Experimental Gerontology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

An overview of nonhuman primates in aging research

Julie A. Mattison [a,*], Kelli L. Vaughan [a,b]

[a] Translational Gerontology Branch, National Institute on Aging, NIH Animal Center, 16701, Elmer School Road, Bldg 103, Dickerson, MD 20842, United States
[b] SoBran, Inc., 4000, Blackburn Lane, Suite 100, Burtonsville, MD 20866, United States

ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form 1 December 2016
Accepted 7 December 2016
Available online xxxx

Keywords:
Monkeys
Macaques
Marmoset
Cognition
Reproduction
Sarcopenia

ABSTRACT

A graying human population and the rising costs of healthcare have fueled the growing need for a sophisticated translational model of aging. Nonhuman primates (NHPs) experience aging processes similar to humans and, as a result, provide an excellent opportunity to study a closely related species. Rhesus monkeys share >92% homology and are the most commonly studied NHP. However, their substantial size, long lifespan, and the associated expense are prohibitive factors. Marmosets are rapidly becoming the preferred NHP for biomedical testing due to their small size, low zoonotic risk, reproductive efficiency, and relatively low-cost. Both species experience age-related pathology similar to humans, such as cancer, diabetes, arthritis, cardiovascular disease, and neurological decline. As a result, their use in aging research is paving the way to improved human health through a better understanding of the mechanisms of aging.

Published by Elsevier Inc.

1. Introduction

Aging is a complex phenomenon affecting every organ system of the body. Our understanding of the aging process is further complicated by the observation that no two individuals age at the same rate or in the same manner. To date, cells, worms, flies, and rodents have provided an extensive groundwork for aging research. However, taking this science from the bench to the bedside requires a more complex species, one with a physiology and aging process that more closely resembles the human experience. Nonhuman primates (NHPs) demonstrate parallel aging characteristics and experience many of the same diseases and pathophysiology as humans. In addition to their phenotypic similarities, NHPs share >92% genetic homology with humans. As a result, they may provide the best opportunity to study the actual mechanisms that lead to the age-related decline seen universally, across species.

The history of NHPs in research is rich with significant contributions to diseases such as HIV/AIDs, Ebola, and Zika, as well as the development of vaccinations, and advancements in organ transplant technology. Phillips et al. (2014) present a comprehensive review of the advantages of a primate model in many areas of biomedical research. This review highlights the contributions to aging research made by two commonly used NHP species—the Old World rhesus monkey and the New World marmoset.

Old World and New World are geographically based general classifications given to NHPs. Old World monkeys originate from Africa and Asia and consists of at least 132 species, including baboons and macaques. These animals range in size from medium to large and typically weigh between 4 and 20 kg. The presence of a tail differentiates monkeys from apes. Whereas, downward-pointing nostrils and only two pre-molars physically distinguish Old World from New World species (Lawrence and Cords, 2012). There are also several physical classifications that distinguish the New World and Old World groups (see Table 1).

New World monkeys originate from South America and are commonly divided into two families; the *Callitricidae and the Cebidae*. Where, the *Callitricidae* are the most primitive group of New World monkeys, and include marmosets and tamarins. The *Cebidae* are larger and are the only monkeys with a prehensile tail. Squirrel monkeys and capuchins are two examples of monkeys in this family.

2. Old World macaques

The macaques are the most widely used NHPs in biomedical research and are now purpose-bred at dedicated facilities. Rhesus macaques (*Macaca mulatta*) have been extensively studied and are the predominant species used in aging research. Other macaque species, such as cynomolgus (*M. fasicularis*), pigtails (*M. nemestina*), stumptails (*M. arctoides*), and bonnets (*M. radiate*), are studied to a lesser extent. Although the various macaque species are certainly similar, information here is specific to the rhesus macaque, unless otherwise specified.

Overall, rhesus monkeys share > 92% genetic homology with humans (Magness et al., 2005). And, their phenotypic similarities extend to almost all aspects of anatomy, physiology, endocrinology,

* Corresponding author.
E-mail addresses: Julie.Mattison@nih.gov (J.A. Mattison), Kelli.Vaughan@nih.gov (K.L. Vaughan).

http://dx.doi.org/10.1016/j.exger.2016.12.005
0531-5565/Published by Elsevier Inc.

Table 1
Comparison of Old World and New World monkeys.

Feature	Old World monkeys	New World monkeys
Origin	Africa & Asia	Americas
Body size	Medium to large	Small to medium
Nose	Downward facing nose (catarrhine) and nostrils	Flat nosed (platyrrhine) with nostrils facing sideways
Tail	Non-grasping; Ischial callosities (sitting pads)	Prehensile
Teeth	8 premolars	12 premolars
Hands	Opposable thumbs; fingernails & toenails	Thumb is in same plane as other digits; no fingernails
Ears	Tympanic membrane connected by bony tube	Tympanic membrane connected by bony ring
Habitat	Wide range, mostly on ground, tendency for single male multi-female social groups	Small range, arboreal, tendency for single-female and multi-male social groups
Infant care	Males rarely contribute	Males contribute
Diet	Omnivores, foraging plants, insects, small animals	Nuts, berries, insects

immunology, neurology, behavior, and aging processes. Rhesus monkeys have a relatively long lifespan, with an average of 25 years and maximum of 40 years in captivity. As a result, age-related changes in NHPs more closely approximate the experience of humans, as compared to that of shorter-lived research models (e.g. mice, rats, etc.). The rate of aging is commonly considered to be three times that of humans, although this ratio is not consistent across every stage of life.

