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Dissecting Toxicity of Tau and β-Amyloid

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Alzheimer's disease · Axonal transport · Frontotemporal dementia · Kinesin · Oligomer · Tau · Transgenic mice · Type 2 diabetes

Abstract
Background: How β-amyloid (Aβ) and tau exert toxicity in Alzheimer's disease is only partly understood. Major questions include (1) which aggregation state of Aβ confers toxicity, (2) do amyloidogenic proteins have similar mechanisms of toxicity, and (3) does soluble tau interfere with cellular functions? ***Methods:*** To determine Aβ toxicity in P301L mutant tau transgenic mice, mitochondrial function was assessed after insult with monomeric, oligomeric and fibrillar Aβ. Amylin and Aβ toxicity were compared in cortical and hippocampal long-term cultures. To determine tau toxicity, K369I mutant tau mice were established as a model of frontotemporal dementia, analyzed biochemically and compared with human diseased brain. ***Results:*** Oligomeric and fibrillar Aβ42 were both toxic, although to different degrees. Human amylin shared toxicity with Aβ42, an effect not observed for nonamyloidogenic rat amylin. Clinical features of K369I tau mice were caused by aberrant interaction of phosphorylated tau with JIP1, a component of the kinesin transport machinery. ***Conclusion:*** Our data support the notion of a synergistic action of tau and Aβ pathology on mitochondria. A specific conformation of Aβ42 and human amylin determines toxicity. Finally, trapping of JIP1 by phosphorylated tau in the neuronal soma emerges as a fundamental pathomechanism in neurodegeneration.

A central question in Alzheimer's disease (AD) research is how β-amyloid (Aβ) and tau, principal components of amyloid plaques and neurofibrillary tangles, exert toxicity. Recent findings highlight the role of distinct Aβ species including Aβ*56, a dodecameric form of Aβ [1]. Others demarcate differences between oligomeric and fibrillar forms [2]. For tau, inducible transgenic mice reveal a toxicity independent of neurofibrillary tangles [3], a notion supported by studies in transgenic flies [4]. Irrespective of the form of toxic species, Aβ and tau seem to confer toxicity synergistically, as Aβ exacerbates a preexisting tau pathology [5], while Aβ toxicity is tau dependent [6].

An excellent read-out for functional impairment is mitochondrial respiration [7]. A sophisticated set of functional assays is available determining activities of all mitochondrial complexes separately, as well as different forms of respiration. Mitochondrial function is vital for any type of cell, in particular neurons; however, mitochondria are also the major source of reactive oxygen spe-

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cies. Microtubules are needed to properly distribute mitochondria, establishing a link to tau as microtubule-stabilizing protein. To determine how mitochondrial function is impaired by Aβ, we isolated mitochondria from P301L tau transgenic mice [5] and incubated them with different forms of Aβ [8]. Both oligomeric and fibrillar, but not disaggregated (mainly monomeric) Aβ42 caused a decreased mitochondrial membrane potential in cortical brain cells obtained from the transgenic mice. This was not observed with cerebellar preparations (an area where the transgene is not expressed), indicating a role for tau in mediating Aβ42 toxicity. Furthermore, we found reductions in state 3 respiration, the respiratory control ratio and uncoupled respiration when incubating transgenic mitochondria either with oligomeric or fibrillar preparations of Aβ42. Finally, aging of the peptides specifically increased the sensitivity of mitochondria to oligomeric Aβ42. We found that oligomeric and fibrillar Aβ42 are both toxic, but to a different degree. Furthermore, we found that aging of the mice increased sensitivity of mitochondria to Aβ damage, in agreement with studies in Aβ plaque-forming amyloid precursor protein transgenic mice [9].

Epidemiological, clinical and biochemical studies establish a link between AD and type 2 diabetes, another leading cause of morbidity and mortality in the elderly [10]. Both diseases are characterized by amyloidosis in their target tissue; amylin aggregation in type 2 diabetes is associated with β-cell loss while Aβ aggregation in AD brain is associated with neuronal loss. Aβ and human amylin are similar in size; however, while sharing little similarities in their primary sequence, they fold into similar secondary structures. Given these similarities, we asked whether human amylin would exert neurotoxic effects similar to Aβ [11]. Cell type specificity of toxicity was explored by comparing cortical to hippocampal long-term cultures, and aged peptide preparations were compared with nonaged preparations. We found that, different from nonamyloidogenic rat amylin, Aβ42 and human amylin both caused a dose-, time- and cell type-specific neurotoxicity, supporting the notion of a similar toxic mechanism [11]. Depending on the cell type, this finding is also supported by coincubation of amylin and Aβ. We observed that in general, hippocampal neurons were more sensitive than cortical neurons to toxicity exerted by either human amylin or Aβ42. We also found that rat amylin, which does not form fibrils, is virtually not toxic to hippocampal neurons but surprisingly, toxic to cortical neurons under some conditions. Coincubation of Aβ42 and human amylin suggests the possibility of a shared pathway in hippocampal neurons, whereas more than one pathway may be activated in cortical neurons. Our results imply that specific conformational changes in peptides are important determinants of toxicity. In support, conformational antibodies can be generated that recognize a generic amyloid fibril epitope found on amyloid-like aggregates derived from proteins such as transthyretin, amylin or β_2-microglobulin [12].

Not only is the toxicity of Aβ42 not fully understood, the same holds true for tau, where soluble species more so than the fibrillar forms seem to be a culprit in disease initiation. To determine tau toxicity, we generated a novel transgenic mouse strain, K3, which expresses human tau carrying the mutation K369I found in a familial case of frontotemporal dementia (FTD). The mice develop a progressive histopathology reminiscent of the human patient. Furthermore, they show early onset memory impairment and amyotrophy, that precedes neurodegeneration as the mice age. Different from our previously generated tau transgenic strains, K3 mice express the transgene in the substantia nigra, associated with an early onset motor phenotype that reproduces parkinsonism with tremor, bradykinesia, abnormal gait and postural instability. Interestingly, motor performance of young, but not old K3 mice could be improved upon L-dopa treatment, which bears similarities to parkinsonism in FTD. The early onset symptoms in the mice are mechanistically related to selectively impaired anterograde transport of distinct cargos, which precedes loss of dopaminergic neurons in aged mice. The impaired axonal transport affects, among others, vesicles containing the dopamine-synthesizing enzyme tyrosine hydroxylase. Distinct modes of transport are also impaired in sciatic nerve, which may explain amyotrophy [13]. We found that impaired axonal transport in the K3 mice is due to a cargo-selective impairment of kinesin-driven anterograde transport by tau. Specifically, formation of the kinesin motor complex formation is disturbed in K3 mice, as hyperphosphorylated tau interacts with JIP1, a protein associated with the kinesin motor protein complex. Consequently, JIP1 transport into the axon is impaired causing accumulation in the soma. Since we found trapping of JIP1 in the soma and a pathological tau/JIP1 interaction also in AD brain, this has pathomechanistic implications for tauopathies. We also found JIP1 sequestration in the soma of tau-transfected primary neuronal cultures. The pathological tau/JIP1 interaction depends on tau phosphorylation, with tau competing with the physiological binding of JIP1 to kinesin light chain. Since JIP1 is involved in regulating cargo binding to kinesin motors, our findings may,

at least in part, explain how hyperphosphorylated tau, independent of effects mediated by amyloid precursor protein/Aβ42, mediates impaired axonal transport in both AD and FTD [14].

Together, this highlights the validity of transgenic animal models [15] and underscores the role of impaired axonal transport in human neurodegenerative disease [16].

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