Opinion article

At the heart of aging: is it metabolic rate or stability?

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Abstract

Foundational changes in science are rare, but in the field of biogerontology there is a new theory of aging that may shake things up. The conventional wisdom about duration of life is based on an old idea known as the "rate of living" theory, which suggests that aging is caused by the loss of some vital substance. The modern version of this theory is that duration of life is influenced by the relative speed of a species' resting metabolism. However, empirical evidence does not consistently support this hypothesis. In an article published recently by mathematician/biologist Lloyd Demetrius, it is suggested that the most important factor involved in duration of life is not metabolic rate or oxidative stress, but metabolic stability. If Demetrius is correct, his theory will have important implications for intervention research. For example, if the metabolic rate/oxidative stress theory is correct, efforts to intervene in the aging process should be directed at finding ways to reduce metabolic rate, lessen the production of reactive oxygen species (ROS), improve antioxidant defenses, or increase the quantity of antioxidants. If the metabolic stability hypothesis is correct, efforts to intervene in the aging process should be directed at finding ways to increase the stability of the steady state values of ROS, increase the robustness of metabolic networks, or improve the stability of antioxidant enzymes. For now there is reason to believe that Demetrius' theory deserves further consideration – whether it meets the test of a paradigm shift has yet to be determined.

Introduction

It is healthy for a scientific discipline to have its foundation shaken by a new idea or theory. When the dust settles, the result is often a change in conventional wisdom or the solidification of an existing theory. Foundational changes in science are rare, but in the field of biogerontology there is a new theory of aging that may shake things up.

The conventional wisdom about why species age and live as long as they do is based in part on the modern version of the very old and now discredited "rate of living" (ROL) theory of aging. According to the old ROL theory, aging is caused by the loss of some vital substance such as water or hormones – the more rapid the vital substance is used up the shorter the lifespan. The modern and more plausible version of ROL is based on Raymond Pearl's hypothesis (Pearl 1921) that the primary determinant of how long species live is influenced by the relative speed of their resting metabolism (mass-specific metabolic rate). That is, metabolic rate is thought to be inversely proportional to maximum lifespan, which means that species that live fast will die young while those that have a slower metabolic rate live slower and longer.

The evolutionary theory of why aging occurs that arose in the 20th century conceptually supports predictions from the metabolic rate theory, although the evolutionary line of reasoning is

silent about the mechanisms involved (Medawar 1952; Williams 1957; Hamilton 1966; Kirkwood 1977). The evolutionary theory of senescence suggests that animals that face high predation must develop quickly (i.e., live fast) in order to pass their genes onto the next generation before death occurs, while animals that face low extrinsic mortality delay development and reproduction, and thus live slower and longer. Species facing low predation also tend to grow larger, which led to the related observation that longevity appears to be positively correlated with the size of an animal as well as its cranial capacity (Sacher 1978; Hofman 1983). The image that should come to mind at this point is the difference between the short-lived mouse and long-lived elephant.

A mechanistic basis for the metabolic rate theory arose in the 1950s when Denham Harman (1956, 1981) suggested that operating the cellular machinery of life leads to the production of reactive oxygen species (ROS) (also known as free radicals) – damaging by-products of metabolism that have been implicated in the aging process. This oxidative stress theory of aging emphasizes the balance between the production of ROS and inherent mechanisms for protecting the organism from ROS or repairing the damage it causes (Ames 2005; Ames et al. 2005). Evidence amassed in the scientific literature linking the rate of free radical production and the ability of species to reduce or repair the damage they cause, to length of life (for a summary see, Partridge and Barton 1993; Beckman and Ames 1998).

