

Aging in Rhesus Monkeys: Relevance to Human Health Interventions

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Progress in gerontological research has been promoted through the use of numerous animal models, which have helped identify possible mechanisms of aging and age-related chronic diseases and evaluate possible interventions with potential relevance to human aging and disease. Further development of nonhuman primate models, particularly rhesus monkeys, could accelerate this progress, because their closer genetic relationship to humans produces a highly similar aging phenotype. Because the relatively long lives of primates increase the administrative and economic demands on research involving them, new emphasis has emerged on increasing the efficient use of these valuable resources through cooperative, interdisciplinary research.

As gerontological research continues to gain both visibility and interest within the broader scientific community, the relevance of various model systems for eventual application of findings to humans has become a critical issue. Although rodents remain the most widely used animal model for gerontology, an increasing use of invertebrates has provided many new insights into aging processes, especially regarding possible longevity genes (1). Given the complexity of human physiology, however, models more phylogenetically similar to humans are needed.

Advantages and Disadvantages of Nonhuman Primate Models

Research using nonhuman primates can provide a valuable approach for elucidating the nature and causes of aging processes observed in humans as well as evaluating potential interventions. An ongoing longitudinal study of aging and nutrition in rhesus monkeys (*Macaca mulatta*) conducted since 1987 by the National Institute on Aging (NIA), as well as studies conducted at other sites, has revealed much about aging and age-related disease in these monkeys and has shed light on the advantages and disadvantages of their use in gerontological research. Because of their genetic homology to humans (92.5 to 95%), many biological similarities are observed in the profile of aging. Another advantage is that rhesus monkeys are well adapted for laboratory research, including established husbandry, nutrition, breeding practices, and veterinary medicine. Disadvantages of rhesus monkeys include their current limited

availability, costs of procurement and maintenance, and genetic heterogeneity. In addition, cross-species risks of disease transmission exist, and issues of animal welfare require constant vigilance. Research in monkeys is only as good as their physical and emotional health.

The major scientific disadvantage is that rhesus monkeys are long-lived. Sexual maturity occurs at 3 to 5 years of age, median life-span is 25 years, and maximum life-span is 40 years (2, 3). With an estimated maximum life-span of 122 years in humans (4), the rate of aging in rhesus monkeys is roughly three times as fast. Thus, rhesus monkeys offer a distinct advantage over long-term human aging research, but longitudinal studies in these primates require a major investment of time, resources, and effort.

Scope of Rhesus Monkey Research

The NIA supports colonies of aging rhesus monkeys at five primate research centers in the United States (5); however, most studies conducted in these monkeys are cross-sectional in design. Ongoing longitudinal studies of aging and age-related disease in rhesus monkeys are being conducted at three sites: the NIA, the Wisconsin National Primate Research Center (WNPRC), and the University of Maryland, Baltimore (UMB). Research at UMB has focused on obesity and diabetes (6). With the assistance of numerous international laboratories, studies at the WNPRC and the NIA are evaluating the hypothesis that a nutritious low-calorie diet can retard the rate of aging (7, 8). These studies use a regimen of calorie restriction (CR) 30% below control levels and represent the first experiments to evaluate effects of CR on aging processes in a primate species. As demonstrated in numerous studies of invertebrate and vertebrate models, CR is the most robust and reproducible method for slowing aging, as evidenced by reduced incidence and delayed onset of age-related diseases, extension of mean and maximum life-span, increased

stress resistance, and improved physiological and behavioral function (9). Emerging from years of research at many sites, abundant information on aging processes in rhesus monkeys has been generated to document parallels and relevance to human aging at organismic, tissue, cellular, and molecular levels of analysis.

