Global aging and the brain

Thomas BL Kirkwood

Intrinsic aging of the brain and its relationship to age-related neurodegenerative diseases need to be understood as part of global aging, which results from gradual accumulation of a variety of kinds of cellular and molecular damage. While certain kinds of molecular lesions are particularly associated with specific diseases, there is substantial overlap between the pathways causing disease and those contributing to global aging. Growing evidence indicates that the global aging process is more malleable than used to be thought. This needs to be taken into account in efforts to improve health and retention of mental capital across the life course.

INTRODUCTION

To dispel any possible misunderstanding of the title, this article will focus on the aging process within the body as a whole rather than population aging as it occurs around the globe. There is, however, a connection between the two, because population aging is a global phenomenon that presents a huge challenge to humanity, making the understanding of the biological basis of human aging an urgent priority. In developed countries, life expectancy has been increasing over the last 200 years, and in most developing countries, the rate of increase in life expectancy is now even faster, as a “catch-up” process is under way. The United Nations as recently as 1980 projected a future that presupposed a limit to life expectancy. This was based on the widely held view that the aging process is biologically determined with a preprogrammed limit so that if people were prevented from dying early in life of infectious diseases, they would simply hit the maximum age limit. Since then, however, it has become clear that life expectancy is continuing to increase. Over the last 2–3 decades it has become clear that the basis of the continuing increase in life expectancy has changed from being primarily the reduction of mortality in the early and middle years of life to being now almost exclusively the reduction of mortality in the later years of life. These demographic data show there is much more plasticity or malleability of the aging process than used to be thought.

CONTROL OF THE AGING PROCESS

The idea that aging is genetically specified and therefore hardwired might appear to have been reinforced in recent years by the discovery of gene mutations that affect lifespan in a range of animal species. Major discoveries have been made in nematode worms,1 in fruit flies,2 and, more recently, in mice.3 It is also known that there are mutations in genetic syndromes of accelerated aging in humans. This might imply that aging is actively controlled by genes, with relatively simple underlying machinery specifying some clock- or gene-regulated process that drives aging. Murphy et al.,4 however, showed in nematodes that although a specific pathway involving elements of insulin/IGF1 signaling produces major effects on lifespan, this pathway acts ultimately on literally hundreds of downstream genes that specify not a clock but a wide variety of cell maintenance systems, such those involved in stress resistance, resistance to microbial infection, and protein turnover. Thus, in terms of the actual mechanisms that act on aging, these appear to be highly complex and to be intimately connected with cell maintenance.

Another feature challenging the idea that aging is hardwired is the remarkable variability seen in the lifespans of individual worms sharing the same genotype and living in highly uniform environments.5,6 Populations of isogenic worms exhibit great precision in their developmental processes, but this tight specification is

Affiliations: TBL Kirkwood is with the Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, United Kingdom.

Correspondence: TBL Kirkwood, Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, United Kingdom. E-mail: tom.kirkwood@ncl.ac.uk, Phone: +44-19-1248-1103, Fax: +44-19-1248-1101.

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not seen in length of life. If aging were programmed, it might be expected that the programs for development and aging would show similar precision. The biology of aging is therefore characterized by a combination of considerable mechanistic complexity and pronounced stochastic variation. In order to explain these features, it is helpful to ask questions about how and why aging occurs, using an evolutionary perspective in the spirit of Theodosius Dobzhansky, the great evolutionary biologist of the 1950s, who stressed that “nothing in biology makes sense except in the light of evolution.”

The aging process appears, at first, to be a curious manifestation of the action of natural selection, since aging limits survival and must therefore run counter to Darwinian fitness. In this regard, the first important observation to note is that field zoological studies show it is actually very rare to see old animals in nature. In wild environments, animals die young. This in itself speaks against the idea of programmed aging, since natural selection could not easily evolve an aging process that acts so late that most individuals are dead before it comes into play.

