ELSEVIER

Neurobiology of Aging 33 (2012) 933–944

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Characterization of 7- and 19-month-old Tg2576 mice using multimodal in vivo imaging: limitations as a translatable model of Alzheimer's disease

Feng Luo[a], Nathan R. Rustay[a], Ulrich Ebert[b], Vincent P. Hradil[a], Todd B. Cole[a], Daniel A. Llano[c], Sarah R. Mudd[d], Yumin Zhang[a], Gerard B. Fox[a], Mark Day[a,*]

[a] *Experimental Imaging/Advanced Technology, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA*
[b] *CNS Discovery Research, Abbott Laboratories, Ludwigshafen, Germany*
[c] *Neuroscience Development, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA*
[d] *School of Pharmacy, University of Wisconsin, Madison, WI , USA*

Received 12 January 2010; received in revised form 7 July 2010; accepted 9 August 2010

Abstract

With 90% of neuroscience clinical trials failing to see efficacy, there is a clear need for the development of disease biomarkers that can improve the ability to predict human Alzheimer's disease (AD) trial outcomes from animal studies. Several lines of evidence, including genetic susceptibility and disease studies, suggest the utility of fluorodeoxyglucose positron emission tomography (FDG-PET) as a potential biomarker with congruency between humans and animal models. For example, early in AD, patients present with decreased glucose metabolism in the entorhinal cortex and several regions of the brain associated with disease pathology and cognitive decline. While several of the commonly used AD mouse models fail to show all the hallmarks of the disease or the limbic to cortical trajectory, there has not been a systematic evaluation of imaging-derived biomarkers across animal models of AD, contrary to what has been achieved in recent years in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Miller, 2009). If animal AD models were found to mimic endpoints that correlate with the disease onset, progression, and relapse, then the identification of such markers in animal models could afford the field a translational tool to help bridge the preclinical-clinical gap. Using a combination of FDG-PET and functional magnetic resonance imaging (fMRI), we examined the Tg2576 mouse for global and regional measures of brain glucose metabolism at 7 and 19 months of age. In experiment 1 we observed that at younger ages, when some plaque burden and cognitive deficits have been reported, Tg2576 mice showed hypermetabolism as assessed with FDG-PET. This hypermetabolism decreased with age to levels similar to wild type (WT) counterparts such that the 19-month-old transgenic (Tg) mice did not differ from age matched WTs. In experiment 2, using cerebral blood volume (CBV) fMRI, we demonstrated that the hypermetabolism observed in Tg mice at 7 months could not be explained by changes in hemodynamic parameters as no differences were observed when compared with WTs. Taken together, these data identify brain hypermetabolism in Tg2576 mice which cannot be accounted for by changes in vascular compliance. Instead, the hypermetabolism may reflect a neuronal compensatory mechanism. Our data are discussed in the context of disease biomarker identification and target validation, suggesting little or no utility for translational based studies using Tg2576 mice.

Keywords: Cerebral metabolism; Hypometabolism; Hypermetabolism; FDG-PET; Functional MRI; Proton MRS; APP; Transgenic mice; Alzheimer's disease; Biomarker

1. Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease, is currently treated with acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists (Roberson and Mucke, 2006). Both therapies only treat symptoms and do not address the underlying

* Corresponding author at: Experimental Imaging/Advanced Technology, Global Pharmaceutical Research and Development, Abbott Laboratories R4DF, AP4-2, 100 Abbott Park Road, Abbott Park, IL 60064, USA. Tel.: +1 847 938 4266; fax: +1 847 938 5286.
E-mail address: mark.day@abbott.com (M. Day).

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2010.08.005

neurodegeneration (Roberson and Mucke, 2006). In addition to potentially improving the accuracy of diagnosis, translational medicine approaches seek to develop biomarkers in humans and animal models that can serve important roles for the development of putative disease-modifying drugs for AD (Thal et al., 2006). By providing evidence of drug activity and indirect measures of disease severity, a change in a biomarker could be considered supporting evidence of disease modification. Moreover, appropriate biomarkers will improve the predictability of drug discovery and development efforts by improving the congruency of preclinical models to clinical reality, thus establishing proof-of-concept for efficacy and safety based on targeted mechanism of action (Day et al., 2008).

