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COMMENTARY

The Unique Value of Primate Models in Translational Research

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This special issue of AJP is focused on research using nonhuman primates as models to further the understanding of women's health. Nonhuman primates play a unique role in translational science by bridging the gap between basic and clinical investigations. The use of nonhuman primates in biomedical research challenges our resolve to treat all life as sacred. The scientific community has responded by developing ethical guidelines for the care and the use of primates and clarifying the responsibility of investigators to insure the physical and psychological well-being of nonhuman primates used in research. Preclinical investigations often involve the use of animal models. Rodent models have been the mainstay of biomedical science and have provided enormous insight into the workings of many mammalian systems that h ave proved applicable to human biological systems. Rodent models are dissimilar to primates in numerous ways, which may limit the generalizability to human biological systems. These limitations are much less likely in nonhuman primates and in Old World primates, in particular, Macaques are useful models for investigations involving the reproductive system, bioenergetics, obesity and diabetes, cardiovascular health, central nervous system function, cognitive and social behavior, the musculoskeletal system, and diseases of aging. This issue considers primate models of polycystic ovary syndrome; diet effects on glycemic control, breast and endometrium; estrogen, reproductive life stage and atherosclerosis; estrogen and diet effects on inflammation in atherogenesis; the neuroprotective effects of estrogen therapy; social stress and visceral obesity; and sex differences in the role of social status in atherogenesis. Unmet research needs in women's health include the use of diets in nonhuman primate studies that are similar to those consumed by human beings, primate models of natural menopause, dementia, hypertension, colon cancer, and frailty in old age, and dedicated colonies for the study of breast cancer. Am. J. Primatol. 71:715–721, 2009.

Key words: primate models; animal models; women's health; translational research

NONHUMAN PRIMATE MODELS OF WOMEN'S HEALTH: INTRODUCTION AND OVERVIEW

Introduction

This special issue of AJP is focused on research using nonhuman primates as models to further the understanding of women's health. Nonhuman primates play a unique role in translational science by bridging the gap between basic and clinical investigations. A comprehensive knowledge of the model system is necessary for appropriate extrapolation to human beings. Thus, there is a continuum of knowledge between the understanding of the basic biology, behavior and social organization of nonhuman primate species, and the preclinical investigation of factors that influence nonhuman primate health and what they may tell us about human health. This continuum stems from the connectedness of all living beings, but relies heavily on the phylogenetic closeness of all primates.

The use of nonhuman primates in biomedical research challenges our resolve to treat all life as sacred. The response of the scientific community

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has been to develop ethical guidelines for the care and the use of primates in the laboratory that clarify the responsibility of investigators to insure the physical and psychological well-being of nonhuman primates used in research. Additionally, the scientific community has made great effort to develop purpose-bred primate colonies to guard against depleting wild populations. An impressive example of such an effort is the consortium between the University of Bogor, Indonesia, the University of Washington, Seattle, and Wake Forest University to populate an island in Indonesia with *Macaca fascicularis* for the purpose of preserving as well as breeding monkeys for biomedical research. A critical aspect of the research enterprise is continued self-policing by the scientific community and vigilant and continuous examination by investigators of laboratory practices that may be modified to improve the well-being of the nonhuman primates in their care.

Preclinical investigations often involve the use of animal models. Rodent models have been the mainstay of biomedical science and have provided enormous insight into the workings of many mammalian systems that have proved to be applicable to human biological systems. Rodent models, however, are dissimilar to primates in numerous ways, which limit the generalizability to human biological systems. Therapeutic interventions in rodents and other nonprimate models may fail to exhibit the same properties in clinical trials. These limitations are much less likely in nonhuman primates and in Old World primates, in particular.

Macaques (Macaca spp.), which include rhesus (*M. mulatta*) and cynomolgus (*M. fascicularis*) monkeys, have been particularly useful owing to their availability, moderate size, ability to adapt to laboratory conditions, and the fact that they have been extensively studied. Macaques have approximately 95% overall genetic coding sequence identity to humans [Magness et al., 2005], and are comparable to humans in multiple physiological systems. Cynomolgus and rhesus monkeys are large enough to noninvasively image (e.g. computed tomography) most systems effectively, yet small enough to house and handle conveniently. Much of animal modeling research has utilized young reproductively mature individuals. Disease processes, however, may be age-dependent. Macaques are long-lived, and thus are effective models for a number of diseases and conditions that increase in frequency with aging. Likewise, animal modeling of human health historically has ignored sex differences, or developed models in males largely for the sake of convenience, even for studies of diseases that are more common in women and are known to be influenced by female reproductive system function. The work presented in this volume specifically focuses on female macaques to model critical health concerns of women.