The rarity of naturally senescent animals, however, can be used to explain the evolution of aging in another way. The manner in which organisms make use of the energy they acquire plays a central role in biology. Darwin’s theory of evolution by natural selection can be paraphrased by the principle that the organisms that make the best use of resources to produce their lifetime output of progeny are the ones that are going to do best in the genetic competition. One consideration is how much energy organisms invest in maintenance and repair activities. These activities account for a very large fraction of metabolism. Logically, one should only invest into maintenance and repair that amount of effort that is sufficient to keep the body in good shape for as long as it might reasonably expect still to be alive, i.e., the disposable soma theory.

This disposable soma concept has clear implications for the biology of aging. First, it emphasizes that aging is driven by the accumulation of damage, which is a lifelong process. Second, although genes do influence the aging process, they do it by regulating the investments that are made in the maintenance and repair processes in the somatic cells, tissues, and organs of the body. Within the reproductive cell lineage – the germ line – the requirement for maintenance is always high, but somatic cells that differentiate away from the germ line do not require nearly as much energy for maintenance processes.

This brief overview of the evolutionary logic that explains aging tells us that global aging – the general deterioration of bodily systems – has its foundation in the fact that, in earlier times, when extrinsic mortality in the young and middle years of life was high, the human genome was under greater selection pressure to reproduce than to build and maintain a body that might last forever. The key to aging, therefore, is in the optimal use of metabolic resources. An interesting extension of this view also explains the discoveries that organisms that are subject to fluctuations in energy availability may modulate their relative investments in reproduction and maintenance to make the best of unpredictable environmental circumstances. In nematode worms, food shortage induces an alternative developmental pathway – the dauer larva – in which the worm enters into a long-lived, stress-resistant dispersal form. It is noteworthy that the genes identified as producing major effects on nematode longevity, such as daf-2 and daf-16, are players in the dauer formation pathway; their involvement in central metabolic regulation is entirely consistent with this role.

A similar adjustment to environmental changes is seen in the rodent response to calorie restriction, which is associated with reduced fertility, increased maintenance, and longer lifespan. It is known that calorie restriction works in short-lived animals, in which there is sound evolutionary logic to suggest it may be sensible in times of famine to divert resources from reproduction to maintenance. However, the same logic indicates it is highly unlikely that calorie restriction will increase lifespan in human beings, in whom a much smaller fraction of total metabolism is allocated to reproduction. Calorie restriction studies in nonhuman primates are under way, but it will be surprising if a dramatic effect is seen on lifespan. Some interesting metabolic effects are evident, but if something as fundamental to an organism’s biology as the amount of food it has available is manipulated, it would be surprising if no effects were observed.

**PROGRESSIVE MOLECULAR DAMAGE AS A MAJOR UNDERLYING PROCESS**

This evolutionary prelude provides the background to understanding the global aging process. The global aging process can be summarized very simply as a process that is driven by the lifetime accumulation of a wide variety of molecular-damaging events. The body accumulates cellular defects that lead, over decades in the case of humans, to age-related frailty, disability, and disease. The genetic regulation is not for aging per se but for longevity, and it relates to the mechanisms that protect against this accumulation of damage.

The recognition that aging is neither more nor less than the gradual lifelong accumulation of damage explains a feature of human aging that has become apparent only over the most recent decades: the whole process of global aging is malleable. Stresses can accelerate the accumulation of damage, whereas protection from stress may slow it down. The importance of nutrition also emerges. Poor nutrition, such as a diet rich in fatty ingre-
dients or sugars, does not simply make one obese and unhealthy, it also impacts the underpinning molecular mechanisms of damage accumulation that drive the aging process. Healthy nutrition, as exemplified by the Mediterranean diet, counters this tendency both by minimizing additional damage and by enhancing natural protection mechanisms. The overall process of metabolism involves the generation of reactive oxygen species that are constantly damaging the DNA and proteins in all cellular structures. To counter this, there is an army of repair enzymes and pathways that are constantly repairing the damaged cellular machinery. Given the appropriate nutrients and other beneficial factors, such as exercise, a great deal of the damage can be combated. The malleability of aging is also influenced by the interplay between inflammatory and anti-inflammatory mechanisms in the body. It is beginning to be possible to examine how all of these factors impinge on the aging process. Although a detailed understanding of all the mechanisms is not yet available, current understanding of the interplay between progressive damage and repair shows a clear malleability within the system, which can explain the continuing increase in life expectancy in terms of the less damaging conditions of modern living.

