Externally Regulated Programmed Aging and the Effects of Population Stress on Mammal Lifespan

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Abstract

Programmed (adaptive) aging refers to the idea that humans, other mammals, and other complex organisms have evolved mechanisms that purposely cause or allow senescence or otherwise internally limit lifespan in order to obtain an evolutionary advantage and that senescence is therefore an evolved adaptation. Until recently programmed aging was thought to be theoretically impossible because of the mechanics of the evolution process. However, there is now substantial theoretical and empirical support for programmed aging in mammals and consequently a comprehensive approach to medical research on aging and age-related diseases must include consideration of programmed aging mechanisms. The detailed nature of such a mechanism is therefore of major importance to such research.

Externally regulated programmed aging theories suggest that in mammals and other more complex organisms the genetically specified senescence mechanisms are equipped with the capability for detecting local or temporary external conditions that affect the optimum lifespan for a species population and adjusting lifespans of individual members in response.

This article describes why regulation of lifespan in response to external conditions adds to the evolutionary advantage produced by programmed aging, and why a specific externally regulated programmed aging mechanism provides the best match to empirical evidence concerning mammal senescence.

Keywords: senescence, evolution, gerontology, health policy, medical research

Introduction

In 1882, Weismann first proposed the idea that aging in humans and other organisms is purposely programmed in order to obtain an evolutionary advantage [1]. This idea is now gaining wider acceptance because of multiple theories (e.g. [2, 3, 4, 5]) to the effect that an internal mechanism or program that purposely limits lifespan benefits the survival (non-extinction) of a *population* of individual members of a species despite being adverse from an *individual* organism's point of view.

Darwin's evolutionary mechanics concept, as widely taught and generally understood, does not support the idea that such a population benefit can offset the obvious individual disadvantage of senescence and so until recently programmed aging was thought to be theoretically impossible. However several developments described in detail elsewhere now support multiple population-oriented evolutionary mechanics concepts that allow programmed aging based on the population benefit of limiting individual lifespan [2, 6]. These developments can be summarized as follows:

- Efforts spanning more than 150 years have failed to produce theories that plausibly explain multi-species senescence observations while fully complying with Darwin's individual-oriented evolutionary mechanics concept.

- Genetics discoveries have exposed multiple issues with traditional evolutionary mechanics and support population benefit theories.

- Empirical evidence of programmed lifespan limitation in various species continues to accumulate.

- Many population benefits of an internally limited lifespan have been proposed. There has been no scientific effort toward showing that any of the suggested population benefits of senescence is invalid.

- Population-oriented programmed aging theories provide an excellent match to multi-species observations related to senescence and lifespan.

- Current published science no longer supports the idea that programmed aging is theoretically impossible.

- Substantial investment in programmed-aging-based medical research has consequently begun.

Multiple post-1952 population-based evolutionary mechanics theories including Medawar's modification [7], group selection [8], kin selection [9], and small group selection [10], suggest that traits that benefit a population can evolve despite producing an individual disadvantage. Programmed aging theories based on these concepts include [3], and [5].

Additional recent evolutionary mechanics theories based on evolvability [11, 2] suggest that organisms can evolve and retain traits that benefit a population by increasing its ability to evolve (adapt by means of genomic change) despite representing an individual disadvantage. Evolvability theories of aging (e.g. [1, 6, 4]) suggest that senescence increases evolvability in multiple ways and that therefore organisms would logically develop biological programs that operate to limit individual lifespan in a species-specific manner.

There is wide agreement that many internal and external factors affect the lifespan needed by members of a species population. Age at reproductive maturity and many other programmed internal aspects of an organism's reproductive design clearly affect needed lifespan. External factors surrounding a population such as the degree of population stress from mortality due to predation, environmental conditions, and starvation also affect needed lifespan as described below.

Nature of the mammal senescence program

For the growing group of those who therefore consider programmed mammal aging to be possible or even likely, the logical next step is to predict the nature of the programmed senescence mechanism and several possibilities exist:

1) Individual cells could each be equipped with genetically defined clock mechanisms that determine at what age and to what degree senescence should be applied to that cell.

2) A functionally common genetically defined biological clock mechanism could determine when and at what rate to apply senescence and send signals to tissues to activate or inhibit cell-level senescence mechanisms in tissues. Such signals could be assertive (signal causes receiving cells to senesce), inhibitive (signal inhibits senescence), or both. Multiple signals could be involved and signaling in such a scheme could involve nervous signaling, chemical (e.g. hormonal) signaling, or both.

3) A mechanism as described in (2) above except that the common clock mechanism could be equipped with the capability for sensing external temporary or local conditions that affect the optimum operation of the aging mechanism and adjusting senescence accordingly, i.e. *externally regulated* programmed aging.

4) A mechanism such as described in (3) above except that it primarily operates by down-regulating maintenance and repair mechanisms that act to prevent symptoms of senescence.

5) A mechanism as described in (4) above except that it provides for coordinated control of senescence *and* reproductive parameters that affect the particular lifespan needed by an organism.

