and offers quantitative and qualitative explanations for a set of seemingly contradictory empirical results. We show that oxidative metabolism can affect cellular damage and longevity in different ways in animals with different life histories and under different experimental conditions. Qualitative data and the linearity between energy expenditure, cellular damage, and lifespan assumed in previous studies are not sufficient to understand the complexity of the relationships. Our model provides a theoretical framework for quantitative analyses and predictions. The model is supported by a variety of empirical studies, including studies on the cellular damage profile during ontogeny; the intra- and inter-specific correlations between body mass, metabolic rate, and lifespan; and the effects on lifespan of (1) diet restriction and genetic modification of growth hormone, (2) the cold and exercise stresses, and (3) manipulations of antioxidant.

1. Introduction

The relationship between energy metabolism and longevity has been a central theme in aging studies since the late 1800s (Speakman et al., 2002). Despite more than a century of theoretical and empirical efforts, the understanding of this relationship is still controversial, and existing theories fail to reconcile the seemingly contradictory empirical evidence (Speakman et al., 2004). The oldest theory in the field—the rate of living theory (RLT) (Rubner, 1908) suggests that the rate of mass-specific energy expenditure (metabolic rate) is negatively correlated with longevity. This theory is supported by two lines of empirical evidence. The first comes from the interspecific scaling laws of metabolic rate and lifespan in wild animals (Speakman, 2005). The negative correlation between mass-specific metabolism and lifespan holds even after the confounding effect of body mass is removed (Speakman et al., 2002). The second line of evidence is that experimentally lowering body temperature, which decreases metabolic rate, extends lifespan of both ectotherms (Klass, 1977; Loeb and Northrop, 1917; McArthur and Sohal, 1982; Miquel et al., 1976; Partridge et al., 2005; Rose, 1994; Van Voorhies and Ward, 1999) and endotherms (Conti et al., 2006; Sohal et al., 2000).

Nonetheless, the RLT faces four types of challenges. First, the predicted correlation between energy expenditure and lifespan does not hold when comparisons are made across taxons. A typical example is that birds have higher metabolic rate than mammals with the same body mass, yet live much longer. Second, RLT also fails to explain why within a species, such as domestic dogs, the larger breeds with lower mass-specific metabolic rates, usually have shorter lifespans (Speakman et al., 2003). Third, a few lifespan extending interventions, such as diet restriction (DR) and genetic modification (GM) of growth hormone, generally do not alter, or only slightly reduce, mass-specific metabolic rate (Brown-Borg, 2003; Hou, 2013; McCarter et al., 1985; Merry, 2002; Westbrook et al., 2009). Moreover, a few studies even showed that when metabolic rate is altered by DR, it is positively correlated with lifespan (Cooper et al., 2004; Houthoofd et al., 2002; Liao et al., 2011; Lin et al., 2002; Roark and Bjorndal, 2009). The fourth challenge comes from experimental manipulations that increase metabolic rate, but do not shorten lifespan. For example, long-term cold expo-

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sure largely increases energy expenditures in mice (Vaanholt et al., 2009), rats (Holloszy and Smith, 1986), and voles (Selman et al., 2008), but has no effects on lifespan. Moreover, voluntary exercises increased food intake in female rats while increasing lifespan (Holloszy, 1993).

The oxidative stress theory of aging (OST), another theory that links energy metabolism and longevity, suggests that the deleterious productions of oxidative metabolism (e.g., reactive oxygen species, ROS) cause various forms of molecular and cellular damage, and the accumulation of the damage is associated with the process of aging (Balaban et al., 2005; Barja, 2004; Hulbert et al., 2007; Sohal et al., 2002). Widely considered by many researchers as a modern version of the RLT at the molecular and cellular level, this theory shares all the supports and challenges of the RLT, as well as a few of its own. New sources of supports include the evidence that (1) external oxidative insults shorten lifespan, (2) the level of oxidative damage to macro-molecules increases with age, and (3) genetic interventions and diet restriction, while extending lifespan, reduce the oxidative damage (Bokov et al., 2004; Muller et al., 2007). New challenges to OST mainly come from the studies, in which adding antioxidants to diet (Bjelakovic et al., 2007; Ristow et al., 2009) or genetically altering the expression of antioxidant enzymes (Pérez et al., 2009; Van Raamsdonk and Hekimi, 2012), which were assumed to change the oxidative damage, failed to affect longevity. In some cases these interventions even yielded results that opposed the theory's predictions (Bjelakovic et al., 2007; Ristow et al., 2009).

The controversial correlation between energy, metabolic rate, and longevity has been considered a long-standing question (Balaban et al., 2005; Brys et al., 2007; Hughes and Reynolds, 2005; McCarter et al., 1985; Pérez et al., 2009; Speakman et al., 2004; Stuart and Brown, 2006). Here we suggest that in considering this question the detailed energy tradeoffs between life history traits and the efficiency of energy utilization have been largely ignored, which, we hypothesize, are the keys to understanding the complex nature of the energy longevity correlation. In this paper we present a simple quantitative model driven by this hypothesis, and use the model to reconcile a series of seemingly contradictory empirical results on the relationship between energy metabolism and longevity.