Reproductive System

Macaques and apes share with women a true menstrual cycle in which the endometrium is shed periodically, rather than absorbed as in the estrous cycles of rodents such as rats and mice. The development of the corpus luteum occurs spontaneously in primates as well as sheep and cows, whereas it is induced by stimulation of the cervix in other species, including rats and mice [Kaplan and Manuck, 2004]. The menstrual cycle of macaques is also similar to that of women in length, variability, and the cyclic pattern of secretion of sex hormones and gonadotropins [Mahoney, 1970; Wilks et al., 1979]. Thus, it is not surprising that some disorders of the reproductive system may be common to macaques and women, including luteal phase deficiencies and hypothalamic amenorrhea [Kaplan and Manuck, 2004]. These similarities in the reproductive system between nonhuman and human primates may contribute to similarities in reproductive tissue responses to therapeutic intervention. For example, in contrast to rodent models, high doses of dietary soy isoflavonoids have minimal uterotrophic or mammotrophic effects in female cynomolgus monkeys [Wood et al., 2006a].

Bioenergetics: Obesity and Diabetes

Studies of various aspects of bioenergetics in nonhuman primates, particularly macaques and baboons, have been very useful in understanding human energy metabolism. These studies have become increasingly critical as human primates face a gross imbalance in energy intake vs. energy expenditure that results in excess adipose tissue and a host of pathologies. Primates are preferred models for the study of whole body obesity [Kemnitz, 1984] as well as some aspects of fat distribution. As in people, obesity is associated with type 2 diabetes in macaques [Wagner et al., 2006]. A central fat pattern is associated with carotid and coronary artery atherosclerosis (CAA) in cynomolgus monkeys and with coronary heart disease (CHD) in people [Shively et al., 1987; Shively et al., 1990]. Macaques have noninvasively measurable pericardial fat, generally absent in wild-type mice and rats [Marchington et al., 1989], the secretions of which may directly influence heart and coronary vasculature function [Baker et al., 2006; Kankaanpaa et al., 2006]. In addition, intra-abdominal adipocytes from the cynomolgus macaque are similar metabolically to human adipocytes [Bousquet-Melou et al., 1995]. Social environmental variables affect the distribution of adipose tissue in macaques as in human primates [Shively et al., 2009].

Cardiovascular Health

Macaques are a well-established model of diet-induced CAA [Jokinen et al., 1985]. Atherosclerosis of the coronary arteries and its complications are the principal pathological processes that result in CHD. Cynomolgus monkeys are a well-characterized animal model of susceptibility of females to diet-induced atherogenesis. Monkeys imported as adults have little or no atherosclerosis. Atherogenesis begins when monkeys begin to consume diets containing fat and cholesterol. Ovariectomy results in extensive CAA [Adams et al., 1985]. If estrogen therapy is begun right after ovariectomy, females are protected from coronary atherogenesis [Adams et al., 1990; Adams et al., 1997; Clarkson et al., 2001; Register et al., 2002]. Likewise, the results of large observational studies, such as the Nurse's Health Study suggest that hormone therapy initiated around the time of menopause reduces the risk for a major coronary event by about 50% [Stampfer et al., 1985; Grodstein et al., 2000]. If, however, estrogen therapy in monkeys is not initiated until 2 years after ovariectomy (approximately equivalent to 6 woman years), there is no beneficial effect on atherosclerotic plaque size [Clarkson, 2002]. This observation essentially predicted the outcomes of both the Heart and Estrogen/Progestin Replacement Study and the Women's Health Initiative, where delayed initiation of estrogen therapy some 14 to 18 years after menopause was associated with no overall cardiovascular benefit [Hulley et al., 1998; Rossouw et al., 2002].

Female cynomolgus monkeys with poor ovarian function develop extensive CAA like that of ovariectomized females [Adams et al., 1985]. This is not surprising, because females with low progesterone concentrations in the luteal phase also have low estradiol concentrations in the follicular phase, i.e. they are estrogen-deficient. Thus, ovarian function, and in particular estrogen, confers protection from CAA in healthy early postmenopausal women and female cynomolgus macaques. The effects of premenopausal ovarian dysfunction on CHD risk in women are difficult to evaluate, because long-term characterization of hormone levels over the menstrual cycle is problematic. Nevertheless, women with a history of irregular menses are at increased risk for CHD [Bertuccio et al., 2007; Solomon et al., 2002]. It is well established that ovarian steroids modulate inflammatory processes, and this may be an important mechanism underlying sex differences in cardiovascular risk [Xing et al., 2009].

