Brief Report

Of Mice and Monkeys: National Institute on Aging Resources Supporting the Use of Animal Models in Biogerontology Research

Nancy L. Nadon

Biology of Aging Program, National Institute on Aging, Bethesda, Maryland.

The preponderance of our understanding of the biological changes that occur with aging has come from studies using rodents. Rodents are a valuable model for biogerontology research because of similarities to humans in the physiology and cell biology of aging. There are, however, many differences between rodents and humans, so application of findings in rodents to human aging requires the use of a model that is closer to humans at the genetic and physiological level. In aging research, the macaque has filled this need. There are many challenges associated with using nonhuman primates in aging research, not the least of which are the limited availability of aged monkeys and the cost of using them. To facilitate this research, the National Institute on Aging has developed several resources to assist investigators and promote the use of the nonhuman primate model in aging research.

Whether investigating the processes involved in normal aging or the progression, prevention, or treatment of age-related diseases, the more closely related the research model is to human biology, the more relevant will be the findings. In that regard, the rhesus monkey is a good model in which to study human aging and age-related diseases. It is close to humans genetically and at the cellular and physiological levels. Many aspects of rhesus aging parallel the aging process in humans, including decline of vision and development of cataracts, decline of hearing, loss of motor skills and impaired memory acquisition, and loss of bone density, to name a few [reviewed by Roth and colleagues (1)]. Species differences are very important when studying the treatment of diseases. Ward and colleagues (2) analyzed literature on the pharmacokinetics of 56 drug compounds for which there were data in the rat, dog, monkey, and human, and found that the monkey was consistently more predictive of the human pharmacokinetics than was the rat or dog.

There are, however, serious problems encountered when using nonhuman primate (NHP) models, including a long life span, limited availability of aged monkeys, and high costs associated with purchase and housing of monkeys. These difficulties impede the extension of research from rodent models to the NHP model. The National Institute on Aging (NIA) has developed new resources addressing these problems to encourage and promote the use of NHP models for aging research. It is hoped that, by making available resources particularly suited to pilot studies, findings in rodent models can be tested in NHP, exploiting the similarities between NHP and humans.

The neurobiology of aging is an area in which the rodent has made a major contribution. The rat in particular has been used in many functional studies, and Erickson and Barnes (3) propose that NHP may provide an important link between functional studies in rodents and cognitive studies in humans. They review some of the similarities in neurological aging across rodents, NHP, and humans, and suggest that more study is needed to confirm the utility of the NHP model for human aging. Bontempi and colleagues (4) compared the effects of nicotinic acetylcholine receptor agonists on age-related cognitive decline in rodents and NHP and found that rodents and rhesus monkeys responded similarly, showing improvements in working memory when on the compound. An example of a physiological difference between rodents and primates is the expression of monoamine oxidase (MAO), for which there are two isoforms, A and B. Mice express approximately equal amounts of the two isoforms, whereas in squirrel monkeys, there is about 10-fold more B activity than A activity (5). Mice show a significant increase in the activity of the B isoform by middle age, but monkeys show no significant age-related change in patterns of the two isoforms. Similar data in humans are not available because MAO measurements can be made only in autopsy material and there has been a lot of variability in reports. Because MAO is involved in several age-related diseases, including Parkinson’s disease (PD), additional data in NHP are essential. For example, inhibitors of MAO-B have been shown to be protective in a mouse model of PD induced by MPTP (methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treatment (6). There have also been reports of differences between rodent and NHP models of...
The field of caloric restriction (CR) has generated a vast literature on the potential to retard aging, primarily in the rodent model. Long-term studies on the physiological effects of CR in humans are not feasible, and in fact CR is unlikely to be a viable intervention in humans due to low compliance. The search for CR mimetics has become an important area of research, again predominantly in the rodent model. There have been few CR projects performed in NHP, but the pioneering studies of this field are now producing exciting preliminary results. The NIA Intramural Research Program has a long-term CR study in rhesus and squirrel monkeys that is nearing the 20-year mark (8). This study is providing data that suggest that many physiological parameters that are improved in rodents by CR respond similarly in NHP (9). In 2001, the life-span data suggested that CR might prolong life span in NHP as it does in rodents (9), but a recent update showed the mortality curves for CR and control monkeys converging (10). It is too early to determine if CR extends life span in monkeys as it does in rodents.

