

Mammal Aging: active and passive mechanisms and their medical implications

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Summary

This article compares two hypotheses regarding the mechanisms responsible for aging in humans and other mammals. In the *passive* mechanism, aging is the result of inadequacies in maintenance and repair functions that act to prevent or repair damage from fundamental deteriorative processes. In the *active* mechanism, a life span management system purposely limits life span by deactivating maintenance and repair processes beyond a species-specific age.

As described here, the active mechanism provides a much better fit to observational evidence while the passive mechanism provides a much better fit to traditional evolutionary mechanics theory. However, there are many other observations that conflict with traditional theory and consequently a number of alternative evolutionary mechanics theories have been developed since 1962. Several of these alternatives support active life span management and aging theories providing a rationale for active life span management have been developed based on each of those alternatives.

This issue is very important to our ability to treat age-related diseases and conditions. If indeed the passive mechanism is correct, then efforts should continue to be exerted to find treatments for each different manifestation of aging, independently of the others. If the active concept is valid, it is clear that there are, in addition, substantial

opportunities for finding agents that generally delay aging and simultaneously ameliorate multiple manifestations of aging.

In the past, the evolutionary issues have been used as essentially the entire justification for summarily rejecting active theories. Given the public health considerations and the increasing number of issues surrounding evolutionary mechanics theory, this is no longer a reasonable or responsible path.

Primary Observation on Aging Mechanisms

The primary observation driving mammal aging theories is that different mammal species exhibit dramatically different life spans in protected environments even though they possess very similar biochemistry and the deteriorative processes implicated in aging are biochemical in nature. The extremely species-unique nature of life span led to the development of *evolutionary* theories of aging in which aging theories are derived from evolutionary mechanics theories, more specifically theories that describe how organisms acquire their species-specific designs. Mammal life spans vary over an approximately 100:1 range between humans (~75 yrs) and the Argentine desert mouse (*Eligmodontia typus* ~ 0.7 yrs).

Active and Passive Aging Mechanisms

This article compares two different types of mechanism proposed for gradual aging in humans and other mammals. In the passive mechanism, aging is the result of generic deteriorative processes such as oxidation, molecular disruption, genetic transcription faults, mechanical damage, and other natural processes that cause deterioration in biological systems. The gross life span differences are explained by the presence of a large number of independent anti-deterioration functions that act to prevent damage from or repair damage resulting from the generic deteriorative processes. A particular longer-lived mammal species possesses more effective anti-deterioration functions than a shorter-lived species.

In the active mechanism concept, humans and other mammals possess life span management systems that actively limit life span to a species-unique value. We can think of these mechanisms as biological suicide, or self-destruction mechanisms. These mechanisms can be expected to vary between species just as evolved mechanisms that provide for vision, digestion, or mobility vary between species. The generic deteriorative processes may be harnessed in implementing a life span management system. The first formal proposal of an active aging mechanism was Weismann's "programmed death" theory of 1882[1].

Evolutionary Mechanics Theories

Orthodox Darwinian evolutionary mechanics theory teaches that it is impossible for an organism to develop through the evolution process a design that limits life span unless that characteristic also conveys some compensating benefit for individual organisms or their direct descendents. (We could imagine in this context some characteristic that decreases life span but also increases reproductive capacity.) Those who believe in orthodox theory therefore contend that active aging mechanisms designed specifically and primarily to limit life span are impossible regardless of any purported supporting observational evidence. A passive mechanism conforms to orthodox theory: Evolution of *anti*-deteriorative functions conforms; evolution of *pro*-deterioration functions does not. Orthodox aging theories contend that because of Medawar's hypothesis[2], different

mammal species had different needs for life span and therefore evolved different anti-deteriorative functions.

However, relatively recently (since ~1960 and more intensively since ~1990), a number of alternative evolutionary mechanics concepts have emerged supporting the idea that a limited life span would convey benefits directly (without individually beneficial compensating effect) and that therefore active life span management could and did evolve. In addition to discrepancies between observations and orthodox theory, some evolutionary issues of an internal logical nature have surfaced that are not answered by orthodox theory. These issues have been described in detail elsewhere[3].