There is great need for disease severity biomarkers in AD (Day et al., 2008; Thal et al., 2006). These should correlate statistically with the disease phenotypes for which therapeutics are developed. Correlation of levels or expression patterns should signify disease initiation, progression, regression, remission, or relapse (Day et al., 2008). In short they should be able to serve as a surrogate for or be superior to clinical assessments (Day et al., 2008; Thal et al., 2006). In the past decade imaging studies using magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computerized tomography (SPECT) have afforded major advancements in our understanding of the disease process confirming, for example, that AD follows a set limbic-cortical trajectory, with the earliest neuropathological features occurring in the entorhinal cortex, spreading into the CA1 region of the hippocampus and then neocortical regions (Norfray and Provenzale, 2004).

Whilst decreases in glucose utilization are not specific to a particular disease, over 20 years of research on brain metabolism has established that the AD brain is regionally hypometabolic even in those genetically at risk but asymptomatic (Norfray and Provenzale, 2004). In addition, decreases in fluorodeoxyglucose (FDG)-PET signals can be seen very early in the disease process. For example, healthy asymptomatic young and middle-aged individuals who carry the APOE4 gene show reductions in metabolism in brain regions affected in AD (Norfray and Provenzale, 2004; Reiman et al., 2005). Further, patients presenting with AD or mild cognitive impairment (MCI) show reductions in cerebral metabolic rates for glucose (CMRglu) in the posterior cingulate, parietal, temporal, and prefrontal cortex (Norfray and Provenzale, 2004). Moreover, this hypometabolism is correlated with dementia severity and predicts progression (Mega et al., 1997; Mosconi, 2005; Norfray and Provenzale, 2004). For example, MCI subjects who decline, compared with those that do not worsen or show spontaneous recovery, have been demonstrated to show decreased metabolism in the parietal and temporal cortex (Jagust, 2006). In MCI-AD converters, the entorhinal cortex shows a marked decrease in metabolic rate (de Leon et al., 2001; Jagust, 2006).

FDG-PET also has advantages as an outcome measure for drug trials. First, FDG-PET signals have shown pharmacological sensitivity to agents known to improve cognition in AD (Potkin et al., 2001; Teipel et al., 2006). In addition, based on longitudinal CMRglu declines in AD patients, researchers have estimated that the number of AD patients per treatment arm needed to detect an effect with FDG-PET is roughly comparable to that needed to detect an effect with volumetric MRI and almost 1 tenth the number of patients needed using clinical end points, suggesting the promise of this imaging technique in proof-of-concept trials (Alexander et al., 2002; Dickerson and Sperling, 2005). Taken together, these data suggest that changes in brain glucose utilization may serve as a disease biomarker and/or a marker for predicting drug efficacy in AD (Jagust, 2006).

Attempts to recapitulate the AD pathologies with transgenic (Tg) mice have led to several models of the disease (McGowan et al., 2006). Amyloid precursor protein (APP) Tg models display extensive plaque pathology and cognitive deficits with age (McGowan et al., 2006). One of the most widely used animal models for amyloid plaques is the Tg (HuApp695.K670N/M671L) 2576 transgenic mouse model, which overexpresses human APP with the double Swedish mutation (Hsiao et al., 1996) and are thought to reflect, in part, AD pathology, including elevated levels of amyloid beta $(A\beta)_{1-40}$ and $A\beta_{1-42}$, the presence of amyloid plaques, inflammation (Hsiao et al., 1996), as well as learning and memory deficits, herein referred to as the Tg2576 model (Hsiao et al., 1996; Irizarry et al., 1997; Jacobsen et al., 2006; Westerman et al., 2002).

In order to evaluate the Tg2576 model for cerebral glucose utilization (CGU)-based disease biomarkers, we investigated the effects of age (7 and 19 months) on CGU using in vivo [^{18}F]-FDG-PET in experiment 1. In experiment 2, using cerebral blood volume (CBV)-based fMRI, we aimed further to determine whether there was intact vascular compliance to hypercapnia in 7-month-old Tg mice compared with wild type (WT) mice (Mueggler et al., 2002). Our results are discussed in the context of Alzheimer's disease biomarker identification and target validation.

2. Methods

2.1. Animal preparation

A total of 30 heterozygous double Swedish mutation (K670N/M671L) female Tg2576 transgenic mice expressing human APP complementary DNA (cDNA) (Hsiao, 1998; Hsiao et al., 1996; Spires and Hyman, 2005) and 30 age-matched wild type mice were employed in the study. Mice were obtained from Taconic (Germantown, NY, USA) at approximately 3 months of age but imaged at approximately 7 and 19 months of age. Different cohorts of animals were used. Mean body weights (mean ± SD) were 23.5 ± 3.0 and 22.2 ± 4.2 g respectively for 7-month-old WT and Tg mice, and 26.5 ± 5.2 and 26.8 ± 5.4 g respectively for 19-month-