Aging Parallels

Regarding morphology, physiology, and behavior, the profile of aging in rhesus monkeys is remarkably similar to human aging (Fig. 1). Sensory systems decline in rhesus monkeys, including presbyopia (loss of near vision) and presbycusis (loss of high-frequency hearing) (10, 11). With advancing age, they lose accommodation of the lens and develop cataracts and macular degeneration (11). Regarding behavioral function, their general level of motor activity declines with age (12) with gradual decrements in fine-motor skills (13). Advancing age does not generally affect simple discrimination learning abilities, but when demands are placed on working memory capacity, the clear age-related decline in learning and memory performance is notably similar to humans (14).

Age-related changes in physiological function include declines in metabolic rate and core body temperature (15). Age-related changes have not been reliably observed in cardiac function, including heart rate, blood pressure, or measures of arterial stiffness, but the possible contribution of dietary sodium to these age-related changes is currently being addressed. Regarding diet, another interesting parallel to humans is an apparent decline in appetite, manifested as a gradual decline in food intake (16).

Structural changes with aging are also evident in rhesus monkeys. Their stature becomes diminished, and bone mineral density in selected sites declines with age (17). Age-related changes in cartilage occur as reduced space between vertebrae, similar to osteoarthritis in humans (18).

Body composition in rhesus monkeys also parallels changes observed in humans. Their fat mass, particularly abdominal fat, increases with age, whereas lean body mass declines (19). Regarding skin quality, age-related deterioration in wound healing has been documented (20). At a biochemical level, glycation of rhesus skin proteins is similar to that in humans but occurs at a predictably faster rate (21).

Age-related changes in the rhesus brain have also been studied. Although overall brain

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mass does not decline with age as measured by weight (22), reductions have been observed in specific regional volumes with magnetic resonance imaging, such as the basal ganglia (23). Similar to humans, no significant loss of hippocampal or neocortical neurons occurs (24, 25). Behavioral deficits associated with hippocampal dysfunction appear to result from decrements in interneuronal signaling rather than cell death (25). Cerebral blood volume decreases with age in the hippocampal dentate gyrus (26), and the cerebral cortex loses dendrites and arbors with age (25). Neurotransmitter receptor and transporter binding in specific regions, including postsynaptic dopamine receptors (27) and presynaptic vesicular acetylcholine transporters (28), show age-related loss in the basal ganglia. Hippocampal cholinergic fibers are also lost with age (29), and there are notable alterations in the integrity of white matter (30).

Rhesus monkeys also develop pathological characteristics of Alzheimer's disease (AD), specifically the deposition of amyloid- β ($A\beta$) plaques with regional deposition similar to humans (31). $A\beta$ plaques are associated with angiopathy (32). Although $A\beta$ accumulates in older rhesus brains, neurofibrillary tangles, another hallmark of AD pathology, have not been observed (33). Driven by the success in mice, there is growing interest in producing transgenic monkeys in which AD and other neurodegenerative diseases can be accurately modeled (34).

Parallels also exist between rhesus monkeys and humans regarding age-related hormonal changes, including decreased plasma levels of melatonin (35) and dehydroepiandrosterone sulfate (DHEAs) (36). Hormonal changes are also observed in the reproductive system. The circulating concentration of testosterone and its pulsatile release decline with age in male rhesus monkeys (37). Rhesus females experience the perimenopausal transition similar to women at similar stages of the life-span, but the age of initiation of endocrine changes varies in both species (38, 39). As the perimenopausal transition progresses in women, gonadotropin levels increase. A simultaneous decrease in ovarian response results in insufficient hypothalamic-mediated stimulation of preovulatory luteinizing hormone release. Ultimately, declining function of the hypothalamic-pituitary-gonadal axis culminates in menopause (40). The rhesus monkey is an appropriate model because of similarities in the perimenopausal transition as well as providing essential data on the consequences of perimenopausal hormonal changes on neural systems (39). These observations are especially relevant considering the controversy surrounding hormone replacement therapy,

and ongoing studies will greatly elucidate clinical applications for women.