Moreover, rhesus monkeys sexually mature around the ages of 2.5–3.5 years, they reach adult stature by 8 years of age, and females undergo menopause by about 25 years. Thus, the rate of aging ratio of human to monkey years can be summarized as follows: 1:4 from birth to sexual maturity, 1:3 during young adulthood, and 1:2 for females before menopause. In general, rhesus monkeys aged 15–22 years are deemed middle aged, while those over 30 years are considered old or elderly.

While offering a robust model, rhesus longevity also poses one of the greatest challenges for aging research. For example, it takes decades before age-related conditions are apparent, resulting in lifespan studies extending beyond a typical scientific career. Moreover, maintaining monkeys for life-span studies is extremely expensive, requiring specialized facilities staffed with dedicated veterinary and husbandry personnel. Thus, monkey studies often suffer from small sample sizes and are generally cross-sectional rather than longitudinal. Another complication is the considerable individual variation between monkeys; because they are not an inbred species, any two monkeys are as different as two humans. Yet, despite the challenges, rhesus monkeys still provide the best translational approach to understanding human aging, age-related diseases, and test interventions.

2.1. Endocrine and reproductive

The neuroendocrine system plays a key role in the coordinated regulation of physiological signaling and function. In conjunction with altered hormone levels, aging results in a disruption of circadian patterns, which in turn may contribute to age-associated dysfunction at multiple systemic levels. For example, both male and female monkeys experience an age-related decline in the Hypothalamic-Pituitary-Gonadal (HPG) axis (the central core of many hormone feedback loops); a process occurring more gradually in males.

Male rhesus monkeys undergo puberty between the ages of 2.5–3.5 years. Although the gonadal axis and the existence of an andropause are not well characterized for males, it is clear that the diurnal patterns of hormone secretion change with age. With age, daytime pulses of luteinizing hormone are significantly reduced, leading to a lower daytime androgen level. In spite of this, levels over a 24-hour period are not significantly affected (Schlatt et al., 2008).

Similarly, hormone profiles for cortisol and dehydroepiandrosterone sulfate (DHEAS) steroids produced by the adrenal cortex, and testosterone, an androgenic steroid produced in the testes, taken from adult (10 years) and aged (26 years) male rhesus monkeys, demonstrate a clear 24-hour rhythm (Downs et al., 2008). Here, testosterone shows a peak at night while DHEAS and cortisol peak in the early morning. There is a significant decline in the amplitude of both testosterone and DHEAS in aged monkeys, while cortisol generally remains unchanged or is slightly increased. In fact, baseline levels of cortisol are elevated, which may be a contributing factor to age-related sleep and metabolic disorders (Downs et al., 2008). A lower DHEAS level has been linked to cognitive decline in rodents and humans but has not been directly demonstrated in NHPs. Although there is a decline in the circulating testosterone level, it is maintained above pre-pubertal levels and, therefore, its decrease may not be as physiologically relevant. Yet, the dampened circadian pattern may contribute to overall hormonal deregulation in aged monkeys (Urbanski and Sorwell, 2012).

Female NHPs are unique in that they are the only mammals that menstruate. In fact, rhesus monkeys have been a model for reproductive studies in women since the early 1900s. In female monkeys, puberty also occurs between the ages of 2.5–3.5 years and their menstrual cycles are ~28 day in length. Similar to humans, aging female rhesus monkeys undergo a decrease in serum estradiol, an increase in follicle stimulating hormone, and have decreased inhibin B accompanied by amenorrhea, the hallmark sign of menopause. A period of irregular cycling, termed peri-menopause, is characterized by a decrease in the total number of regular menstrual cycles and percentage of normal length cycles, precedes menopause (Downs and Urbanski, 2006). Paralleling humans, female rhesus commonly experiences normal cycling through the age of 22 years, with the onset of perimenopause at about 24 years, and become postmenopausal at 25 years. The average age of menopause in women is 51 years. Compared to humans, female monkeys have a shorter post-reproductive period of life.

2.2. Musculoskeletal

Age-related bone loss and deterioration are the hallmark changes associated with osteoporosis. These changes lead to bone fragility and fractures, which is a significant health concern among the aging population. Compared to men, women are at greater risk for bone loss due to a lower peak bone mass, as well as accelerated bone loss occurring at menopause. However, both elderly men and women experience a significant number of hip fractures. These osteoporotic fractures result in reduced mobility and independence, and increased health care costs and mortality rate.

Rhesus monkeys experience age-related structural and body composition changes similar to humans. Among humans and NHPs, postural changes seen with aging are associated with reduced bone mineral density and a break down in cartilage, leading to reduced intervertebral space and subsequent osteoarthritic characteristics. The pattern of disc degeneration observed in NHPs is similar to humans (Bailey et al., 2014), and both age-related and hormone-deficiency induced loss of bone density and strength are evident in rhesus monkeys.

In female monkeys, loss of bone mass occurs with the menopause transition, beginning during perimenopause. As measured by lumbar spine and proximal radius, post-menopausal monkeys have 11–13% lower bone density than their younger counterparts (Colman et al., 1999a). Elevated osteocalcin also indicated increased bone turnover in post-menopausal females, similar to the human condition. For these reasons, female rhesus monkeys provide a valuable model for understanding the effect of hormone loss due to natural menopause, as well as loss resulting from surgical interventions (Colman et al., 1999a).

In males, the effect of age-related changes in bone mass is not as well studied but is apparent at the lateral spine and radius after 10 years of age in monkeys. Similarly, with age, males have a reduction in serum osteocalcin and carboxyterminal telopeptide of type I collagen,

Please cite this article as: Mattison, J.A., Vaughan, K.L., An overview of nonhuman primates in aging research, Exp. Gerontol. (2016), http://dx.doi.org/10.1016/j.exger.2016.12.005