This metabolic rate/oxidative stress theory and its free radical mechanism have as its foundation, accumulated damage. Damage to nucleic acids, proteins and lipids accumulates throughout the lifespan, sooner or later overwhelming the repair capacity of the cells of one or more vital organs, eventually leading to death. Variation in age at death *within* species is accounted for by differences in inherited genetic susceptibility to damage, diversity in inherent repair capacity, the stochastic nature of accumulated damage, and differences in lifestyle. Variation in lifespan *across* species is thought to be a product of species-specific metabolic rates, which in turn are attributes that in theory are driven by the unique life history traits of each species that evolved to regulate growth, development, and reproduction – with the timing of senescence and death as an inadvertent by-product (Kirkwood and Holliday 1979; Partridge and Harvey 1988). Thus, longevity determination in species is incidental to the main goal of reaching reproductive maturity and is only indirectly determined by the genome (Hayflick 2004). Three important predictions follow from the metabolic rate/oxidative stress theory:

1. The rate of increase in death rates should rise as a function of age.
2. Smaller animals should have higher metabolic rates relative to larger animals – implying there is a gradient of longevity based on body size.
3. The life expectancy and maximum lifespan of species should be negatively correlated with tissue concentrations of ROS and positively correlated with tissue concentrations of antioxidants.

The problem with the metabolic rate/oxidative stress theory is that it is faced with persistent contradictions from the available data. For example, it has been known since the time of Benjamin Gompertz in the early 19th century that death rates for humans and other species rise exponentially throughout most of the lifespan (Gompertz 1825; Carnes et al. 1996; Olshansky and Carnes 1997), but for some species at later ages (including humans) there is evidence for a deceleration in the rise in death rates – leading to what has come to be known as a mortality plateau (Carey et al. 1992). Scientists try to account for mortality plateaus by suggesting they are a product of the expression of unique mortality risks among long-lived subgroups of the population that are revealed with the passage of time (i.e., selective survival; Kirkwood and Austad 2000). *A plateau or decline in mortality at later ages does not follow from the metabolic rate/oxidative stress theory.*

Another discrepancy involves anomalies between body size and duration of life. The metabolic rate/oxidative stress theory predicts that smaller animals should live fast and die young and that larger animals should live slow and long. *Yet, some small animals such as certain birds and bats that are known to have a high*

metabolic rate live considerably longer than some comparable or larger sized mammals, and increasing metabolic rate can actually reduce ROS production (Austad and Fischer 1991; Austad 1997). Then there are a few species such as lobsters and some fish that do not appear to senesce as predicted from the metabolic rate/oxidative stress theory. For reasons unknown, biological attributes of older members of a species are the same as those exhibited by younger members of the species (Finch 1990).

Experimental studies also demonstrate that antioxidant supplementation in the diets of long-lived laboratory animals – an intervention that in theory should lengthen life because of the expected reduction in free radicals – does not significantly increase either their life expectancy or maximum lifespan (Rattan 2004). A recent study even suggests that large doses (>400 IU) of the free radical scavenger, vitamin E, leads to increased total mortality in humans (Miller et al. 2004). However, it has yet to be determined whether dietary supplements containing antioxidants negatively influence the body's production of its own potent free radical scavengers (e.g., SOD), influence caloric intake, or in some cases become transformed into "pro-oxidants" once they are metabolized.

Finally, there are now some discrepancies appearing with one of the earliest findings in the field of biogerontology – the observation that animals that are calorically restricted without being malnourished, live longer. According to the metabolic rate/oxidative stress theory, calorically restricted animals live longer because a lower caloric intake should lead to declines in metabolic rate and/or reductions in the quantity of free radicals. In recent studies, caloric restriction has been shown to have varying effects on both metabolic rate and lifespan (Masoro et al. 1982; Sohal and Weindruch 1996; Kirk 2001).

Metabolic stability–longevity hypothesis

When such inconsistencies arise, scientists tend to explain the anomalies by suggesting that the problem is not with the theory, but with the data or the way in which they are collected or interpreted. On the surface, this would also seem to apply to the metabolic rate/oxidative stress theory. After all, natural selection has already produced such great variation in lifespan that evolution may very well have given rise to different biological rules and thus exceptions to the theory. However, when these anomalies are considered together, the consistent pattern of departure from the theory implies that the problem may have less to do with the data or exceptions to a general rule, but with the theory itself.

In an article published last year by the mathematician/biologist Lloyd Demetrius, a new theory of aging – referred to as the "metabolic stability–longevity hypothesis" (herein after referred to as MSH) – may be poised to make the field of biogerontology take notice (Demetrius 2004). Particularly appealing about Demetrius' MSH is that the theory generates testable research hypotheses with quantifiable attributes that make it amenable to evaluation using the methods and materials that already exist in biogerontology, and initial evidence lends support to its underlying premise (Demetrius 2005).