Aging in human immune function is believed to manifest itself, at least in part, as an increased susceptibility to infectious and autoimmune disease and cancer. This may be related to age-related changes in cytokine production. Studies in rhesus monkeys have demonstrated age-related increases in interleukin (IL)-6 and IL-10 production and decreased interferon γ (41, 42), similar to reports in humans (43).

Pathology

Accompanying the biological changes that parallel aging in humans, these animals develop and die from similar chronic diseases. Although with normal diets rhesus monkeys do not develop severe atherosclerosis, other cardiac pathologies occur, including aortic valve calcification, interstitial fibrosis, hypertrophy of cardiac muscle, myocardial infarction, cardiac arrest, and congestive heart failure (3). On high-fat diets, however, rhesus monkeys do develop atherosclerotic plaques (44). They also develop cancer, including carcinomas and sarcomas with intestinal adenocarcinomas as the most common malignant neoplasm (45). Additionally, endometriosis occurs in females (46). Interestingly, although prostate gland hypertrophy occurs in males (47), prostate neoplasia is rarely observed (48). Rhesus monkeys that are fed normal laboratory diets also develop diabetes, with increased incidence observed on high-fat or high-calorie diets (3, 6). Considered together with altered body composition, reduced bone mineral density, increased serum triglycerides, and increased insulin resistance, rhesus monkeys provide an important new model of the increasingly prevalent "metabolic syndrome" (49).

Interventions

Evaluation of treatments designed to retard aging, such as CR, requires a virtual "head-to-toe" approach. Aging processes should be analyzed from molecular to behavioral levels. Table 1 provides a current overview of selected parameters from the NIA and WNPRC rhesus monkey aging studies evaluating the effects of CR. Clearly, findings indicate better health and lower disease risk for CR monkeys compared to controls. However, both studies are still ongoing, and data are still being amassed on CR effects on aging processes, mortality, and morbidity.

The widest application of rhesus monkeys has been to evaluate interventions bearing on brain aging and disease. Rhesus monkeys have shown great utility in evaluating hormone replacement therapies on cognition (50). In addition, successful studies of neurotrophic factors, including nerve growth factor and glia-derived neurotrophic factor, to treat AD and Parkinson's disease, respectively, have provided a basis to evaluate these treatments in humans (51, 52). Rhesus monkeys have also been used to investigate gene therapy for neurodegenerative disorders (53). As stem cell therapies emerge for age-related brain diseases, rhesus monkeys will serve as a valuable model for evaluating their success, especially in treatment of disorders involving loss of specific neural systems, such as Parkinson's disease. Effective gene transfer into rhesus hematopoietic stem cells has already proven successful (54). In addition, monkeys have been successfully used in studies to induce breast cancer-specific antibodies (55) and prostate-specific antigen immune response (56) and to test ovarian cancer chemoprevention (57).

Because rhesus monkeys can develop diet-dependent obesity and diabetes, they will also

