Neurodegenerative Diseases

Neurodegenerative Dis 2008;5:140–142
DOI: 10.1159/000113684

Published online: March 6, 2008

# Intraneuronal β-Amyloid Is a Major Risk Factor – Novel Evidence from the APP/PS1KI Mouse Model

Thomas A. Bayer[a] Henning Breyhan[a] Kailai Duan[b] Jens Rettig[b]
Oliver Wirths[a]

[a]Department of Psychiatry, Division of Molecular Psychiatry, University of Goettingen, Goettingen, and
[b]Institute of Physiology, Saarland University, Homburg, Germany

**Key Words**
Intraneuronal β-amyloid · Transgenic mouse · Neuron loss · Working memory · Synaptic plasticity · Alzheimer's disease

**Abstract**
Accumulating evidence points to an important role of intraneuronal β-amyloid (Aβ) in the development of Alzheimer's disease (AD), with its typical clinical symptoms like memory impairment and changes in personality. We have previously reported on the Aβ precursor protein and presenilin-1 knock-out (APP/PS1KI) mouse model with abundant intraneuronal $A\beta_{42}$ accumulation and a 50% loss of CA1 neurons at 10 months of age. In addition, we observed reduced short- and long-term synaptic plasticity, hippocampal neuron loss, and reduced performance in a working memory task. These observations support a pivotal role of intraneuronal Aβ accumulation as a principal pathological trigger in AD.


The concept of the β-amyloid (Aβ) cascade in Alzheimer's disease (AD) [1] provided the basis for AD therapeutic strategies. However, this concept is also a matter of ongoing controversial discussions, since the plaque load in AD brains, in contrast to the load of tau neurofibrillary tangles [2], does not correlate with the disease state. The extracellular plaques mainly contain Aβ peptides [3], which are derived from two proteolytic cleavages of the larger amyloid precursor protein (APP). In addition to the neuropil deposition of Aβ peptides into amyloid plaques, there is increasing evidence that Aβ accumulation occurs in neurons and that this represents an initial step in the disease process. A modified Aβ hypothesis with intraneuronal accumulation of the Aβ peptide as a first step of a fatal cascade has been formulated and reviewed in detail elsewhere [4].

Mice transgenic for APP have been proven to be a valuable model system for AD research. In several studies, early pathological changes, like deficits in synaptic transmission [5], behavioral alterations, differential glutamate responses and deficits in long-term potentiation have been reported [6]. In addition, learning deficits [7–11] were evident in different APP models. Intraneuronal Aβ accumulation preceded plaque formation in different

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com


1660–2854/08/0054–0140$24.50/0

Accessible online at:
www.karger.com/ndd

Thomas A. Bayer, PhD
Department of Psychiatry, Division of Molecular Psychiatry
University of Goettingen, Von-Siebold-Strasse 5
DE–37075 Goettingen (Germany)
Tel. +49 551 39 2911, Fax +49 551 39 10291, E-Mail tbayer@gwdg.de

**Table 1.** Chronology of pathological events in months (M)

| | 2 M | 6 M | 12 M |
|---|---|---|---|
| (1) Intraneuronal aggregation of different N-terminally modified $A\beta_{42}$ peptides (including N3pE)<br>(2) Axonal degeneration<br>(3) Reduced short-term synaptic plasticity | ⇒ | | |
| (4) Complete loss of long-term potentiation<br>(5) CA1 neuron loss (approx. 30%)<br>(6) Learning deficits | | ⇒ | |
| (7) CA1 neuron loss (approx. 50%)<br>(8) Hippocampal atrophy (approx. 20%) | | | ⇒ |

transgenic mice expressing mutant human APP [12–15]. Interestingly, CA1 neuronal loss did not correlate with the amount of extracellularly deposited Aβ in 2 APP/PS1 mouse models [16], including the APP/PS1KI model processed in the present report [17]. In the APP/PS1KI mouse model, human mutant APP751 harboring the Swedish and London mutations is expressed under the control of the murine Thy-1 promoter, whereas murine PS1 with two familial AD-linked mutations (PS1M233T and PS1L235P) is expressed under the control of the endogenous mouse PS1 promoter. All mice named as PS1KI were homozygous for PS1 knock-in mutations, in comparison to the APP/PS1KI mice, which harbored one additional hemizygous APP751SL transgene.