Many theorists believe in some version of the passive concept or some version of the active concept. In order to provide a more focused discussion, the particular concepts and supporting arguments provided here are specifically those of myself as a proponent of active mechanisms[3] and Aubrey de Grey as a proponent of passive mechanisms[4]. De Grey and I agree that, considering only the primary observation, the passive concept fits the primary observation as well as the active concept. Further, we agree that given that the passive concept works equally as well in any particular case there would be no evolutionary motivation to develop and retain a more complex active concept. However, there are many other observations that provide direct evidence as to the nature of the aging mechanism, and there are also benefits that can be produced by the active concept and not by the passive concept. These are discussed further below.

Observation 2: Semelparous Species

Semelparous species, in which life span limitation is associated with reproduction rather than gradual deterioration, represent obvious instances of active life span management. Some mammals (marsupial mouse[5]) are semelparous, and some multiparous species (e.g. some salmon) also possess active life span management. In my view the existence of obvious active suicide mechanisms in some species suggests that others including humans possess more subtle active mechanisms. Further, since mammals are generally more complex than salmon or octopus, and possess more complex mechanisms for vision, digestion, mobility, and other functions, we would expect them to also have more complex and capable mechanisms for life span management.

Darwin (~1859) provided a rationale[6] for the general observation that organisms seemed to be designed to have a species-specific life span as well as for the semelparous species that were more obviously designed to have a particular life span: Since his mechanics theory demanded it, there must be some hidden theory-conforming (individual) benefit to offset the individually adverse observation. Of course this was a circular “explanation.” The theory was being used to predict the observation as opposed to the reverse. The same “explanation” could be used to “explain” any observation of an apparently individually adverse organism design characteristic.

At the time this was a reasonable position. There were perhaps thousands of non-conforming life span observations as opposed to millions of conforming observations. Any high-school student could easily observe myriad examples of plant and animal design characteristics that obviously aided the organism’s ability to survive or reproduce

and Darwin had a reasonable expectation that, eventually, conforming offsetting benefits would be discovered for the minority of apparently non-conforming observations. Subsequently, most efforts to develop evolutionary aging theories were limited by the need to demonstrate compensating individual benefit.

However, by ~1960, even semi-plausible conforming compensating benefits for the majority of the semelparous animal observations had still not been discovered. In addition, other apparently non-conforming observations (of individually disadvantageous or neutral design characteristics) eventually surfaced including sexual reproduction, excess male puberty age in some species, some mating rituals, altruism, and some aspects of inheritance systems[7].

The protracted existence of thousands of non-conforming observations was not scientifically acceptable to many people. Alternatives to orthodox evolutionary mechanics theory including group selection[8](1962), kin selection[9](1963), selfish gene theory[10](1975), and evolvability theory[11](~1995) were consequently proposed as modifications or adjustments to orthodox theory. All of the alternatives propose that design characteristics that aid groups of the same species (beyond direct descendents) or that aid the evolution process could evolve despite some degree of individual disadvantage.

Specific biological aging theories supporting the evolution of active life span management have been developed for group selection[12], kin selection[13], and evolvability[14,15]. Several of these theories hold that life span management is generally beneficial, even essential, to complex species and even suggest that gradual aging is superior to semelparous life span management specifically because it is gradual and multi-system.

It is certainly true that currently there is no single generally accepted alternative to orthodox evolution mechanics theory. However, it is also true that there is a wide understanding that orthodox theory has major problems; there are hundreds of journal articles extant discussing various aspects of this issue.

De Grey, unlike most other proponents of passive theories, accepts that one or more of the alternative evolutionary mechanics theories may be valid. He also concedes that semelparous species are indeed examples of active life span management. However, he uses essentially Darwin's "explanation" to justify his position that the semelparous species are irrelevant to gradual mammal aging: We should disregard the semelparous species because they are the "exception to the rule" among the much larger number of gradually aging species. We should assume, without evidence, that *each and every* semelparous species has some hidden need, not possessed by *any* gradually aging species, for active biological suicide where most mammals and other gradually aging species, even though generally more complex, can get by with the simpler and less flexible "default" passive mechanism. By definition, no believer in any of the alternative evolutionary theories accepts these arguments. All the alternatives (like Einstein's relativity theory) are based on a minority of observations. All are based on the idea that we should not simply ignore conflicting observations.

