What Determines Longevity: Metabolic Rate or Stability?

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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 a hypothesis formulated by Raymond Pearl (1921) in the early 20th century where it was suggested that the primary determinant of how long species live is influenced by the relative speed of their resting metabolism. 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.

Introduction

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. According to evolution theory, animals that face high extrinsic mortality such as predation and infectious diseases 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 (Kirkwood and Holliday, 1979). Species facing low extrinsic mortality 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). The image that should come to mind at this point is the difference between short-lived rodents (which is a meal for many other species) and the long-lived elephant or whale (with few predators).

A mechanistic basis for the metabolic rate theory arose in the 1950s when Denham Harman (1956) 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. Evidence has 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 (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 differ-
ences 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. Thus, longevity determination in species is incidental to the main goal of reaching reproductive maturity and is only indirectly determined by the genome. 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, 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. 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. 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. Then there are a few species such as lobsters and some fish that do not appear to age 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.

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. 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 (Sohal and Weindruch, 1996). One important question of interest today is whether caloric restriction would extend life in humans to the same extent it does so in shorter-lived species.

**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.

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.

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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. 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.

What Demetrius has done is integrate 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 increases lifespan by increasing metabolic stability, but the benefits of caloric restriction 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. An emphasis on caloric restriction studies involving humans would be well justified. If Demetrius' metabolic stability hypothesis is correct, caloric restriction probably would not have much of an effect on human longevity and the focus of efforts to intervene in the aging process should therefore 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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References and Further Readings