We have previously reported on the APP/PS1KI mouse model with abundant intraneuronal $A\beta_{42}$ accumulation [17]. These mice exhibit early and robust brain and spinal cord axonal degeneration, as shown by the occurrence of axonal spheroids, together with a reduced ability to perform motor performance tasks, including balance beam, string suspension or the rotarod. Cognitive deficits, studied by the use of the Y-maze and the T-maze continuous alternation task, were also evident as early as at the age of 6 months. A phenotypical characterization revealed that APP/PS1KI mice were smaller and showed the development of a thoracolumbar kyphosis, together with an incremental loss of body weight. Finally, a 50% loss of hippocampal CA1 neurons was found at 10 months of age [17–19]. In addition, we observed that there was a significant CA1 neuron loss in the hippocampus already at 6 months of age, together with a complete loss of synaptic plasticity. Interestingly, hippocampal atrophy was observed later in 1-year-old APP/PS1KI mice, and can be regarded as a downstream event. Between 2 and 6 months of age, a significantly increased accumulation of intraneuronal Aβ peptides, including N-terminally modified species like pyrGlu-Aβ, was detected, which correlated well with hippocampal neuron loss, synaptic dysfunction and reduced performance in working memory tasks (table 1). In summary, these observations provide further evidence for a pivotal role of intraneuronal Aβ as a main pathological trigger in AD, and question the importance of hippocampal atrophy as a predictive hallmark of the development of AD.


## Acknowledgements

Financial support was provided by a Sanofi-Aventis Research Grant and the Fritz Thyssen Stiftung (to T.A.B.), and the German Research Council (to J.R. and T.A.B.) and a Klaus Murmann PhD Scholarship from the Foundation of German Businesses (to H.B.).


## References


1 Hardy J, Allsop D: Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 1991;12:383–388.

2 Braak H, Braak E: Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.

3 Glenner GG, Wong CW: Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun 1984;120:885–890.

4 Wirths O, Multhaup G, Bayer TA: A modified beta-amyloid hypothesis: intraneuronal accumulation of the beta-amyloid peptide – The first step of a fatal cascade. J Neurochem 2004;91:513–520.

5 Hsia AY, Masliah E, McConlogue L, et al: Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models. Proc Natl Acad Sci USA 1999;96:3228–3233.

6 Moechars D, Dewachter I, Lorent K, et al: Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. J Biol Chem 1999;274:6483–6492.

7 Holcomb L, Gordon MN, McGowan E, et al: Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. Nat Med 1998;4:97–100.

8 Puolivali J, Wang J, Heikkinen T, et al: Hippocampal A beta 42 levels correlate with spatial memory deficit in APP and PS1 double transgenic mice. Neurobiol Dis 2002;9:339–347.

9 Billings LM, Oddo S, Green KN, McGaugh JL, Laferla FM: Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. Neuron 2005;45:675–688.

10 Oakley H, Cole SL, Logan S, et al: Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J Neurosci 2006;26:10129–10140.
11 Gimenez-Llort L, Blazquez G, Canete T, et al: Modeling behavioral and neuronal symptoms of Alzheimer's disease in mice: a role for intraneuronal amyloid. Neurosci Biobehav Rev 2007;31:125–147.
12 Wirths O, Multhaup G, Czech C, et al: Intraneuronal Abeta accumulation precedes plaque formation in beta-amyloid precursor protein and presenilin-1 double-transgenic mice. Neurosci Lett 2001;306:116–120.
13 Wirths O, Multhaup G, Czech C, et al: Intraneuronal APP/Abeta trafficking and plaque formation in beta-amyloid precursor protein and presenilin-1 transgenic mice. Brain Pathol 2002;12:275–286.
14 Blanchard V, Moussaoui S, Czech C, et al: Time sequence of maturation of dystrophic neurites associated with Abeta deposits in APP/PS1 transgenic mice. Exp Neurol 2003;184:247–263.
15 Shie FS, LeBoeur RC, Jin LW: Early intraneuronal Abeta deposition in the hippocampus of APP transgenic mice. Neuroreport 2003;14:123–129.
16 Schmitz C, Rutten BP, Pielen A, et al: Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease. Am J Pathol 2004;164:1495–1502.
17 Casas C, Sergeant N, Itier JM, et al: Massive CA1/2 neuronal loss with intraneuronal and N-terminal truncated Abeta42 accumulation in a novel Alzheimer transgenic model. Am J Pathol 2004;165:1289–1300.
18 Wirths O, Weis J, Kayed R, Saido TC, Bayer TA: Age-dependent axonal degeneration in an Alzheimer mouse model. Neurobiol Aging 2007;28:1689–1699.
19 Wirths O, Breyhan H, Schafer S, Roth C, Bayer TA: Deficits in working memory and motor performance in the APP/PS1ki mouse model for Alzheimer's disease. Neurobiol Aging DOI: 10.1016/j.neurobiolaging.2006.12.004.