Observation 3: Similarity of Aging Manifestations in Short-lived and Long-lived Mammals

Symptoms of aging (grossly increased incidence of many diseases including cancer, skin and hair conditions, arthritis, cataracts and other sensory deterioration, muscle weakness and other mobility deterioration, etc.) are generally similar between short-lived and long lived mammals. This suggests that the causing deteriorative processes all operate over a relatively short time span (less than the life span of a short lived mammal). If this were not so, short lived mammals would not display some of the manifestations. Therefore all mammals need all of the maintenance functions. Without the maintenance functions mammal life spans would be limited to a matter of months, probably less. De Grey agrees that the deteriorative processes are short-term. Since the deteriorative processes and corresponding maintenance functions are respectively universally present and necessary in mammals and other complex organisms, they are an obvious choice as components of an active life span management system.

Consider the candidate or straw-man concept for an active mammal life span management system diagrammed in Fig. 1. In this concept, maintenance and repair functions exist to counter damage from the generic deteriorative processes. A biological clock gradually disables the maintenance functions at a species-specific age allowing the deteriorative processes to subsequently produce aging symptoms. The difference between short-lived and long-lived species is not in the maintenance functions but in the biological clock. Similar species differences exist regarding the clock that determines age of puberty. This scheme matches observation 3 as well as the other observations and is generally more capable and flexible than the passive system.

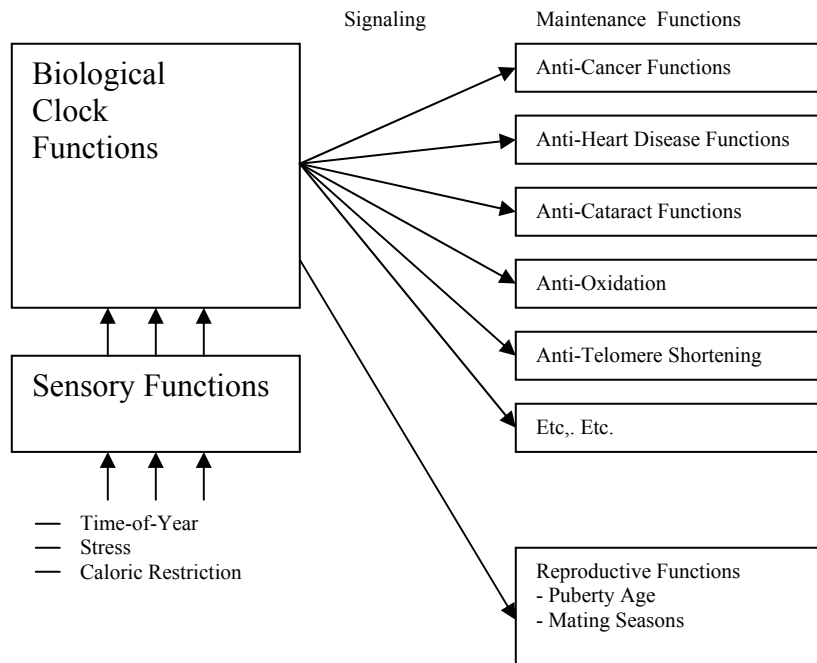


Fig. 1 Candidate Active Aging Mechanism Functional Diagram

In the passive scheme, for progressively longer-lived mammals each of the many maintenance mechanisms is in some way better and more capable than the corresponding mechanism in the next shorter-lived mammal. This requires an undemonstrated assumption: that for some reason, *each* of the maintenance tasks is more difficult or otherwise needs a different design in its corresponding mechanism as the life span of the animal increases. This is counter-intuitive. Is “replace dead cells” or “repair short telomeres” a different process at age 100 than at age 1? Is “change the oil” a different automobile maintenance process at 100,000 km than at 10,000 km? It also requires another undemonstrated assumption: that each maintenance process can be incrementally improved as opposed to discrete steps of improvement. We would need “replace dead cells”, “replace dead cells better”, “replace dead cells better yet”, and so forth. The active scheme does not require either assumption.

De Grey suggests that indeed a process like “replace dead cells” would become more difficult with increasing life span because of increasing prevalence of mutational changes but does not suggest the type of incremental improvement that would fit the second assumption.

Observation 4: Progeria and Werner’s Syndrome

Hutchinson-Guilford progeria[16] and Werner syndrome[17] are human conditions in which a single-gene malfunction causes acceleration of many or even (Werner) most symptoms of aging. In the active concept of Fig. 1 it is clear that such a malfunction could affect the clock function or another of the serial processes involved (sensing, signaling) and therefore result in the accelerated symptoms.

