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Development of Alzheimer-disease neuroimaging-biomarkers using mouse models with amyloid-precursor protein-transgene expression

Stefan J. Teipel [a,b,*], Ralph Buchert [c], Johannes Thome [a], Harald Hampel [d], Jens Pahnke [b,e]

[a] Department of Psychiatry, University of Rostock, Rostock, Germany
[b] DZNE, German Center for Neurodegenerative Diseases, Rostock, Germany
[c] Department of Nuclear Medicine, Charité, University Medicine of Berlin, Campus Mitte, Berlin, Germany
[d] Department of Psychiatry, Psychosomatic Medicine & Psychotherapy, Goethe University, Frankfurt, Germany
[e] Department of Neurology, Neurodegeneration Research Laboratory (NRL), University of Rostock, Rostock, Germany

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ABSTRACT

There are important recent developments in Alzheimer's disease (AD) translational research, especially with respect to the imaging of amyloid pathology in vivo using MRI and PET technologies. Here we exploit the most widely used transgenic mouse models of amyloid pathology in order to relate the imaging findings to our knowledge about the histopathological phenotype of these models. The development of new diagnostic criteria of AD necessitates the use of biological markers to diagnose AD even in the absence of overt dementia or early symptomatic mild cognitive impairment. The validity of the diagnosis will depend on the availability of an in vivo marker to reflect underlying neurobiological changes of AD. Transgenic models with essential features of AD pathology and mechanisms provide a test setting for the development and evaluation of new biological imaging markers.

Among the best established imaging markers of amyloid pathology in transgenic animals are high-field MRI of brain atrophy, proton spectroscopy of neurochemical changes, high-field MRI of amyloid plaque load, and in vivo plaque imaging using radio-labelled ligands with PET. We discuss the implications of the findings as well as the methodological limitations and the specific requirements of these technologies. We furthermore outline future directions of transgene-imaging research. Transgene imaging is an emerging area of translational research that implies strong multi- and interdisciplinary collaborations. It will become ever more valuable with the introduction of new diagnostic standards and novel treatment approaches which will require valid and reliable biological markers to improve the diagnosis and early treatment of AD patients.

Contents

Abbreviations: AD, Alzheimer disease; APP, amyloid precursor protein; CSF, cerebrospinal fluid; FDG, [F-18]fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; PET, positron emission tomography; PIB, Pittsburgh Compound B; PS1, presenilin 1; SPECT, single photon emission computed tomography.

* Corresponding author at: Department of Psychiatry and Psychotherapy, University of Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany. Tel.: +49 381 494 9610; fax: +49 381 494 9682.
E-mail address: stefan.teipel@med.uni-rostock.de (S.J. Teipel).

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1. Introduction

Imaging-derived biomarkers are currently being implemented as a defining criterion for the diagnosis of AD according to currently discussed revised research criteria (Dubois et al., 2007, 2009). The revision of the NINCDS-ADRDA criteria of AD (McKhann et al., 1984) suggests several new diagnostic entities (http://www.alz.org/research/diagnostic_criteria): the presence of positive biomarkers including imaging and CSF markers together with clinically probable AD defines the entity of "highly probable AD"; together with positive biomarkers the clinical syndrome of amnestic mild cognitive impairment (MCI) becomes "MCI of the Alzheimer type" or even "prodromal AD". Moreover, a new entity of "preclinical AD" will solely be defined by CSF and imaging biomarkers in the absence of any cognitive decline. These new entities are intended to enable the early diagnosis in clinical diagnostic studies and the enrichment and stratification of samples for testing the effects of potential disease modification in clinical trials of AD (Hampel et al., 2010, 2011).

With regard to current discussions about diagnostic criteria, the question remains, what the evidence might be that imaging markers of atrophy or neurochemical and functional abnormalities represent essential features of (preclinical) AD pathology? The validity of biomarkers regarding their supposed neurobiological substrate is crucial for the evaluation of disease-modifying treatment strategies. Several lines of research support the use of imaging biomarkers for the early diagnosis or the detection of intervention effects, including the clinical validity of a marker to predict a clinically relevant endpoint, such as cognitive decline (Teipel et al., 2008), the pathological validity of an atrophy marker to represent regional neuronal density (Bobinski et al., 2000) or the neurochemical validity of a marker to specifically bind to Aβ-containing amyloid plaques in the brain (Lockhart et al., 2007). One important line of evidence that is gaining increasing relevance for the validation of in vivo markers of AD are studies in transgenic animal models with amyloid pathology or other AD-related pathological features. Studies in transgenic animals serve a double function: Firstly, they provide independent evidence for potential pathological processes underlying specific imaging changes. Secondly, they represent a testing field for the development of new imaging technologies and sequences. Below we will give an overview of widely used transgenic models of amyloid pathology and discuss the findings on changes of cerebral anatomy, neurochemistry and neuronal function using in vivo imaging techniques in these models.

