Ageing Research Reviews 39 (2017) 29–35

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Nutrition, metabolism, and targeting aging in nonhuman primates

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ARTICLE INFO

Article history:
Received 19 December 2016
Received in revised form
29 December 2016
Accepted 15 February 2017
Available online 20 February 2017

Keywords:
Aging
Nutrition
Nonhuman primates
Caloric restriction
Mimetics
Translational research

ABSTRACT

This short review focuses on the importance of nonhuman primate nutrition and aging studies and makes the case that a targeted expansion of the use of this highly translatable model would be advantageous to the biology of aging field. First, we describe the high degree of similarity of the model in terms of aging phenotypes including incidence and prevalence of common human age-related diseases. Second, we discuss the importance of the nonhuman primate nutrition and aging studies and the extent to which the outcomes of two ongoing long-term studies of caloric restriction are congruent with short-term equivalent studies in humans. Third, we showcase a number of pharmacological agents previously employed in nonhuman primate studies that display some potential as caloric restriction mimetics. Finally, we present nonhuman primates as an important model for translation of mechanisms of delayed aging identified in studies of shorter-lived animals. Proof of efficacy and safety of candidate longevity agents in nonhuman primates would be a cost-effective means to bring these exciting new avenues a step closer to clinical application.

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1. Rhesus monkeys as a model for human health and disease

Nonhuman primate species are an excellent model for human biology due to their genetic and physiological similarity to humans. Nonhuman primate studies bring the promise that the insights into aging biology gleaned will be highly translatable to human aging biology. The rhesus monkey (*Macaca mulatta*) genome shares ~93% sequence identity with the human genome (Zimin et al., 2014). Similarity between monkeys and humans at the genomic level extends to numerous aspects of anatomy, physiology, neurology, endocrinology, immunology, and behavior (Bowden and Williams, 1984). Rhesus monkeys develop and age in similar ways to humans but on a compressed time-scale (Uno, 1997; Colman and Anderson, 2011). In captivity, the median lifespan for rhesus monkeys is ~26 years of age and the maximum lifespan of a captive rhesus monkey is ~40 years. A reasonable rule of thumb considers macaques aging at a rate of two and a half to three times

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http://dx.doi.org/10.1016/j.arr.2017.02.002
1568-1637/

that of humans (King et al., 1988; Tigges et al., 1988) with the caveat that not all aging and developmental milestones are paralleled. For example, females are reproductively fit relatively early and maintain menarche relatively longer than humans. Nonhuman primate studies have considerable advantages over human studies in terms of experimental design; the environment, dietary intake, and medical oversight can be fully defined, thus limiting confounding issues arising due to lack of uniformity in these parameters. Unlike rodents, rhesus monkeys display patterns of eating and sleeping behavior that mirror those of humans. Yet unlike human subject studies, rhesus monkey studies can be designed to facilitate comprehensive monitoring of subjects and strict adherence to the study protocol. Given the high degree of translatability and the tractability in study design, nonhuman primates are a vital link between basic research and clinical application. The links between aging and adiposity in nonhuman primates has been reviewed recently (Vaughan and Mattison, 2016), so here we will focus on caloric restriction (CR) and putative CR mimetics. We present that increased understanding of the biology of aging in rhesus monkeys will be extremely illuminating for human aging, and efforts to understand causative elements in rhesus monkey aging and age-related disease vulnerability are highly likely to reveal novel approaches for application in preventative human health care.

2. Delayed aging by caloric restriction in rhesus monkeys

Caloric restriction is the only environmental intervention that repeatedly and strongly increases maximum lifespan and delays biological aging in laboratory rodents (Weindruch and Walford, 1988). Over the last 20 years, astonishing progress has been made in defining longevity pathways and identifying factors that contribute to age-related changes in short lived species (Fontana and Partridge, 2015). In many of these studies CR is viewed as the gold-standard model of delayed aging and the reference to which other models of delayed aging are compared. The translatability of mechanistic insights from the study of CR in shorter-lived species hinges on the effects of CR being conserved in primates including humans and nonhuman primates. To address this, three independent rhesus monkey studies were initiated in the late 1980's. Two of these studies are ongoing: one at the National Institute on Aging (NIA) (Lane et al., 1992) and the other at the Wisconsin National Primate Research Center based at the University of Wisconsin (UW)-Madison (Ramsey et al., 2000a). The third study, performed at the University of Maryland reported favorable effects of CR, although the study was focused on obesity and glucoregulation with only a small cohort designated to CR (Bodkin et al., 2003a). At the UW, the CR intervention in a cohort of 76 adult monkeys was associated with significant improvements in morbidity and mortality (Colman et al., 2009). These findings contrasted with the report from the parallel NIA study, where a difference in survival was not observed between groups within the cohort of 121 monkeys, although a trend towards lower morbidity was reported for CR monkeys compared to controls (Mattison et al., 2012). Two major differences in study design included the timing of onset of CR where CR was implemented in adults at UW and in juveniles and advanced-age animals at NIA, and in the implementation of the diet including feeding protocols and diet composition. Subsequent analysis indicated that a direct comparison of longitudinal data from both studies is warranted (Colman et al., 2014). A joint initiative from both UW and NIA research teams has been developed to directly compare the two studies with a view to uncovering the basis for differences in outcome and the publication of this work is highly anticipated.