According to Demetrius, duration of life of species is certainly influenced at some level by quantities of free radicals that roam through the body as well as species-specific maintenance and repair capacity. However, Demetrius suggests that the most important factor involved in duration of life is not metabolic rate or oxidative stress, but metabolic stability, which is defined as the ability of cells to resist fluctuations in the steady state concentration of metabolites within the cell. Fluctuations in the state of equilibrium are normal in the daily life of a cell, but overall metabolic stability can be quantified as the rate of return to a steady state. At its foundation, MSH predicts that longevity is positively correlated with *stability* of the steady state concentrations of ROS. By contrast, the metabolic rate/oxidative stress theory predicts that longevity is positively correlated with *production rates* of ROS. There is qualitative evidence for Demetrius' prediction (Finkel and Holbrook 2000).

According to Demetrius, highly stable metabolic networks evolved in longer-lived, so called equilibrium species, defined by populations subject to limited but relatively stable resource conditions. Weakly stable metabolic networks evolved in shorter-lived, so called opportunistic species,

defined by populations, which are subject to fluctuating resource conditions. Unstable networks are defined by a loss of equilibrium, leading to death. Although all animals that live long enough experience a transformation from stable to unstable networks, according to Demetrius, the rate at which this occurs is defined by a species' inherited level of metabolic stability (e.g., robustness) and/or the relative efficiency of mechanisms for repairing damage. Thus, even though species with dramatically different lifespans may house similar cells, tissues, organs, and biochemical means of operation, the distinction between them according to Demetrius is the ability of cells to bounce back to a state of equilibrium.

The maintenance of cellular homeostasis by returning rapidly to a steady state concentration after a perturbation may be demonstrated in terms of redox couples, ADP/ATP ratios, ionic pumps and chaperone-networks, to name a few major molecular markers of metabolic stability. One study has already demonstrated that cultured diploid cells from eight mammalian species had a positive relationship between species lifespan and the ability of cells to tolerate oxidative stress (Kapahi et al. 1999). Similar comparative studies with isolated cells, tissues or whole organisms from a range of species exposed to various kinds of stresses and monitored for their ability to maintain metabolic stability in terms of the molecular parameters above would be a crucial test of this theory.

In the paper describing the details of MSH, Demetrius (1997, 2001, 2005) has integrated the evolutionary theory of senescence, which is based on demographic entropy (e.g., a measure of the age-specific variability in the fecundity and mortality of a population), with the dynamics of metabolic networks in order to explain the large variation in life span between species. Particularly appealing are the quantitative predictions relating metabolic rate, species-specific life span, and entropy. The four main predictions are:

1. The rate of increase in death rates should abate at advanced ages in equilibrium species (e.g., species with long stationary growth phases such as bats).
2. There is a positive correlation between metabolic stability and longevity.
3. Maximum longevity is positively correlated with demographic entropy.
4. Caloric restriction (CR) increases lifespan by increasing metabolic stability, but the benefits of CR should diminish in species that already have high rates of metabolic stability (e.g., long-lived species such as humans).

The implications of Demetrius' theory to the science of intervention research may be important. For example, if the metabolic rate/oxidative stress theory is correct, the focus of efforts to intervene in the aging process should be directed at finding ways to reduce metabolic rate, lessen the production of ROS, improve antioxidant defenses, or increase the quantity of antioxidants in the body. If the metabolic stability hypothesis is correct, the focus of efforts to intervene in the aging process should be directed at finding ways to increase the stability of the steady state values of ROS, increase the robustness of metabolic networks, or improve the stability of antioxidant enzymes. Scientists attempting to find ways to intervene in the aging process of model organisms may want to consider the alternative pathways to intervention offered by this new theory.

There are a number of other appealing features of Demetrius' MSH theory, including specific predictions about the evolutionary theory of senescence and its relationship between duration of life and such life history attributes as fecundity and demographic entropy. For now at least, there is reason to believe that Demetrius' MSH theory deserves further consideration – whether it meets the test of a paradigm shift has yet to be determined.

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