Neurobiology of Aging 35 (2014) 159–168

Contents lists available at ScienceDirect

Neurobiology of Aging

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

SAMP8 mice have altered hippocampal gene expression in long term potentiation, phosphatidylinositol signaling, and endocytosis pathways

Harvey J. Armbrecht [a,b,c,*], Akbar M. Siddiqui [d], Michael Green [d], Susan A. Farr [a,b], Vijaya B. Kumar [a,b], William A. Banks [a,b,e,1], Ping Patrick [f], Gul N. Shah [f], John E. Morley [a,b]

[a] Geriatric Research, Education and Clinical Center (GRECC), St Louis Veterans Affairs Medical Center, St Louis, MO, USA
[b] Division of Geriatric Medicine, Saint Louis University School of Medicine, St Louis, MO, USA
[c] Department of Biochemistry and Molecular Biology, Saint Louis University School of Medicine, St Louis, MO, USA
[d] Department of Molecular Microbiology and Immunology, Saint Louis University School of Medicine, St Louis, MO, USA
[e] Department of Pharmacology and Physiology, Saint Louis University School of Medicine, St Louis, MO, USA
[f] Division of Endocrinology, Saint Louis University School of Medicine, St Louis, MO, USA

ARTICLE INFO

Article history:
Received 24 August 2012
Received in revised form 11 June 2013
Accepted 19 July 2013
Available online 19 August 2013

Keywords:
SAMP8 mouse
Hippocampal gene expression
Memory loss
Long term potentiation
Phosphatidylinositol signaling
Clathrin-mediated endocytosis

ABSTRACT

The senescence-accelerated mouse (SAMP8) strain exhibits decreased learning and memory and increased amyloid beta (Aβ) peptide accumulation at 12 months. To detect differences in gene expression in SAMP8 mice, we used a control mouse that was a 50% cross between SAMP8 and CD-1 mice and which showed no memory deficits (50% SAMs). We then compared gene expression in the hippocampus of 4- and 12-month-old SAMP8 and control mice using Affymetrix gene arrays. At 12 months, but not at 4 months, pathway analysis revealed significant differences in the long term potentiation (6 genes), phosphatidylinositol signaling (6 genes), and endocytosis (10 genes) pathways. The changes in long term potentiation included mitogen-activated protein kinase (MAPK) signaling (N-ras, cAMP responsive element binding protein [CREB], protein phosphatase inhibitor 1) and Ca-dependent signaling (inositol triphosphate [ITP] receptors 1 and 2 and phospholipase C). Changes in phosphatidylinositol signaling genes suggested altered signaling through phosphatidylinositol-3-kinase, and Western blotting revealed phosphorylation changes in serine/threonine protein kinase AKT and 70S6K. Changes in the endocytosis pathway involved genes related to clathrin-mediated endocytosis (dynamin and clathrin). Endocytosis is required for receptor recycling, is involved in Aβ metabolism, and is regulated by phosphatidylinositol signaling. In summary, these studies demonstrate altered gene expression in 3 SAMP8 hippocampal pathways associated with memory formation and consolidation. These pathways might provide new therapeutic targets in addition to targeting Aβ metabolism itself.

Published by Elsevier Inc.

1. Introduction

We have extensively studied the SAMP8 mouse, an animal model that spontaneously and gradually develops cognitive impairments by 12 months of age (Morley et al., 2002a, b). At 12 months, the SAMP8 mice show impaired foot shock avoidance, object recognition with a 24-hour delay, lever press operant condition, and 3-way brightness discrimination compared with 4-month-old animals (Morley et al., 2002b). During this age span there is a 100% increase in amyloid beta (Aβ) peptide (Kumar et al., 2000; Morley et al., 2002a). Aβ is thought to play a key role in age-related memory loss and Alzheimer's disease (AD) (Rosenberg, 2000; Viola et al., 2008).