2. Methods

2.1. The conceptual framework of the theory

We illustrate the framework of the theory in Fig. 1. The oxidative damage producing process starts from the overall energy expenditure (measured as oxygen consumption rate). Under many circumstances, energy expenditure is proportional to the production rate of ROS, which is in turn proportional to the net oxidative damage. Assuming that the net oxidative damage is the cause of aging and the determinant of lifespan, in these cases there is a direct and simple link between lifespan and metabolic rate. However, as shown in Fig. 1, two factors, namely antioxidant scavenging and damage repair mechanisms, can alter the damage level (the output of the process) while keeping the energy expenditure rate (the input) roughly unchanged (Bokov et al., 2004; Sohal et al., 2002). Scavenging ROS is carried out by a series of anti-oxidative enzymes, such as superoxide dismutase (SOD), peroxidredoxin (Prx), and glutathione peroxidase (GP), and non-enzymatic antioxidants such as vitamins, (Balaban et al., 2005). Non-scavenged ROS causes damage to lipid, DNA, and protein. Organisms have evolved highly efficient mechanisms to repair the damage, such as removal of peroxidized acyl chains from phospholipids (Hulbert et al., 2007), DNA double strand break or base excision repair (Madhusudan and Middleton, 2005), and methionine sulfoxide repair (Stadtman,

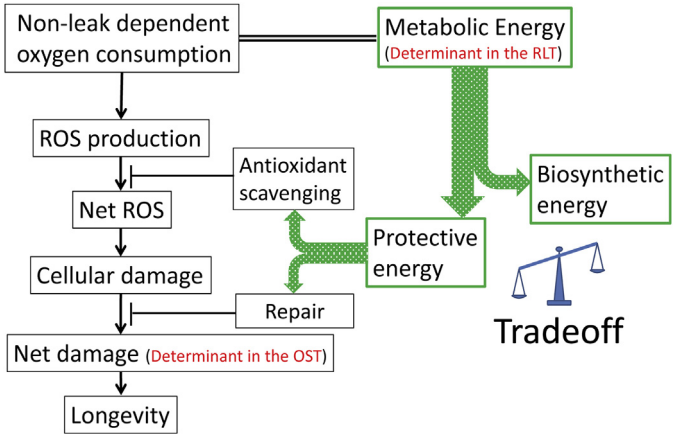

Fig. 1. Schematic illustration of the oxidative damage producing process. The discussion of this process in this paper starts with the non-leak dependent oxygen consumption, which is equivalent to the metabolic energy available to the animals, and is the determinant of lifespan in the rate of living theory (RLT). The metabolic energy is partitioned between the energy for protection and the energy for biosynthesis. The energy for protection and the efficiency of utilization of it determine the overall protective effects of radical scavenging and cellular damage repair. The net damage, which may or may not be proportional to oxygen consumption, is the determinant of lifespan in the oxidative stress theory (OST).

2006). Enhancing or weakening these two factors can result in a nonlinear correlation between net cellular damage level and oxygen consumption, and therefore a complex relationship between energy expenditure and longevity. The nonlinearity between damage and oxygen consumption may also be partially attributed to the incomplete mitochondrial coupling due to proton leak and electron leak, which causes a fraction of consumed oxygen not to produce ROS (Barja, 2013; Brand, 2000). But, as we discuss in Appendix A, if these two factors are kept fixed, incomplete coupling alone cannot fully explain the disproportionality between oxygen consumption and net damage level (Appendix A). Thus, in this paper our discussion starts from the non-leak dependent oxygen consumption as shown in Fig. 1.

We need to emphasize that the protective mechanisms of anti-oxidative scavenging and damage repair require energy. So, the overall protective efficacy depends on the amount of energy allocated to these mechanisms and the efficiency of energy utilization for this purpose (Hou, 2013, 2014; Kirkwood, 1990; Kirkwood and Holliday, 1979). Thus, we hypothesize that there are two ways to enhance the protection.

The first way is to allocate more energy to protection. More energy for protection does not necessarily require an increase in overall energy expenditure. Some lifespan extension interventions can reshuffle the energy allocation and induce tradeoffs between protection and other life history traits. One of the most important traits that is often manipulated to tradeoff with protection is biosynthesis during growth. For example, when growth is retarded by diet restriction or genetic modification of growth hormone, the energy requirement for biosynthesis is reduced accordingly. Thus, animals can channel extra energy to protection without increasing the overall metabolic energy pool, and therefore enjoy a longer lifespan (see quantitative details in Section 3.2). We will show that the biosynthetic energy associated with growth rate also has significant effects on oxidative damage profile over ontogeny and the inter- and intro-specific relationship between lifespan and body mass.

The second way is to enhance the protective efficiency, so that one unit of the energy is associated with less molecular damage. Protective efficiency can be altered by experimental manipulations, such as down- or up-regulating genes for antioxidant enzymes