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Review

The problem of genotype and sex differences in life expectancy in transgenic AD mice

Eric A. Rae, Richard E. Brown*

Department of Psychology and Neuroscience, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada

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ABSTRACT

The lifespan of mice shows genotype, sex and laboratory effects, but little is known about genotype or sex differences in life expectancy of mouse models of Alzheimer's disease (AD). This paper examines the lifespan of males and females of different mouse models of AD and their wildtype strains. Genotype and sex dependent differences in longevity have important implications for designing experiments with Alzheimer's mouse models, comparing genotype and sex differences in aging mouse models, designing drug treatment regimes and the translation of mouse data to human clinical studies. We conclude that the concept of aging and age-related disorders in mice must be reconsidered based on genotype and sex differences in mouse life expectancy data. Use of concepts such as relative age, prospective lifespan and proportion of lifespan remaining should be included in studies of age-related changes in mouse brains and behavior. Finally, measures such as the Frailty Index, which is independent of chronological age might be used to determine a common scale of aging for all mouse strains.

Contents

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; B6, C57BL/6J; C3, C3He/J; D2, DBA/2J; MCI, mild cognitive impairment.

* Corresponding author at: Department of Psychology and Neuroscience, Dalhousie University, 1355 Oxford Street, PO Box 15000, Halifax, Nova Scotia B3H 4R2, Canada.
E-mail addresses: eric.rae@dal.ca (E.A. Rae), rebrown@dal.ca (R.E. Brown).

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1. Lifespan and Alzheimer's disease

1.1. Factors affecting human lifespan

Life expectancy is the average expected lifespan of an individual at birth. Over the last century human life expectancy has been increasing from about 40 years to over 80 years (Bongaarts, 2006; Sanderson and Scherbov, 2008). While human lifespan has a genetic basis (Bloss et al., 2011), the increase in life expectancy appears to be the result of environmental changes (Fraga, 2009; Huidobro et al., 2013). The factors most often credited for increasing human life expectancy are improved medical care, reduced disease rates, reduced occupational dangers, improved nutrition, life style changes and increases in education and income (Bongaarts, 2006; Costa, 2005). However life expectancy differs based on race and gender. Men generally have a shorter life expectancy than women (Arias, 2012; Bongaarts, 2006) and, while African-Americans have a shorter life expectancy than white Americans, Hispanic Americans have a longer life expectancy (Arias, 2012). Likewise New Zealand Maoris have a shorter lifespan than white New Zealanders (Statistics New Zealand, 2013).

1.2. Human Alzheimer's disease and the lifespan

People diagnosed with Alzheimer's disease (AD) have a shorter remaining life expectancy than those who do not have AD (Brookmeyer et al., 2002; Kammoun et al., 2000; Molsa et al., 1986; Xie et al., 2008). Three factors have been associated with the duration of remaining life expectancy in AD patients: age at diagnosis of AD; sex; and rate of cognitive decline (Rountree et al., 2012). Patients who have an early diagnosis of AD have a longer remaining life expectancy than those diagnosed at later years; females have a longer remaining life expectancy than males; and those with a slower rate of cognitive decline have a longer remaining life expectancy than those with a steep rate of decline. Diagnosis of AD is not easy (Buntink et al., 2011) as it progresses through a series of stages (Braak and Braak, 1991) and, although there are a number of putative biomarkers for AD (Blennow and Zetterberg, 2013), diagnosis is done primarily through the analysis of cognitive and behavioral symptoms (Cummings et al., 2013; Lischka et al., 2012; Weintraub et al., 2012). The search for cognitive and physiological biomarkers for predicting the early onset of AD has resulted in the development of AD risk scores for middle aged people (Kivipelto et al., 2006) and testing for AD-like symptoms can now begin early in the lifespan. For example, cerebrospinal fluid concentrations of amyloid-beta have been reported to decline 25 years before the onset of AD-like symptoms (Bateman et al., 2012).

Concepts such as "early onset", "middle age" and "late-life" can be defined only with respect to life expectancy (Solomon et al., 2013) and in order to predict life expectancy, actuarial tables are utilized (Arias, 2012; Statistics New Zealand, 2013). But as life expectancy has increased, the concepts of "middle age" and "old age" have changed, requiring new measures of aging. Rather than simple chronological age in years, the concepts of prospective age (number of years a person can expect to live at a given age) and remaining life expectancy are being used to examine age-related changes in health and to forecast the costs associated with increased lifespan (Sanderson and Scherbov, 2008, Sanderson and Scherbov, 2010). Another approach to the study of human lifespan is to examine the rate of healthy aging versus the rate of senescence (age-related health deterioration) (Blagosklonny, 2010).

1.3. Factors affecting mouse lifespan

As with humans, there are genotype and sex differences in life expectancy of mice (Flurkey et al., 2007; Yuan et al., 2009, 2011), and over the last 50 years the life expectancy of mice has been increasing (Table 1). For example, a male C57BL/6J (B6) mouse born in the 1960s had a life expectancy of 676 days while one born in 2011 was expected to live 901 days. This increase in life expectancy has been observed for both sexes of almost all strains tested, with the possible exception of the DBA/2J (D2) mice (Table 1). Genetic effects underlie strain differences in longevity in mice (Goodrick, 1975; Yuan et al., 2011) and mouse strains have been bred to have short or extended lifespans (Flurkey et al., 2007; Liang et al., 2003; Pallas, 2012). Life expectancies of male and female mice differ within strains: in many strains females live longer than males, but in some strains males have the longer life expectancy (Yuan et al., 2009, 2011). While there has been considerable speculation about the causes of sex differences in longevity (Maklakov and Lummaa, 2013; Partridge et al., 2005; Tower, 2006) there is no explanation for why females have longer life expectancy in some strains and males in others.

Environmental changes in mouse husbandry and their epigenetic effects may explain the general increase in longevity of mice over the last 50 years (Fraga, 2009). Housing conditions, husbandry procedures, breeding experience, exercise, stress levels and diet all affect the lifespan of mice and, as these factors differ across laboratories, there are laboratory effects on the life expectancies of mice (Goodrick, 1975; Swindell, 2012; Vanhooren and Libert, 2013). For example, dietary restriction increases life expectancy in mice but there are strain, sex and laboratory differences in the effects of caloric restriction on lifespan (Barger et al., 2003; Forster et al., 2003; Swindell, 2012; Umezawa et al., 1990).

Despite their limitations (Bales, 2012; Buxbaum, 2009; Jucker, 2010) mouse models have become invaluable resources for understanding the neurobiological mechanisms underlying AD and other neurodegenerative disorders and for the development of new treatments for these disorders. There are over 100 mouse models of AD, which differ in their background strain and genetic manipulations (Chin, 2011; Hall and Roberson, 2012; LaFerla and Green, 2012). The Alzheimer's Research Forum website (www.alzforum.org/res) indicates that some mouse models of AD have a normal lifespan while others have early mortality (Chin et al., 2004; Hsiao et al., 1995; Zhang et al., 2004). However, little comparative study has been made of the life expectancy of mouse models of AD. Most reports on the longevity of AD mice have small sample sizes, arbitrary cut off ages, and do not examine sex differences in mortality.

1.4. The effect of lifespan on mouse AD research

When studying age-related disorders in transgenic mouse models of AD it is important to consider the expected lifespan of each genotype in order to measure phenotypic changes at comparable

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