Ageing Research Reviews 13 (2014) 13–37

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

The behavioral, pathological and therapeutic features of the senescence-accelerated mouse prone 8 strain as an Alzheimer's disease animal model

Xiao-rui Cheng, Wen-xia Zhou*, Yong-xiang Zhang*

Beijing Institute of Pharmacology and Toxicology, Beijing 100850, China

ARTICLE INFO

Article history:
Received 28 July 2013
Received in revised form 10 October 2013
Accepted 30 October 2013

Keywords:
Alzheimer's disease
Senescence-accelerated mouse prone 8 strain
Cognition
Learning and memory
β-Amyloid deposit
Tau hyperphosphorylation

ABSTRACT

Alzheimer's disease (AD) is a widespread and devastating progressive neurodegenerative disease. Disease-modifying treatments remain beyond reach, and the etiology of the disease is uncertain. Animal model are essential for identifying disease mechanisms and developing effective therapeutic strategies. Research on AD is currently being carried out in rodent models. The most common transgenic mouse model mimics familial AD, which accounts for a small percentage of cases. The senescence-accelerated mouse prone 8 (SAMP8) strain is a spontaneous animal model of accelerated aging. Many studies indicate that SAMP8 mice harbor the behavioral and histopathological signatures of AD, namely AD-like cognitive and behavioral alterations, neuropathological phenotypes (neuron and dendrite spine loss, spongiosis, gliosis and cholinergic deficits in the forebrain), β-amyloid deposits resembling senile plaques, and aberrant hyperphosphorylation of Tau-like neurofibrillary tangles. SAMP8 mice are useful in the development of novel therapies, and many pharmacological agents and approaches are effective in SAMP8 mice. SAMP8 mice are considered a robust model for exploring the etiopathogenesis of sporadic AD and a plausible experimental model for developing preventative and therapeutic treatments for late-onset/age-related AD, which accounts for the vast majority of cases.

Contents

* Corresponding authors. Tel.: +86 10 66931625; fax: +86 10 68211656.
E-mail addresses: zhouwx@bmi.ac.cn (W.-x. Zhou), zhangyx@bmi.ac.cn (Y.-x. Zhang).

1568-1637/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.arr.2013.10.002

1. Introduction

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is a progressive amnesic disorder. The clinical phenotype of AD is typically concentrated on the presence of significant and progressive dementia that includes episodic memory (McDowd and Craik, 1988; Ohta et al., 1981), working memory and spatial memory impairment (Sharps, 1991; Weber et al., 1978). Impairments in other cognitive, behavioral, and neuropsychiatric domains or skills that prevent normal social functioning and activities of daily living are also often present (Dubois et al., 2010). The specific and typical neuropathological hallmarks of AD include brain atrophy due to neuronal and synapse loss, extracellular senile plaques composed largely of amyloid-beta peptide (Aβ) and intraneuronal neurofibrillary tangles (NFTs) caused by intracellular aggregates of hyperphosphorylated Tau protein in the brain (Cummings, 2004; Goedert and Spillantini, 2006; Querfurth and LaFerla, 2010).