In the passive scheme, it is assumed that each of the maintenance mechanisms evolved separately and independently to counter each different manifestation of aging. If cancer at too young an age was becoming a problem, the species would evolve better anti-cancer mechanisms, and so forth. It seems improbable that a single-gene malfunction would similarly affect all of the independent maintenance mechanisms in the passive scheme.

Observation 5: Caloric Restriction, Exercise, and Stress

Caloric restriction, exercise, and some other instances of stress have been found to result in the counter-intuitive observation that they all increase life span[18]. In the active scheme of Fig. 1, the organism has a method for sensing these conditions and adjusting the self-destruction timer. This satisfies various adaptive theories of aging that contend that the optimum life span for a species varies depending on local or temporary conditions.

De Grey suggests that the life span response to these external conditions is not related to the aging mechanism.

Observation 6: Aging Genes

Some investigators have reported the discovery of genes that promote aging in various organisms with no observable individual benefit. They further suggest involvement of signaling in implementing life span “regulation”[19]. These findings directly support active mechanisms.

Orthodox theorists contend that the “aging genes” must have some hidden individually beneficial purpose.

Flexibility Argument

One argument in favor of the active system is that it is generally more flexible in *adapting* to changes in an organism’s situation. As described above, an active system could adapt non-genetically and instantaneously to local or temporary conditions that alter the optimum design-life-span for that organism. It could also genetically adapt more rapidly as follows: In the passive scheme, if an organism needed a shorter life span, we can imagine that deleterious mutations to *each* of the many maintenance mechanisms would rather rapidly (in evolution terms) accumulate thus shortening life span (requires the above described assumption that all the maintenance functions are continuously variable). However, if the need was for a longer life span, the organism would have to evolve improvements to the designs of all of its many mechanisms, a likely very much longer process. In the active concept a much simpler change to the clock could increase as well as decrease life span much more rapidly. The ability to adapt more rapidly would be a competitive advantage.

De Grey contends that the passive mechanism is sufficiently adaptive and that it has not been proved that any gradually aging species needs more adaptability.

Diversity Argument

Life span is one of the most superficial of all animal characteristics. There are species that are virtually identical (e.g. salmon varieties) and yet have grossly different life spans. This suggests that there is value in having a flexible life span management system. It also suggests that life span is controlled by a relatively small number of genes, which also favors the active concept and corresponds with observation 6.

Conclusions and Medical Implications

A schism has existed in the science of biology for many decades (some would say ~150 years). On one side are believers in strict orthodox evolutionary mechanics theory. On the other are those who support one of the alternative theories or who otherwise have a less restrictive interpretation of the word “benefit” as it appears in the sentence: “Organisms evolve design characteristics that benefit them.” No one would be surprised if this academic argument persisted for another 150 years.

Despite de Grey’s professed neutrality, this issue essentially dictates one’s position on the question of human aging. Those believing in orthodox theory are logically forced toward some version of the passive concept or other orthodox-compatible theory. The

others are driven inexorably by logic, empirical evidence, and Occam's razor toward some version of the active concept.

It is now clear that this endless academic wrangling could dramatically limit the approaches we take in attempting to find treatments for age-related diseases and conditions and that therefore this argument has come to have major public health implications. Perhaps it is time for some sort of national or international commission to evaluate all the available evidence and produce a conclusion regarding aging mechanisms. There are doubtless experiments that could be devised to more definitively distinguish between the very different aging mechanism concepts.

The major medical issue is the degree of commonality that exists between the various diverse and apparently unrelated manifestations of aging. The passive theories (as well as the generic molecular damage theories held by many members of the general public) lead to the conclusion that each manifestation is functionally independent of the others and thus suggest that attempts to treat each individual manifestation represent the only valid approach to the aging problem, a continuation of the existing medical paradigm. The active theories lead to the conclusion that there are potentially many elements of commonality between the various manifestations and that therefore agents could be found for modifying those common elements so as to simultaneously treat many different manifestations, a potentially major addition to the current approach.

While one can argue either side of the evolutionary mechanics issue it is increasingly difficult to argue, given the observational evidence summarized here, that there are no potentially treatable common factors between different manifestations of aging. Further, there are hints that some agents capable of affecting multiple diverse manifestations may already exist. Example: Statins are reported to beneficially affect heart disease and some cancers[20].

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