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EDITORIAL

Protein aggregation in Alzheimer's disease: Aβ and τ and their potential roles in the pathogenesis of AD

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This issue of *Acta Neuropathologica* includes a cluster of three review papers focusing on amyloid β-peptide (Aβ) and/or τ-protein aggregates in Alzheimer's disease (AD). Since the first description of the disease by Alzheimer [1], Aβ-containing amyloid plaques and τ-derived neurofibrillary tangles (NFTs) have been identified to represent the pathological hallmarks of AD [1, 6, 8]. These two types of protein aggregates share a number of biochemical features. Both form fibrils, which are the major compounds of amyloid plaques (Aβ fibrils) and neurofibrillary tangles (τ fibrils; NFTs). Both proteins were shown to undergo post-translational modifications, such as phosphorylation, truncation and/or pyroglutamate formation in the AD brain. These modifications may accelerate the speed of aggregation in vitro. Moreover, Aβ has been shown to promote τ aggregation [5, 7], suggesting that protein aggregation represents a key starter and/or promoter of the disease. The ability of Aβ to functionally interact with τ may depend on other proteins such as *N*-methyl-D-aspartate (NMDA) receptors that act as molecular switches to induce neuronal dysfunction and neurodegeneration. Figure 1 provides a schematic representation of the roles of Aβ and τ as presented in this cluster. The clinical manifestation of AD is, thereby, associated with high levels of mature Aβ and τ aggregates widely distributed throughout the brain.

The first article by Thal et al. provides an overview about the current knowledge of the biophysical and biochemical mechanisms of Aβ aggregation and its relationship to AD pathology. A key neuropathological feature of AD is its stage-wise development as represented by the spreading of Aβ plaques and NFTs from one brain region to another [4, 10]. More recent data demonstrated that these stages are also reflected by biochemical changes of Aβ, and specifically by posttranslational modifications that could be correlated with the progression from preclinical to clinical forms of AD.

In the second article, Viola and Klein summarize the current knowledge about the generation and stability of Aβ oligomers and their toxic effects on neuronal cells. The authors further highlight the cellular mechanisms by which Aβ exerts its toxic activity and outline possible inhibitory strategies with antibodies and other agents.

The third review by Nisbet et al. focuses on τ protein and its interactions with Aβ. The manuscript describes the aggregation of τ into NFTs, the effects of Aβ aggregates on τ as well as the involvement of NMDA-receptors and Fyn protein kinase. The authors conclude with a short overview about therapeutic strategies targeting Aβ and τ.

Taken together, these three review papers draw a current concept of AD pathogenesis according to which AD results from protein aggregation, posttranslational modification of these proteins and from the interaction of these aggregates with other proteins. Toxicity of Aβ and τ is at the cell biological level mainly related to toxic intermediates (oligomers and protofibrils). Fibrillar aggregates of Aβ and τ may enhance the effects of the toxic intermediates by generating mechanical barriers for diffusion, sprouting and cell migration in the brain parenchyma (Aβ fibrils) or