Central Nervous System and Behavior

The major adaptation that distinguishes primates from all other animals is the expansion and elaboration of the brain, particularly the cerebral cortex. This adaptation supports sophisticated cognitive processes, behavioral flexibility, and complex social relationships and organizations, and a shared similarity in central nervous system organization. The macaque hippocampus, for example, bears greater resemblance to the human hippocampus than does the rat with regard to nuclear organization, projection pathways, and innervation patterns [Amaral and Lavenex, 2007]. Likewise, the serotonergic system of the monkey shares more similarities with the human than does the rat with regard to nuclear organization, projection pathways, innervation patterns, axonal morphologies, and serotonin 1A receptor localization [Amaral and Lavenex, 2007; Azmitia and Gannon, 1986; Buckmaster and Amaral, 2001]. Thus, nonhuman primates are optimal models for investigations involving central nervous system organization and its relation to function. Some notable examples especially relevant to women's health include the extensive investigations into the behavioral biology of the mother–infant bond [Suomi, 1997], self-injurious behavior [Tiefenbacher et al., 2005], anxiety [Bakshi and Kalin, 2000], depression [Shively et al., 2006] cognitive decline, and Alzheimer's disease [Gallagher and Rapp, 1997; Kulstad et al., 2005; Voytko and Tinkler, 2004; Zeng et al., 2006]. Ovarian steroid modulation of inflammatory processes also may be an important influence on neurodegenerative disease progression [Vegeto et al., 2008].

Musculoskeletal System and Aging

Macaques have been used as models to understand the musculoskeletal system. Skeletal metabolism in primates differs from that in rodents, as cortical bone in rodents undergoes only limited Haversian remodeling [Jerome, 2004]. Also unlike primates, rodents continue to grow slowly throughout life. Macaques are useful models for age-related [Black et al., 2001] and hormone deficiency-induced loss of bone density [Register et al., 2003] and bone strength [Jerome and Peterson, 2001]. Thus, macaques are widely used to study osteopenia, osteoporosis [Jerome and Peterson, 2001], and osteoarthritis [Carlson et al., 1994, 1996]. Furthermore, percentage declines in estimated skeletal muscle mass with age in macaques are similar to those seen in humans with advancing age, suggesting their utility as a primate model of sarcopenia [Colman et al., 2005]. Microarray analysis of aging macaque muscle tissue demonstrates selective upregulation of transcripts involved in inflammation and oxidative stress, and downregulation of genes involved in mitochondrial electron transport and oxidative phosphorylation [Kayo et al., 2001]. With respect to menopause, a condition of aging and ovarian senescence in the female, the National Institute of Aging Workshop on Primate Models of the Menopause concluded that female reproductive aging in the nonhuman primate

is a more appropriate model for the human menopausal process and its connections with menopause-related health problems than nonprimate species [Bellino and Wise, 2003]. Because of their utility as models of several systems and disease processes, nonhuman primates are ideal models for the study of co-morbidities common in aging populations [Lane, 2000].

Research Needs in Women's Health

Although much progress has been made in the development and characterization of nonhuman primate models for research on women's health, there remain unmet needs for modeling diseases and disorders affecting women primarily at mid-life and beyond. One of the barriers to the development of appropriate primate models of diseases of aging is an important lack of support for special colonies of monkeys fed a diet comparable in composition to that consumed by most women in North America, and maintained sufficiently long to allow for natural menopause and the development of diseases and disorders of aging. Except for the breeding colonies of cynomolgus monkeys and vervets at Wake Forest University, virtually all other large colonies are fed commercial monkey chow, which derives its primary protein from isoflavone-rich soy meal. The result is that the plasma concentrations of genistein, daidzein, and equol of monkeys consuming such diets are several orders of magnitude greater than endogenous estrogen concentrations, and remarkably dissimilar to plasma concentrations in women. These isoflavones and the daidzein metabolite, equol, all bind to estrogen receptors α and β and can produce both receptor and nonreceptor-mediated biological effects. Compared with a soy-free diet, monkeys fed monkey chow increased the plasma concentrations of genistein from $\sim$5 to $\sim$50 ng/ml, and daidzein from $\sim$10 to $\sim$140 ng/ml and, of key importance, equol from $\sim$8 to $\sim$730 ng/ml [Stroud et al., 2006].

Natural Menopause

The need for monkeys that have undergone natural menopause is great. Interestingly, there have been only a few case reports on monkeys having undergone natural menopause. That the apparent low numbers may be diet related is the basis of a hypothesis now under study at Wake Forest University. Recently, we observed that the ovarian reserve (the capacity of the ovary to provide viable ova) of middle-aged monkeys consuming a diet with soy as the source of protein predicted menopause would not occur for more than 15 additional years, whereas middle-aged monkeys consuming a diet high in animal protein, fat, and cholesterol (comparable to that eaten by women) had lower ovarian reserve with a hypothetical trajectory that would predict menopause within the next 3–4 years, with perhaps, like women, a remaining third of their life span being postmenopausal [Appt et al., 2009].