There is another long-term study on the effects of CR on rhesus monkeys being conducted at the University of Wisconsin with preliminary data supporting the beneficial effects of CR on NHP (11). Also, a third study on a small number of rhesus monkeys maintained on a long-term CR protocol also provided evidence that CR may extend life span in monkeys and delay the onset of some age-related diseases (12). These studies show promise that the benefits of CR demonstrated in rodents will hold true in NHP, but they are preliminary. Much more research is needed, and a solid understanding of the basic physiology of aging across species is essential if we are to fully develop the field of CR mimetics.

Along this same line, identification of biomarkers of aging that transcend species will be an important step towards modeling the full extent of age-related changes in humans. Ingram and colleagues (13) review the value of the NHP in the search for biomarkers of aging and suggest many criteria for the use of biomarkers. One criterion is that age-related changes in the biomarker be proportional to the life span of model organisms (Table 1). Another criterion is that the biomarker must be valid across species. Although few parameters have been analyzed across species, this is one of the opportunities presented by the NIA resources.

The NIA provides many resources vital to the use of rodent models for biogerontology research (aged rodent colonies, aged rodent tissue bank and tissue arrays) and has recently increased its investment in resources to facilitate the use of the NHP model, with the hope that many of the exciting findings in rodent models will be investigated in a model more closely related to humans (see Table 2 for URLs). The NHP tissue bank contains both fresh-frozen and fixed tissue from aged monkeys. The holdings are primarily from rhesus monkeys now, although the goal is to obtain tissue from a number of species to allow comparative studies. The tissue is donated from primate colonies around the country, and the health status of each donor is documented.

The Primate Aging Database (PAD) was developed through a collaboration involving the NIA Intramural Research Program and several members of the extramural research community (13). PAD brings together data from thousands of monkeys at multiple primate centers and primate colonies. The data are primarily blood chemistry parameters and body weights, and are derived from healthy monkeys. PAD provides a resource for analyzing age-related changes across species, addressing a key need in the search for biomarkers of aging. It is also a useful tool for staff responsible for husbandry and veterinary care of NHP, and provides a mechanism to identify normal ranges for physiological values. Smucny and colleagues (14) used PAD to demonstrate age-related changes in 15 blood chemistry measurements in rhesus monkeys. An update 3 years later showed increased statistical significance for some of the findings because more data had been entered into PAD in the interval (15). PAD is provided on a password-protected Web site and is open to investigators and veterinarians in academia and industry. PAD currently has almost 400,000 data points from 16 species, and submission of data by the research community is encouraged.

Another resource supported by the NIA that facilitates comparative work is the NIA Microarray Facility. It offers both mouse and human filter-based complementary DNA microarrays (16). Microarray studies have the potential to identify large numbers of changes in gene expression associated with aging. Lee and colleagues demonstrated the power of microarray analysis, showing age-related changes...
in gene expression in mouse muscle, brain, and heart [(17–19), respectively]. Some of these changes were attenuated by CR, identifying potential targets for therapeutic intervention. Kayo and colleagues (20) reported similar findings in rhesus monkeys, using a human gene microarray to demonstrate numerous age-related changes in gene expression in muscle. The authors noted that it is difficult to compare their findings to those of Lee and colleagues (17) in mouse because of the differences in terminology between species. This problem can be addressed with the RESOURCERER, an annotation database developed at The Institute for Genomic Research to assist in cross-species and cross-platform comparisons of microarray data (21). It is essential to validate the results from rodent studies in an NHP model, and the NIA resources (such as the NHP tissue bank, PAD, and the NIA Microarray Facility) can be used in experiments to identify age-related changes in NHP.

Lastly, the NIA Aged Cell Bank contains a large number of cell lines from 11 different species of NHP. These lines include fibroblasts, lymphoblasts, and a few differentiated smooth muscle lines. DNA samples are also available, individually and in panels, and two of the most popular offerings are the phylogenetic primate panel and the young and aged primate panel. The former contains DNA from nine NHP species and the latter contains DNA from skin fibroblasts from young and old individuals of five NHP species.

To summarize, the rodent has been the true workhorse of biogerontology research, but the field is ripe to begin testing some of the findings from the rodent studies in a model more closely related to humans. Research with NHP presents many challenges, including the limited availability of old monkeys, the cost of purchasing and housing monkeys, and the dearth of preliminary data. The NIA promotes investigations with the NHP model by providing resources to address those challenges.

Correspondence:
Address correspondence to Nancy L. Nadon, PhD, Biology of Aging Program, NIA, 7201 Wisconsin Ave., GW 2C231, Bethesda, MD 20892. E-mail: nadonn@nia.nih.gov

References

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