Two types of AD have been described. Sporadic AD is a general deterioration of cognition without any association with a genetic element. Familial AD, on the other hand, is associated with mutations in some genes. In a small percentage (<2%) of cases, AD is inherited as an autosomal dominant trait (Campion et al., 1999; Müller et al., 2013; Selkoe, 2012). Inherited missense mutations in any of three genes can cause autosomal dominant AD. These include the genes for amyloid precursor protein (APP) on chromosome 21 (Goate, 2006; Goate et al., 1991; Levy et al., 1990), presenilin 1 (PSEN1) on chromosome 14 (Edwards-Lee et al., 2006; Müller et al., 2013; Pantieri et al., 2005; Sherrington et al., 1995), and the closely related presenilin 2 (PSEN2) on chromosome 1 (Levy-Lahad et al., 1995a,b; Rogaev et al., 1995). Clinically, patients with these three autosomal dominant genes usually have early onset dementia, which occurs in patients younger than 65 years old. However, mutations in these three genes explain the disease in only approximately 13% of patients with early-onset AD (Campion et al., 1999). More than ten risk genes for late-onset AD have also been identified (Bettens et al., 2013), including TREM2 (Guerreiro et al., 2013; Jonsson et al., 2013), CLU, CR1 and PICALM (Barral et al., 2012; Carrasquillo et al., 2010; Corneveaux et al., 2010; Harold et al., 2009; Jun et al., 2010), ABCA7, MS4A4A/MS4A6E, EPHA1, CD33 and CD2AP (Hollingworth et al., 2011; Naj et al., 2011), BIN1 (Lambert et al., 2011; Lee et al., 2011; Wijsman et al., 2011), and IL-12/IL-23 (Vom Berg et al., 2012). Much attention has been given to these genes by neurologists, patients and scientists, but they are not well-established risk factors for AD. Thus, most cases of AD are senile, late-onset AD, which occurs in patients aged 65 years or older, or sporadic AD with a multifactorial cause, i.e., both genetic variants and environmental factors contribute to the disease. In these cases, the ε4 allele of the apolipoprotein E gene (APOE) is the most important predisposing genetic variant, and the most important environmental factor is advanced age (Bickeboller et al., 1997; Elias-Sonnenschein et al., 2011; Genin et al., 2011; Verghese et al., 2011).

The etiology of AD is thought to be complex and remains elusive. There are still no effective treatments to prevent, halt, or reverse AD. Therefore, the availability of suitable animal models is essential for developing and evaluating effective therapeutic strategies for AD (Sabbagh et al., 2013). Mutations causing familial early-onset AD with autosomal dominant inheritance provide genetic tools for the construction of transgenic mouse models that recapitulate many of pathological features of AD. In fact, current models of AD are mainly restricted to transgenic mice with AD-related pathology caused by specific mutations present in early-onset familial AD, including the PDAPP mouse carrying mutant APP (V717F) (Games et al., 1995), the Tg2576 mouse carrying mutant APPswe or APP695 with double mutations at KM670/671NL (Hsiao et al., 1996), the TgCRND8 mouse carrying both KM670/671/NL (Swedish mutation) and APP717V-F sequences (Indiana mutation) (Chishti et al., 2001; Janus et al., 2000), the APP23 mouse carrying mutant APP751 with K670M/N671L (Sturchler-Pierrat et al., 1997), the mThy1-hAPP751 mouse carrying mutant APP751 with Swedish (K670M/N671L) and London (V717I) mutations (Rockenstein et al., 2001), the APP/PS1 mouse expressing mutant APPswe/PS1dE9 (Holcomb et al., 1998), the 3xTg-AD mouse expressing mutant APPswe, PS1M146V, and tauP301L (Oddo et al., 2003) and the 5xFAD mouse expressing mutant APPswe/Ind/fl and PS1 with double FAD mutations (M146L and L286V) (Oakley et al., 2006). However, AD is predominantly a sporadic late-onset disease with exponentially increasing prevalence starting at the age of 65 years (Jonsson et al., 2013). The majority of cases are most likely caused by complex interactions among multiple genetic, epigenetic, and environmental factors. Therefore, the spontaneous senescence-accelerated mouse prone 8 (SAMP8) strain has several distinct advantages over the gene-modified models. The phenotypes of the SAMP8 mouse resemble the symptoms of late-onset and age-related sporadic AD patients (Pallas et al., 2008). It has even been suggested that SAMP8 mice may more closely represent the complexity of the disease than other transgenic mouse lines because of the multifactorial nature of AD (Morley et al., 2012; Pallàs, 2012; Pallas et al., 2008; Pang et al., 2006; Tomobe and Nomura, 2009; Woodruff-Pak, 2008). SAMP8 mice are being used to characterize the physiological and behavioral consequences of AD and for basic and therapeutic investigations of AD. However, the cognitive behavioral patterns and pathological AD-like hallmarks of SAMP8 mice have not been well-collated and summarized. To systematically clarify the appropriateness of SAMP8 mice as an AD animal model and to provide simple and clear information to researchers who study AD in SAMP8 mice, this review summarizes the behavioral, pathological and the therapeutic features of SAMP8 mice as an AD animal model.