Because the hippocampus is important in memory formation, we hypothesized that there might be differences in hippocampal gene expression in SAMP8 mice. These differences might affect key pathways involved in memory formation. The purpose of this study was to compare hippocampal gene expression with age and strain and determine whether specific pathways are altered. Aβ can act through a number of membrane receptors to affect a number of biochemical pathways (summarized by Balleza-Tapia and Pena, 2009). These pathways include phosphatidylinositol-3-kinase

* Corresponding author at: Geriatric Center (11G-JB), St Louis Veterans Affairs Medical Center, 1 Jefferson Barracks Drive, St Louis, MO 63125, USA. Tel.: +1 314 894 6511.
E-mail address: hjarmbrec@aol.com (H.J. Armbrecht).
[1] Current address: Geriatric Research, Education, and Clinical Center (GRECC), Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA, and Division of Gerontology and Geriatric Medicine, Department of Medicine, School of Medicine, University of Washington, Seattle, WA, USA.

0197-4580/$ – see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.07.018

(PI3K), Ca signaling, extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), cAMP responsive element binding protein (CREB), rat sarcoma oncogene (RAS), p38, c-Jun N-terminal kinase (JNK), nitric oxide, and reactive oxygen species.

Previous studies have characterized gene expression changes in the SAMP8 hippocampus but used the SAMR1 mouse as a control (Carter et al., 2005; Cheng et al., 2007). The SAMR1 has been bred over many generations, and so it is not closely related to the SAMP8 mouse. To minimize strain differences, we developed a 50% cross between SAMP8 and CD-1 mice, which showed no memory deficits (50% SAMP8). We then compared gene expression in the hippocampus at 4 and 12 months in the 50% SAMP8 (control) and SAMP8 mice. Pathway analysis revealed differences in 3 interdependent pathways, some of which have been previously associated with cognitive deficits.

2. Methods

2.1. Animals and experimental design

SAMP8 mice were from our in-house animal colony, and CD-1 mice were originally obtained from Charles River Laboratories (Wilmington, MA, USA). The 50% SAMP8 mice were rederived from the SAMP8 and CD-1 mice as previously described (Flood et al., 1995) (see Results). Mice were housed 4 to a cage with a 12-hour light-dark cycle and access to food and water ad libitum. All studies were approved by the Institutional Animal Care and Use Committee of the St Louis Veterans Affairs Medical Center. The general experimental design consisted of 4 age/strain groups of 8 mice each: (1) 4-month-old control (50% SAMP8); (2) 4-month-old SAMP8; (3) 12-month-old control (50% SAMP8); and (4) 12-month-old SAMP8.

2.2. Behavioral measures

T-maze foot shock avoidance and novel object recognition were measured as previously described (Farr et al., 2012). T-maze is a declarative memory task that requires an intact hippocampus (Farr et al., 2000). Briefly, the maze consists of a black plastic start alley with a start box at one end and 2 goal boxes at the other (T-maze). The goal box that the mouse first enters on the initial trial is designated as "correct." The mouse is trained until it makes 1 avoidance (acquisition). The mouse is then retested 1 week later on the same task until it makes 5 avoidances in 6 consecutive trials (retention). Object-place recognition is a declarative memory task that involves the hippocampus when, as performed here, the retention interval is 24 hours (Hammond et al., 2004). On the first day of training, 2 similar objects are placed in the maze. Mice are placed in the maze and allowed to explore the objects for 5 minutes. In the 24-hour retention test, 1 of the same objects is placed in the maze, and a new object in a new location. The percent time spent exploring the new versus the old object is recorded. The higher the percent of time the mouse spends exploring the new object, the greater its memory of the old object.