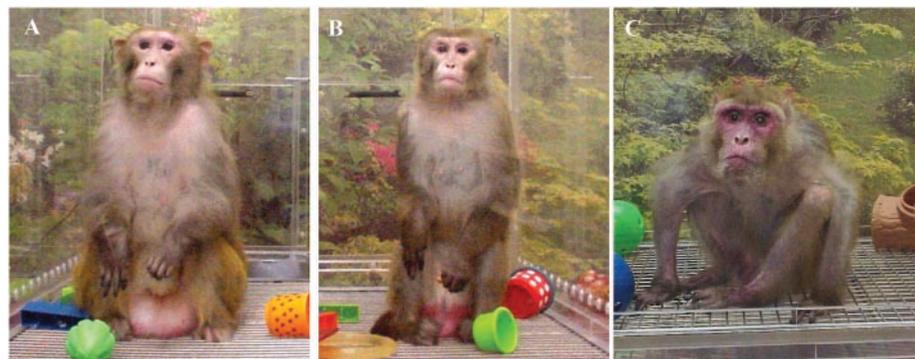


Fig. 1. (A) A 19-year-old male rhesus monkey weighing 13.6 kg on the control diet. (B) A 19-year-old male rhesus monkey weighing 7.9 kg on CR for 17 years. Notably, the CR monkey generally appears smaller. (C) A 38-year-old (estimated age) male rhesus monkey weighing 6.8 kg on CR for 17 years. This monkey is one of three in the NIA study for which the exact birth date was unknown, but he first arrived at NIH in July 1968 with an estimated age of 4 to 8 years on the basis of body size and dentition. He was placed on CR in 1987. He died 18 April 2004 at a minimal estimated age of 40 years, but he could have been as old as 44 years, making him one of the oldest recorded of this species. This monkey had stooped posture, loss of hair, and wrinkled and sagging skin with broken blood vessels, and he exhibited arthritis, osteoporosis, and cataracts.

serve as highly useful models for discovering anti-obesity and antidiabetic treatments. The amino acid sequence of the nuclear receptor, peroxisome proliferator-activated receptor alpha (PPAR α), is highly homologous between humans and rhesus monkeys; thus, synthetic compounds, such as the fibrates, that can regulate lipid and lipoprotein metabolism through PPAR α receptors have similar effects in both species (58). Studies have further shown the potential therapeutic value of antidiabetic and anti-obesity drugs in obese or insulin-resistant rhesus monkeys (58–60).

Mechanisms and Markers of Aging

Insight into basic mechanisms responsible for the age-related changes described above can also be obtained. Oxidative stress purported to be a major cause of aging and age-associated diseases is partially ameliorated by CR (61). Similarly, other forms of

stress, glycation, and biological disordering in general are thought to contribute to aging and are attenuated by CR (61). As reviewed above, many age-related changes in humans occur in rhesus monkeys, boding well for the use of these nonhuman primates to devise interventions that delay or reduce dysfunction and pathology and possibly extend the quantity and quality of life.

In this regard, recent interest was focused on three “biomarkers of longevity” apparently common to both CR rhesus monkeys and longer lived human males not practicing CR (62). These are lower levels of plasma insulin and body temperature, and maintenance of higher plasma levels of DHEAs. The first two have been demonstrated in CR rodents (9) as well as in monkeys, although DHEA (the sulfated form is the major species) levels are too low to evaluate in rodents. Nevertheless,

cross-species similarities in CR effects on two markers and changes during normal aging in all three markers further underscore their value for both mechanistic and intervention studies. Most recently, short-term (about 6 months) 25% CR in humans of both sexes has reduced both temperature and insulin levels (63).

A fundamental metabolic shift occurs in organisms on CR, from a growth and reproductive strategy to one of a life maintenance strategy. A drop in body temperature is evidence of this shift concomitant to increased protective mechanisms against various insults and pathologies, slower rate of tissue deterioration, and more reserve capacity observed in rodents on CR (62). Moreover, loss of insulin sensitivity during aging is probably tissue specific and secondary to changes in insulin signal transduction. Age-related decreases in circulating DHEAs may reflect a loss of adrenal parenchymal cells and/or reduced secretory function of surviving cells, which might affect important feedback mechanisms. This altered hormonal status is relevant for current discussion of the benefits of androgen replacement therapy. Because lower insulin levels and increased insulin sensitivity is protective against diabetes and DHEAs are purported to protect against both cancer and metabolic syndrome (36), the relevance of the rhesus model for age-related disease research and possible intervention strategies for eventual human application is obvious.

Conclusions

Thus, we envision even more extensive use of the aging rhesus model in future research. Initial efforts to sequence the rhesus genome have also been initiated that will increase the value of this animal model. To aid in the further development of nonhuman primate models of aging, the NIA and the WNPRC are developing the Primate Aging Database (PAD), which involves a multisite cooperative effort to share and analyze data in multiple species. A preliminary report that uses the PAD has been published demonstrating the utility of cooperative efforts to increase information in this area of research and promote efficient use of nonhuman primate resources (64).