This article argues that (5) has the best theoretical basis and is also best supported by empirical evidence. *Mammal senescence is controlled by an evolved biological program that coordinates senescence with reproductive parameters and external conditions in order to provide the best outcome for a population.*

Regulated Maintenance and Repair Controls Lifespan

There are many very different deteriorative processes that affect living organisms: cells die, hairs and nails wear away, wounds occur, infectious agents attack. It is also obvious that corresponding very different and complex maintenance and repair (M&R) processes exist: cells, hairs, and nails are replaced, wounds are healed, and infections are combatted.

We can easily imagine different M&R mechanisms that act to prevent the very different symptoms of senescence. An anti-cancer mechanism could act to deter cancer or even a particular type of cancer. A very different M&R mechanism could act to prevent heart disease, and so forth. As suggested here, an aging program could act by down-regulating multiple M&R mechanisms at a species-specific age and rate thus allowing senescence symptoms to appear on a species-specific schedule. This model provides a good fit to the observation that different

mammals have very different internally-determined lifespans (more than 200:1 difference between some mice and some whales) but also have rather similar symptoms of senescence such as cancer, heart disease, sensory deficits, and mobility deterioration. In this model, an early case of cancer could result from carcinogens that add to damage mechanisms or a flaw in a cancer-specific M&R mechanism while cancer and other highly age-related diseases and conditions in older individuals would be largely the result of the senescence program. Generally accelerated senescence (e.g. Hutchinson-Gilford progeria or Werner syndrome [12]) would result from a flaw in the common part of the senescence mechanism that caused senescence to be significant at an earlier than typical age. Similarly, a flaw that prevented activation of senescence at the proper age could result in a population that did not display measurable senescence such as seen in some species [13]. Such a population would lack the many population benefits of senescence and would therefore be more likely to become extinct.

Lifespan control by means of a mechanism that directly causes senescence symptoms (as opposed to or in addition to indirectly by down-regulating M&R mechanisms) is certainly possible. Indeed the octopus suicide mechanism operates by causing the organism to cease eating [14]. However, the model suggested here has advantages in that the M&R mechanisms are required in any case so senescence based on M&R mechanisms is arguably simpler. It has also been suggested that gradual multi-symptom senescence has substantial evolvability advantages over acute single-symptom lifespan limitation [2, 4]. It is also possible that M&R processes can consume significant material and energy resources that must be obtained from food. Therefore senescence by down-regulating M&R mechanisms could reduce a population's food requirements relative to a gradual direct-damage scheme, creating an evolutionary advantage for the population.

Regulation in Response to Local or Temporary Conditions

It is common for organisms to possess mechanisms in which a genetically specified inherited design parameter (trait) can be adjusted (within some range) during the organism's life in order to accommodate local or temporary external conditions that affect the optimum value of that parameter. For example, mammals have a large number of genetically specified skeletal muscles. However, the size, strength, and associated blood supply of a muscle can be adjusted to accommodate local or temporary conditions much more rapidly than possible with an evolutionary adaptation that modifies its genome. An animal that happened to live in a mountainous area can acquire larger and stronger leg muscles. A genetically identical animal living in a flatland could acquire relatively smaller muscles and consequently lower body mass, more maneuverability, and reduced energy needs, an obvious advantage for a population. Similarly, many mammals seasonally alter their fur coats. Capability for such regulation or "real-time adaptation" has obvious evolutionary value in increasing the probability that a population will survive and/or produce descendant species.

Any such regulation scheme (Fig 1) requires four elements: There must exist the capability for detecting or sensing the relevant condition(s); there must exist a logical process for determining what action to take as a result of the detected condition(s); and there must exist a means for altering the genetically specified parameter (e.g. muscle size, fur coat, or lifespan), generally in a proportional response to the magnitude of the detected condition(s). Because the part of the organism performing the sensing function is likely to *not* be the part requiring modification, *signaling* would typically be required. Time is a factor in lifespan and many other biological regulation schemes requiring a *biological clock mechanism*.

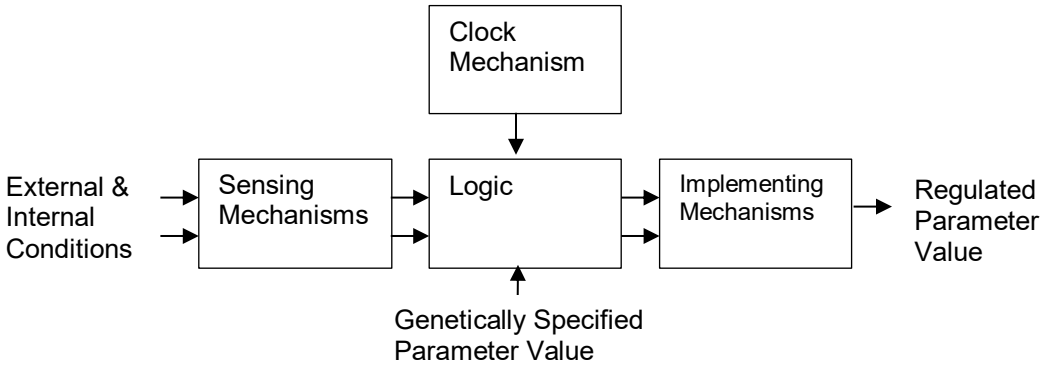

Fig. 1 Typical Biological Regulation Scheme
Functional Diagram

It is clear that many internal or external conditions, which can be temporary or local, can alter the optimum lifespan for an organism. More specifically, obviously programmed and regulated internal reproductive parameters like age-at-reproductive-maturity, gestation time, litter size, seasonal timing and duration of mating activities, and strength of reproductive urges, affect needed lifespan. Trivial example: We can agree that a population that exhibited significant senescence prior to reaching puberty would not be a viable population.