THE CHALLENGE OF MALLEABLE AGING AND AGE-RELATED DISEASES

The malleability of the aging process implies there are opportunities to decrease exposure to damage through, for example, improved nutrition, lifestyle, and environmental changes, or perhaps by enhancing natural protection mechanisms. It is also important to consider how changing lifespans are associated with possible changes in the incidence and prevalence of age-related diseases. There has long been a difference of opinion as to whether global aging and age-related diseases are distinct aspects of the biology of aging, or whether they are inseparably linked. The distinction, however, seems increasingly pointless as more is discovered about the causes of age-related diseases, most of which, like global aging itself, are driven by the accumulation of molecular and cellular damage. The key relationships include the extent to which the damage underlying the various diseases overlaps with the global aging process or whether the disease process involves specific degenerative outcomes. In order to better understand the common ground between aging and age-related diseases, there is a need to work upstream in the causal pathways. It is becoming apparent that in many cases there are common underlying processes, an observation that has significant implications.

In Newcastle upon Tyne, in the United Kingdom, a major study is presently examining the variability of aging in the extreme elderly. It is known that people >85 years of age comprise the most rapidly growing segment of the population demographically, but thus far there is remarkably little information on the spectrum of health status in this age group. The Newcastle 85+ Study has collected extensive data on the biological, clinical, functional, and psychosocial aspects of a cohort of more than 1,000 individuals born in 1921. Prospective analyses are also under way to see which factors influence good and bad trajectories in health beyond age 85. The baseline data showed good levels of both self-rated health and functional ability, despite significant levels of disease and impairment. Hypertension, ischemic heart disease, atrial fibrillation, depression, and dementia may be underdiagnosed by this self-rating system, but it is clear that there are notable differences between the sexes: women outnumber men and have more disease and disability. ¹¹

TELOMERE CHANGES, MITOCHONDRIAL AGING, OR PROTEIN AGGREGATION AS THE KEY?

Inevitably, different research groups focus on their particular area of interest. Yet, on a cellular basis, there are whole systems and networks of mechanisms that are vulnerable to damage. These involve the whole molecular pathway from DNA stability to RNA processing to protein synthesis and the control of protein degradation.¹² This system and the mitochondrial oxidative mechanisms are all interconnected.¹³ It is probably also necessary to distinguish between dividing cells and postmitotic cells. In dividing cells, telomere erosion, gene mutation, and epigenetic dysregulation are the most important processes, whereas in postmitotic cells, processes like protein aggregation and mitochondrial dysfunction may prove more important, with oxidative stress affecting both cell types.

The recently established Centre for the Systems Biology of Aging and Nutrition (CISBAN) is examining the interconnections and interactions between different mechanisms. It has long been known that there is an extraordinary heterogeneity from cell to cell in the way that aging progresses.¹⁴ Research within CISBAN has highlighted the synergy and interactions among different mechanisms. Using a combination of computer modeling and detailed experimental analyses of different candidate mechanisms, it has been possible to assess telomere-driven replicative senescence to see whether mitochondrial dysfunction might play a role. The findings have indeed shown such interaction, with the mitochondrial component providing a very compelling explanation of cell-to-cell heterogeneity. Systems biology is helping to replace simplistic explanations of the Hayflick limit, i.e., the limited replicative capacity of cells based on strict cell-division-counting mechanisms, with a more convincing explanation that takes account of the intercommunicating
cycles of damage between the mitochondria, the telomeres, and the general chromosomal DNA of the cells.\textsuperscript{15}