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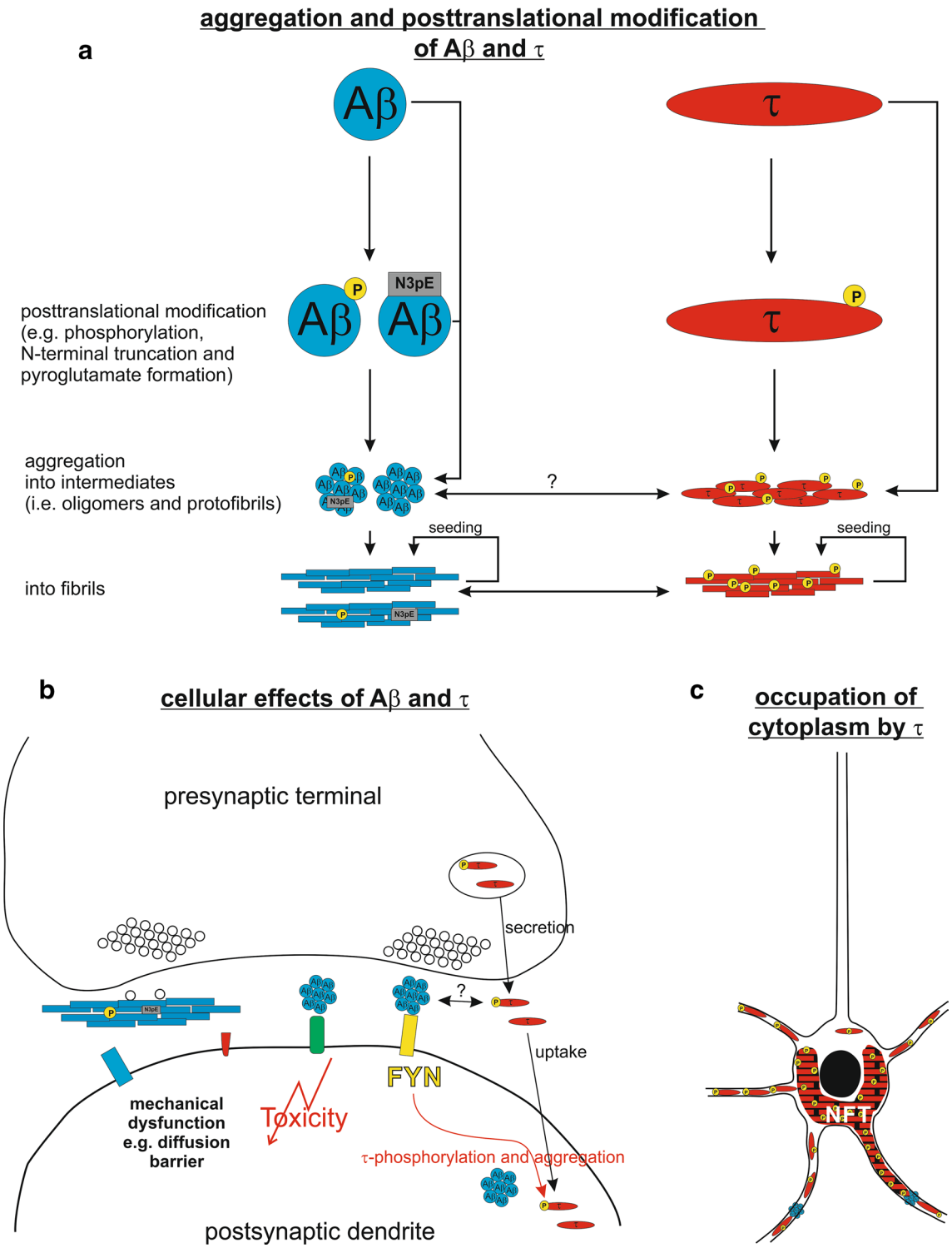

Fig. 1 Schematic representation of the potential roles of Aβ and τ in the pathogenesis of AD as covered in this cluster. **a** Aggregation and posttranslational modification of Aβ and the presence of intermediates and fibrils in the human brain is reviewed in detail by Thal et al. (this issue). A similar aggregation pattern for τ including its abnormal posttranslational phosphorylation leading to fibrillar aggregates finally forming NFTs is described in the review of Nisbet al al. (this issue). **b** The toxic effects of Aβ oligomers at the cellular level are discussed by Viola and Klein (this issue), that of τ and its interactions with Aβ by Nisbet et al. (this issue). Interactions of Aβ intermediates (i.e., oligomers and protofibrils) with τ may have influence on the generation of abnormal phosphorylated τ-protein via Fyn. Extracellular fibrillar amyloid may be maleficent due to its mechanical properties that limit diffusion within the extracellular space and that alter the integrity of the extracellular matrix (e.g., vessel wall destruction in cerebral amyloid angiopathy). **c** Intracellular NFTs may also act mechanically deleterious to neurons as they occupy their cytoplasm, displace cell organelles and finally lead to neuron death [2, 3, 9]

by displacement of functional cytoplasm within the cells (τ-containing NFTs). Since similar biophysical mechanisms of protein aggregation apply for Aβ aggregation and deposition as well as for the generation of τ-derived NFTs, it is tempting to speculate that AD results from any kind of event that is capable to kick off the biophysical process of τ and Aβ aggregation. For disease progression, posttranslational modifications of Aβ and τ appear to play a crucial role.

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