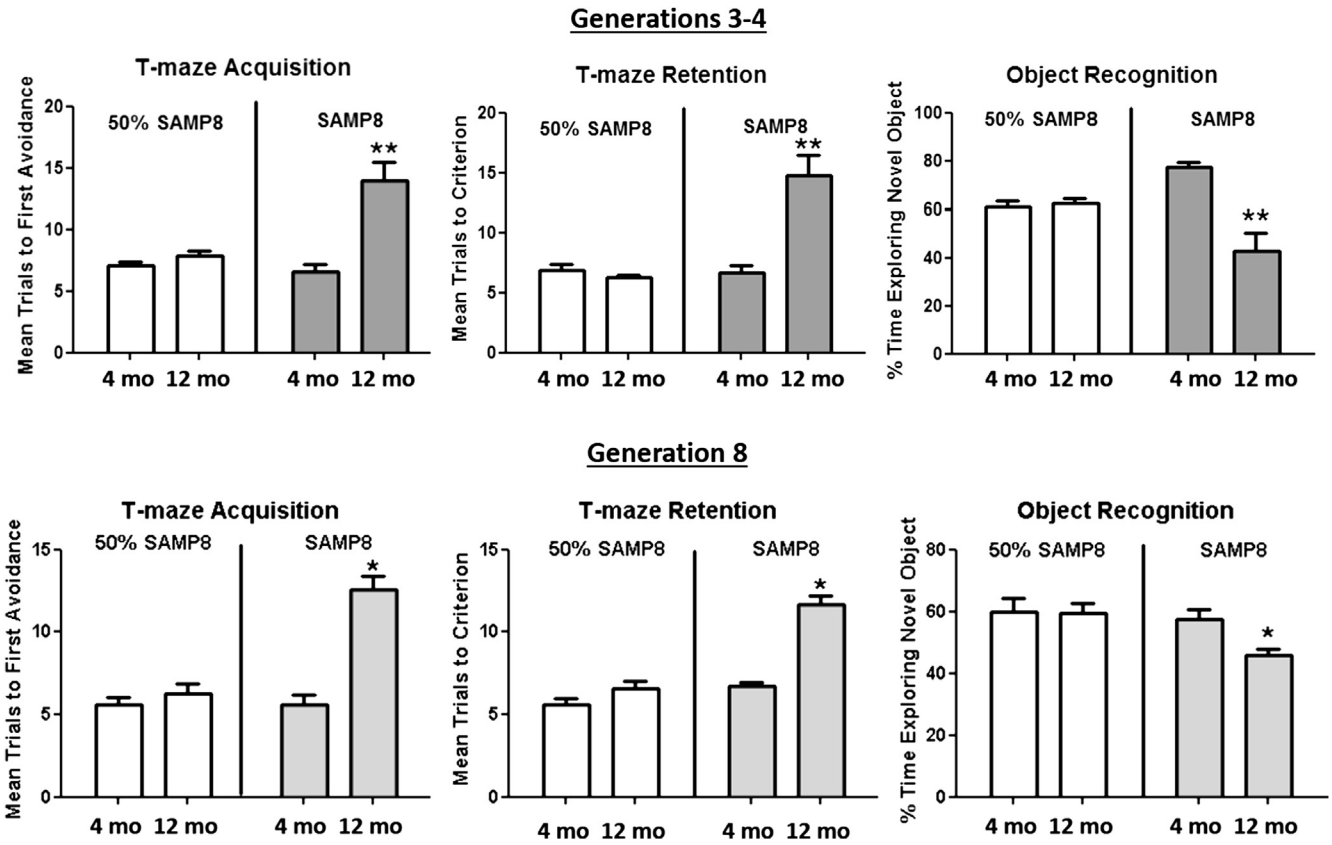

Fig. 1. Cognitive deficits in SAMP8 versus 50% SAMP8 mice. T-maze acquisition (learning) and T-maze retention (memory) and object recognition were measured as previously described (see Farr et al., 2012 and Methods). The top row of graphs is from generations 3–4 and the bottom row is from generation 8 of the 50% SAMP8 mice. Bars are the mean ± SD of 8–10 animals. Asterisks indicate significantly different from 4 months in post hoc testing ($p < 0.05$). There was a significant strain by age effect in all measures.