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Table 1. Effects of CR on selected parameters of morphology, physiology, aging, and disease in rhesus monkeys. X indicates whether CR has been shown to decrease, increase, or produce no change in the these parameters.

Category/parameter	Decrease	Increase	No change
<i>Body composition</i>			
Body weight	X		
Fat and lean mass	X		
Trunk: Leg fat ratio	X		
Height	X		
<i>Development</i>			
Time to sexual maturity		X	
Time to skeletal maturity		X	
<i>Metabolism</i>			
Metabolic rate (short term)	X		
Metabolic rate (long term)			X
Metabolic rate (long term:nighttime)	X		
Body temperature	X		
Thriodothyronine (T3)	X		
Thyroxin (T4)			X
Thyroid-stimulating hormone			X
Leptin	X		
<i>Endocrinology</i>			
Fasting glucose/insulin	X		
IGF-1/growth hormone	X		
Insulin sensitivity		X	
Age-related maintenance of melatonin and DHEAs		X	
Testosterone; estradiol			X
<i>Cardiovascular parameters</i>			
Systolic blood pressure	X		
Heart rate	X		
Serum triglycerides	X		
Serum HDL2B		X	
Low-density lipoprotein interaction with proteoglycans	X		
Lipoprotein (a)	X		
<i>Immunological parameters</i>			
IL-6	X		
IL-10	X		
Interferon- γ		X	
<i>Oxidative stress</i>			
Oxidative damage to skeletal muscle	X		
<i>Cell biology</i>			
Proliferative capacity of fibroblasts		X	
Glycation products	X		
<i>Functional measures</i>			
Locomotor activity			X
Acoustic responses		X	

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REVIEW

What Can Progeroid Syndromes Tell Us About Human Aging?

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Human genetic diseases that resemble accelerated aging provide useful models for gerontologists. They combine known single-gene mutations with deficits in selected tissues that are reminiscent of changes seen during normal aging. Here, we describe recent progress toward linking molecular and cellular changes with the phenotype seen in two of these disorders. One in particular, Werner syndrome, provides evidence to support the hypothesis that the senescence of somatic cells may be a causal agent of normal aging.

Aging is the universal, progressive, and intrinsic accumulation of deleterious changes. These compromise the physiological effectiveness of an organism, ultimately leading to death (1). Many have argued that the way to understand the aging process is to manipulate it (2). Today, our technological ability to take this approach is changing the study of the biology of aging from a field concerned primarily with

description to one that is increasingly marked by intervention.

Strengths and Weaknesses of a Model System Approach to Human Aging

Various single-gene mutations increase the life-span of model species, including *Drosophila melanogaster*, *Caenorhabditis elegans*, and *Mus musculus* (3–5). These organisms offer obvious benefits as models for human aging, combining sequenced genomes with simple growth conditions and relatively short life-spans. Historically, this model system approach has met with great success in biology, partly because many of the processes under study (e.g., DNA replication) are highly conserved. The molecular machinery required to carry out such

processes is also conserved, and thus meaningful cross-species insights are regularly obtained. However, an important philosophical question is to what extent this model system approach can be used to understand human aging. Aging may be a rather atypical biological process, because no genes appear to have evolved specifically to cause it (6, 7). Indeed, because age-related changes are the unprogrammed results of stringent selection for early reproductive success, aging may be an example of a biological phenomenon in which there is a low level of mechanistic conservation between diverse metazoans.

One might reasonably expect closely related species to share some aging pathologies, reflecting similar solutions to the same evolutionary pressures; however, there is no a priori reason why the mechanisms that produce degenerative pathology should be uniform across all metazoan species. The lack of obvious selective pressure to evolve common aging mechanisms makes it all the more remarkable that common pathways controlling life-span may exist, as suggested by the re-

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