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

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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...
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 PSI 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 Aβ42 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.).

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

<table>
<thead>
<tr>
<th>Event</th>
<th>2 M</th>
<th>6 M</th>
<th>12 M</th>
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<tbody>
<tr>
<td>(1) Intraneuronal aggregation of different N-terminally modified Aβ42 peptides (including N3pE)</td>
<td>=</td>
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<td>(2) Axonal degeneration</td>
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<td>(3) Reduced short-term synaptic plasticity</td>
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<td>(4) Complete loss of long-term potentiation</td>
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<td>(5) CA1 neuron loss (approx. 30%)</td>
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<td>(6) Learning deficits</td>
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<td>(7) CA1 neuron loss (approx. 50%)</td>
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<td>(8) Hippocampal atrophy (approx. 20%)</td>
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References


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Neurodegenerative Dis 2008; 5:140–142

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