Dementia

The dementias are among the most feared disorders of aging women. Alzheimer's disease is the most common form of dementia in North America. Although there have been a few case reports of age-related neuropathologic changes in the brains of rhesus monkeys that are consistent with Alzheimer's disease of human beings, there has been no supporting evidence that the monkeys lacked the ability to live normally in a social situation. To identify more monkey cases, not only do we need more colonies fed human-like diets into old age, but also we need approaches to the assessment of cognitive decline that can be applied to large numbers of animals.

Hypertension

Hypertension is common among women in North America and greatly increases the risk of both death and disability. Among women over age 60 years, hypertension is present in about 51% of white women and 72% of black women. There are currently no suitable monkey models of hypertension. The lack of development in this area may have been related to inadequate means of following blood pressure in large groups. New approaches such as high definition oscillometry may make large-scale evaluations possible.

Breast Cancer

Breast cancer is the most frequently diagnosed cancer of women and is the second highest cause of cancer death in North American women (after lung cancer). Because of the public health significance of breast cancer, there is a need to develop a repository of breast cancer monkeys for research. That should be possible in a nationally coordinated effort. Recently, Wood and co-workers determined, by retrospective analysis, the lifetime incidence of breast cancer in aged female macaques [Wood et al., 2006b]. The result was based on colonies at six institutions and was about 6% (compared with about 8–10% for women).

Colon Cancer

After lung and breast cancer, colorectal cancer is the next most common cause of cancer death among U S and Canadian women. There are a large number of questions in need of study in a monkey model. Examples are the potential interactions between dietary fat and calcium, the possible protective effects of nonsteroidal anti-inflammatory drugs and of estrogen replacement. It is uncertain whether macaques offer a possible model, although as in

human beings, macaque colon shows a relatively high level of expression of ERβ [Register and O'Sullivan, 1998]. Colon cancer has been described in macaques [O'Sullivan and Carlson, 2001] and has been observed to be relatively frequent in a large colony of aging female rhesus monkeys (Christian Abee, personal communication).

Frailty

Multi-system decline is a hallmark of frailty in older adults and may include a combination of weakness, fatigue, decreased balance, low levels of physical activity, slowed motor processing and performance, social withdrawal, mild cognitive changes, and increased vulnerability to stressors [Walston et al., 2006]. The resulting decline in physical function is a leading cause of decreased quality of life owing to the inability to independently perform activities of daily living. Age-related decline in physical function is associated with sarcopenia (loss of muscle tissue), increased adipose tissue mass, which becomes increasingly centralized with age, and fatty infiltration into other organs including muscle, liver, and pericardium [Zamboni et al., 2005]. Macaques have noninvasively measurable hepatic and pericardial fat (Thomas C. Register and Jeffrey J. Carr, personal communication) [Marchington et al., 1989] and declines in estimated skeletal muscle mass with age is similar to those seen in humans with advancing age [Colman et al., 2005]. These characteristics suggest they may be a useful model of age-related decline in physical function. Efforts are underway to develop methods for more accurate assessment of physical functioning in primate models.

Overview of This Special Issue

In this special issue about nonhuman primate models of women's health, Abbott et al. discuss fetal to adult phenotypes of polycystic ovary syndrome in prenatally androgenized female rhesus monkeys. Wagner et al. consider the impact of soy protein and associated isoflavones like those in monkey chow, compared with mammalian protein, on body weight and glycemic control in mothers and their offspring. Cline and Wood review the similarities between macaques and women in breast and endometrial responses to dietary soy isoflavones and consider the implications of feeding standard monkey chow diets high in soy isoflavones content. Smith et al. review estrogen deficiency-induced bone loss in postmenopausal females. Clarkson reviews adult reproductive life stage and extent of atherosclerosis as major determinants of the cardiovascular benefits of estrogen. Register summarizes the effects of exogenous estrogens and dietary soy protein/isoflavones on inflammation and atherogenesis in pre- and postmenopausal female cynomolgus monkeys. Shively et al. review the relationship between social stress and visceral obesity, and how it may impact CAA. Voytko et al. address the neuroprotective effects of estrogen therapy on cognition and underlying neurobiological mechanisms. Finally, Kaplan et al. use meta-analysis to consider the evolutionary implications of the differing role of social status in atherogenesis in males and females. The research presented is multidisciplinary and includes multiple levels of analysis. Simultaneous multi-system investigations exploring the effects of treatments and therapies on different disease outcomes in the same group of animals serves to maximize scientific gain and translational applicability in this unique and valued resource. A central theme of this edited volume is the critical translational role played by female nonhuman primates in basic and preclinical research to inform clinical investigations in women's health.

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