**AGING AND THE BRAIN**

It is now time to use this review of mechanisms of global aging to ask how, if at all, these mechanisms contribute to aging of the brain. In terms of brain function, the challenge is to start looking for evidence of similar molecular malfunctions occurring in the brain generally. An important turning point in understanding the fundamental mechanisms of intrinsic neurodegenerative processes will involve bringing together a comprehensive view of the modulation of these intrinsic mechanisms. It is already known that there is evidence of mitochondrial dysfunction in normal brain aging in the form of increased numbers of cells that carry a heavy burden of mitochondrial DNA (mtDNA) mutations. In conditions such as Alzheimer’s disease, there is an increase in the percentage of cytochrome-C-oxidase (COX) negative neurons in the hippocampus and choroid plexus of Alzheimer’s disease patients. These COX-negative cells are likely to possess significant levels of mtDNA mutations, since COX is mitochondrially encoded, and this can be confirmed by laser microdissection of the individual brain cells with analyses of the genomic sequence of the mitochondrial genes. COX-negative cells are found in greater numbers in Alzheimer’s disease patients than in controls in whom aging is not accompanied by significant cognitive deterioration.\textsuperscript{16} Similar effects are also seen in Parkinson’s disease,\textsuperscript{17} so it seems that these generic underlying mechanisms are accumulating in normal brain aging as well, but at a faster rate in specific age-associated neurodegenerative conditions. Understanding is also emerging of the connections between these mitochondrial changes and the process of the age-related breakdown in protein homeostasis that appears responsible for the formation of pathogenic protein aggregates. If mitochondria are damaged, one might expect more reactive oxygen species to be produced with less ATP generation, so that energy-demanding protein clearance mechanisms may not work as well. Proctor et al.\textsuperscript{18} are studying the relationship
between neurodegeneration and the control of protein aggregation using systems biology computational models. This leads to some very interesting questions about the accumulation of protein aggregates seen in many age-related disorders. This is another facet of the accumulation of generalized damage seen with global aging, and the resulting accumulation of protein aggregates seen in age-related brain diseases may simply reflect the action of this mechanism.

AGING, MENTAL CAPITAL, AND WELL-BEING

As populations age, it is increasingly important to understand the effects of global aging on the mental capital and well-being of older people. This has been the focus of a major Foresight project within the United Kingdom, under the auspices of the Chief Scientist and the Government Office for Science. The Foresight report “Mental Capital through Life” integrates an extensive review of the science.19 Like the Marabou meeting, for which the present work was prepared, it reflects a growing focus on how best to improve the trajectory of mental capital throughout life. An individual is born with an uneducated, unformed brain that has to develop and then sustain its mental capital until, as late as possible, it falls prey to intrinsic aging and the possible impact of neurodegenerative diseases (see Figure 1). The big challenge is to elucidate what determines this trajectory of mental functioning; the goal is to keep the trajectory as high as possible for as long as possible.20 Given new insights into the plasticity and malleability of the global aging process, new opportunities need to be considered to delay the onset of age-related deterioration in the functions of the brain and to maintain mental functioning.21

CONCLUSION

Research into the mechanisms underlying aging of the brain needs to take careful account of new discoveries concerning the mechanisms of intrinsic global aging. Aging results not from any direct genetic programming but from the gradual accumulation of damage. The longevity and health trajectory of an individual is influenced by a combination of the following factors: 1) genetic factors conferring the degree of maintenance and repair of cellular systems; 2) environmental factors, including lifestyle and nutrition, which act both on the exposure to damage and the capability of repair systems; and 3) the play of chance at the level of how damage affects molecules and cells in the brain and other organs of the body. This tripartite underpinning of health across the life course is consistent with growing evidence for the malleability of aging. It offers scope for novel interventions to improve the trajectory of brain health.

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REFERENCES