3. Caloric restriction impacts health indices in rhesus monkeys

Similar to humans, rhesus monkeys undergo changes in body composition with age including increased adiposity and a redistribution of body fat (Hudson et al., 1996). Not surprisingly, animals on caloric restriction tend to be smaller than their control fed counterparts and this is disproportionately evident in the reduction in adiposity (Colman et al., 1999; Ramsey et al., 2000b; Mattison et al., 2003). Along with these favorable changes in body composition, improved glucoregulatory function was one of the first identified benefits of CR in rhesus monkeys, including lower circulating glucose levels and improved insulin sensitivity (Bodkin et al., 2003a; Lane et al., 1995; Kemnitz et al., 1994a). Incidence of insulin resistance and diabetes are significantly lower in CR animals (Mattison et al., 2012; Anderson et al., 2009). Similar to humans, obesity in rhesus monkeys is associated with a number of risk factors for disease including insulin resistance and elevated serum triglycerides and cholesterol (Kemnitz et al., 1989; Ding et al., 2007a; Winegar et al., 2001). CR lowers circulating levels of triglycerides and improves lipoprotein profiles where levels of HDLs are higher with CR and levels of VLDLs are lower (Edwards et al., 1998; Rezzi et al., 2009; Verdery et al., 1997). These outcomes are consistent with improved metabolic homeostasis and reduced risk for diabetes and cardiovascular disease.

Further evidence for delayed aging in rhesus monkeys on CR comes from studies focused on specific tissues including skeletal muscle, brain, bone, and the immune system. Sarcopenia is the age-related loss in skeletal muscle mass and function and begins in middle age in rhesus monkeys (Colman et al., 2005; McKiernan et al., 2009). The onset and progression of this age-related condition is delayed in CR monkeys (Colman et al., 2008), where cellular atrophy and muscle fibrosis are both attenuated (McKiernan et al., 2012; McKiernan et al., 2011). Aging of skeletal muscle in rhesus monkeys is gradual, similar to humans, and the onset set of aging phenotypes is linked to changes in mitochondrial activity and redox metabolism (Pugh et al., 2013). The age-related decline in physical activity is also attenuated in rhesus monkeys on CR and the intervention is associated with improved metabolic cost of movement (Yamada et al., 2013). Measures of resting metabolic rate suggest that it is lower with CR (Yamada et al., 2013; Ramsey et al., 2000c), however, analysis of the data is complicated by overt difference in body composition, and it is unclear how meaningful the small differences reported might be. Brain aging is also delayed by CR. MRI based studies of brain volume reveal preservation of white matter and neuronal volume, and markers of inflammation are significantly lower (Colman et al., 2009; Sridharan et al., 2012; Bendlin et al., 2011). The caudate nucleus and putamen regions are vulnerable to age-associated atrophy and are protected by CR (Colman et al., 2009; Matochik et al., 2004). The age related increase in iron deposition in the globus pallidus and the substantia nigra is also attenuated by CR (Kastman et al., 2012). Correlation analysis of brain volume against peripheral insulin sensitivity suggests a role for systemic homeostasis in protection against age-related atrophy (Willette et al., 2012). CR has long been associated with lower bone mass and lower bone mineral density that, until quite recently, was viewed as a potentially negative outcome (Huang and Ables, 2016). It has become clear that bone density is markedly influenced by body weight and in this light the lower bone density measured in CR animals could be viewed as an adaptive rather than a pathological outcome of the diet (Colman et al., 2012; Black et al., 2001). Although the starting point is different for control and CR monkeys, the rate of decline in bone mass and bone density is greater in the controls suggesting a protective effect of CR. The ability of CR to delay aging of the immune system has also been investigated and reports suggest that CR delays senescence of T cells and pre-