2. Transgene models of cerebral β-amyloidosis

The nosological models of AD keep shifting as a consequence of the lack of more precise knowledge about its etiology. This makes it difficult to design animal models precisely according to the human disease context and always requires an adaptation of mouse models to the changing concepts of human AD. Mutations in the amyloid precursor protein (APP) or one of the presenilins are sufficient to cause the complete AD phenotype of plaques, tangles, neuronal loss, and clinically progressive cognitive impairment in inherited AD cases. However, the expression of the same human mutations in the brain of mice replicates only some, but not all, histopathological features of 'human' AD.

In the early 1990s, transgenic mouse strains replicating essential features of the amyloid pathology in AD became available for the first time. The first transgenic models expressed mutant amyloid precursor protein (APP) in order to reproduce human amyloid pathology in mice. Subsequently, familial mutations derived from presenilin 1 (PS1) families, were introduced in transgenic animals. APP-transgenic mice develop memory loss and plaques, but no tangles and only minimal or no neuronal loss. Nevertheless, these models represent valuable tools for simulating pre-dementia or early phases of AD, although they fail to completely replicate the human disease.

Presenilin mutations alone do not result in neuropathological changes but potentiate amyloid-plaque deposition in human APP overexpressing mice. In some models, the combined APP and PS1 mutations led to a rapid onset (1.5–2 months) of cerebral amyloidosis (Oakley et al., 2006; Radde et al., 2006) enabling a rapid investigation of the early deposition phases and the resulting microglial reactions (Scheffler et al., in press). Recent attempts in introducing five familial mutations in APP (Swedish, London, Iowa) and two in PS1 (146, 283) in a single mouse model revealed no higher amyloid levels and no further benefits in modelling disease specific pathology (Oakley et al., 2006). The additional introduction of tau mutations, however, which have not been reported in AD patients but in fronto-temporal dementia (Spillantini et al., 1998), led to the expression of amyloid and tau pathology in a single mouse model (Oddo et al., 2003a,b). However, according to our current understanding of AD development abnormal APP processing represents probably an upstream event of the AD pathomechanism. This concept has been formalized in the "amyloid cascade hypothesis" suggesting that Aβ aggregation from monomers via oligomers and fibrils to plaques precedes the tau hyperphosphorylation and final neuronal death (Hardy, 1999, 2002; Hardy et al., 1986).

2.1. Cerebral amyloidosis mouse models expressing APP transgenes

A variety of mouse models have been established during recent years using different promoters and APP variants (for details refer to www.alzforum.org). Attempts to use mouse APP variants/transgenes did not result in β-amyloid deposition. Mouse β-amyloid shows much lower aggregation propensity than human β-amyloid due to three amino acids differences in its N-terminal sequence at the positions 5, 10 and 13. Human APP carrying mutations in the β- and/or γ-secretase sites (as known from inherited AD) reliably lead to sufficient β-amyloid plaque deposition in mice. In contrast, mutations in the central region of Aβ (Dutch, Arctic and Italian-type) result in predominant vascular Aβ deposition, as seen in families carrying these mutations. The first transgene model with substantial Aβ accumulation was the PDAPP line carrying a hAPP minigene driven by the PDGF promoter (Games et al., 1995). This model enables the expression of three different APP isoforms (695, 751, and 770 amino acids) and causes Aβ deposits in the hippocampus and cortex at the age of 6–8 months as well as in vessel walls (Games et al., 1995; Irizarry et al., 1997). The most widely used APP-transgenic mouse-lines are listed in Table 1. APP transgenic animals are useful models for studying the early effects of cerebral β-amyloidosis. It is incidentally not necessary to model all histological features of AD to investigate distinct changes during the start of Aβ deposition prior to the clinical presentation, since these metabolic and histological changes enable imaging research for the investigation of early disease biomarkers.

3. In vivo imaging of transgenic models of AD

In vivo imaging techniques in transgenic models focus on (i) structural changes, (ii) biochemical changes, and (iii) in vivo amyloid-plaque load, employing technologies of high-field MRI, MR spectroscopy and PET. A summary of the methodological aspects is given in Table 2, while details are discussed in the following section.