Lifespan and Reproduction Regulation Scenarios and Strategies

How would we expect organism lifespans and reproductive parameters to be regulated in response to various conditions that could vary on a time-scale that was short relative to the time required for genomic adaptation? External conditions that affect needed lifespan and reproductive parameters include degree of population stress caused by predation, infectious diseases, severe environmental conditions, famines, and overcrowding. We can discuss strategies that might be employed by a regulated senescence program in response to these conditions:

It is clear that evolvability is less urgent than a more immediate threat to a population's survival because a species might exist for a long period without evolving. Under famine conditions, it would therefore be logical for an organism to increase individual lifespan while simultaneously reducing reproduction effort relative to genetically specified values. Because reproduction requires more food resources than mere survival, this strategy would allow a population to survive with less food at the expense of a temporary reduction in evolvability.

A temporary increase in predation conditions would increase mortality. Here a population could logically respond by temporarily increasing lifespan while possibly increasing reproductive effort.

Overpopulation would tend to reduce evolvability [2] and otherwise threaten a population [5]. Here a logical response would be to reduce reproductive effort and/or reduce lifespan. Some

mating behaviors (such as seen in Bighorn sheep) clearly act to inhibit reproduction in a population-sensitive manner [2].

Sensing of Conditions Affecting Optimum Lifespan

Altering lifespan and reproductive parameters in response to external conditions requires appropriate sensing mechanisms. We can imagine that there would be many internal consequences of famine and consequent caloric restriction that could be sensed. Detection of overpopulation could involve sensing pheromones.

Detection of predation could involve sensing of physiological conditions likely to exist in predation survivors. The predation-stress hypothesis suggests that lives of typical mammals consist of hours of relatively relaxed boredom interrupted by moments of sheer terror and consequent intense physical activity, and that the frequency of terror episodes would be a measure of predation. Predation could therefore be sensed by sensing adrenal hormones or other internal indicators of terror. Similarly, survivors would have experienced typically brief but intense physical activity that could be detected by a senescence control mechanism. This model suggests that exercise (even periodic brief intense exercise) would act to generally delay mammal senescence.

Biological Clocks

The nature of biological clocks has historically been a rather academic question but the emergence of modern programmed aging theories has caused a situation where understanding the aging clock could be critical to understanding senescence and age-related diseases. Many biological clocks such as those involved in mating seasons and circadian rhythm are obviously synchronized to external cues and therefore involve detection of external conditions. The aging clock could similarly be derived from or synchronized to external cues such as day/night cycle, or in longer-lived organisms, a seasonal cycle.

Empirical Evidence Favoring Externally Regulated Programmed Aging

There is already considerable empirical evidence supporting these scenarios: Exercise and some other forms of physical stress are widely thought to increase lifespan. Recent experiments [15] suggest that High Intensity Interval Training (HIIT) or an exercise regimen calling for periodic brief but intense aerobic exercise has a greater anti-aging effect than other forms of exercise. This finding supports the predation-stress hypothesis. The caloric restriction effect seen in some mammals [16] demonstrates increases in lifespan resulting from dietary limitation.

Regulation of life-cycle events is common. Internal and even external (pheromone) signaling and detection of external conditions are involved in reproduction. Nervous or chemical (hormone) signaling is ubiquitous in coordinating the operation of diverse tissues in performing biological functions.

Hetero-chronic experiments in which aged cells are exposed to blood components from youthful subjects have demonstrated that blood signals can change cell senescence indicators [17]. Hetero-chronic plasma exchange (HPE) has been proposed as a method for studying the effect of blood plasma components on senescence regulation [18]. A human clinical trial is underway to study the effect of young plasma infusion on aging biomarkers [19].

Sensing of pheromones has been demonstrated in lifespan regulation of simple organisms [20].

Many human hormones vary with age [21]. Calcitonin, aldosterone, growth hormone, renin, estrogen, prolactin, and testosterone typically *decrease* with age. Follicle-stimulating hormone, luteinizing hormone, norepinephrine, and parathyroid hormones *increase* with age. Many others are unaffected by age. If the model suggested here is correct, it is essentially inescapable that age-related hormone changes in later life are signaling manifestations of the aging program and that therefore replacement of hormones that decline with age and/or interfering with hormones that increase with age represents an obvious research avenue. Hormone replacement therapy and HPE have been proposed as *treatments* for senescence [22].

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