Clinical Implications of Basic Neuroscience Research

Amyloid-β and Tau
The Trigger and Bullet in Alzheimer Disease Pathogenesis

George S. Bloom, PhD

The defining features of Alzheimer disease (AD) include conspicuous changes in both brain histology and behavior. The AD brain is characterized microscopically by the combined presence of 2 classes of abnormal structures, extracellular amyloid plaques and intraneuronal neurofibrillary tangles, both of which comprise highly insoluble, densely packed filaments. The soluble building blocks of these structures are amyloid-β (Aβ) peptides for plaques and tau for tangles. Amyloid-β peptides are proteolytic fragments of the transmembrane amyloid precursor protein, whereas tau is a brain-specific, axon-enriched microtubule-associated protein. The behavioral symptoms of AD correlate with the accumulation of plaques and tangles, and they are a direct consequence of the damage and destruction of synapses that mediate memory and cognition. Synapse loss can be caused by the failure of live neurons to maintain functional axons and dendrites or by neuron death. During the past dozen years, a steadily accumulating body of evidence has indicated that soluble forms of Aβ and tau work together, independently of their accumulation into plaques and tangles, to drive healthy neurons into the diseased state and that hallmark toxic properties of Aβ require tau. For instance, acute neuron death, delayed neuron death following ectopic cell cycle reentry, and synaptic dysfunction are triggered by soluble, extracellular Aβ species and depend on soluble, cytoplasmic tau. Therefore, Aβ is upstream of tau in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances Aβ toxicity via a feedback loop. Because soluble toxic aggregates of both Aβ and tau can self-propagate and spread throughout the brain by prionlike mechanisms, successful therapeutic intervention for AD would benefit from detecting these species before plaques, tangles, and cognitive impairment become evident and from interfering with the destructive biochemical pathways that they initiate.

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Author Affiliation: Departments of Biology and Cell Biology, University of Virginia, Charlottesville.

Corresponding Author: George S. Bloom, PhD, University of Virginia, Department of Biology, PO Box 400328, Charlottesville, VA 22904-4328 (gsb4g@virginia.edu).

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The histopathological signature of Alzheimer disease (AD), amyloid plaques, and neurofibrillary tangles and their association with dementia have been known since the early 20th century, when Alois Alzheimer published his historical treatise that formally introduced the world to the disease that bears his name.[1,2] More than a century later, AD afflicts nearly 6 million Americans, is considered to be the most expensive disease in the United States,[3] and responds only marginally and briefly to currently available drugs that have been approved by the Food and Drug Administration for its treatment. Unless new, disease-modifying drugs become available soon, the number of AD cases in the United States could increase more than 2-fold by the middle of the 21st century.[4]

Despite these discouraging statistics, advances at the basic science level are providing a detailed view of the molecular basis of AD pathogenesis and, by extension, are bound to foster the development of far better tools for early diagnosis and treatment than are currently available. Among such recent discoveries are those that have implicated soluble forms of amyloid-β (Aβ) and tau, the respective building blocks of the insoluble plaques and tangles, as the principal toxic agents in AD, and have revealed pathways that connect Aβ to tau in seminal steps of AD pathogenesis (**Table**).

In Vivo Evidence for Tau-Dependent Aβ Toxicity

The first experimental evidence that functionally links Aβ to tau was described in a pair of landmark articles published sequentially in *Science* in 2001. Both studies made use of transgenic mice that accumulate tangles owing to overexpression of human tau with a P301L mutation, which causes the non-Alzheimer tauopathy, frontotemporal dementia with parkinsonism–17. In 1 case, injection of synthetic Aβ into brains of the mice induced a 5-fold increase in the number of tangles in regions near the injection sites.[5] The other study took a different approach by crossing tau_{P301L} mice with a transgenic strain that accumulated plaques caused by overexpressing human amyloid precursor protein (APP) with the Swedish (K670N/M671L) double mutation, which causes familial early-onset AD. The resulting hybrid mice exhibited plaque formation that was indistinguishable from the parental APP_{Swe} strain, but their tangle formation was markedly accelerated compared with the parental tau_{P301L} strain.[6] In a more recent spatiotemporal study comparing tangle progression in PS19 mice, which overexpress the human tau_{P301S} mutant that causes frontotemporal dementia with parkinsonism–17,

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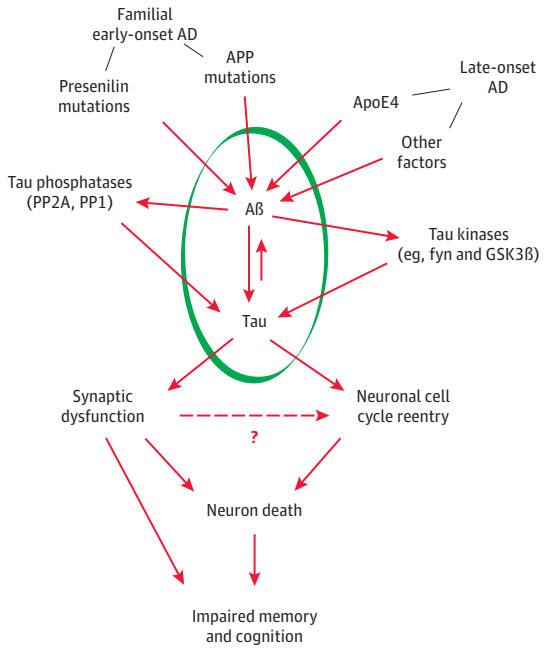
Table. Tau-Dependent Effects of Aβ

Study	System	Summary of Main Results
Götz et al,[5] 2001	Mouse	Tangle formation accelerated by injection of Aβ fibrils into the brain
Lewis et al,[6] 2001 and Hurtado et al,[7] 2010	Mouse	Mutant APP expression accelerates tangle formation by mutant tau
Roberson et al,[8] 2007	Mouse	Tau required for learning and memory deficits when plaques are present
Leroy et al,[9] 2012	Mouse	A feedback loop connects Aβ and tau pathologies
Ittner et al,[10] 2010	Mouse	Aβ causes tau-dependent excitotoxicity at NMDA receptors
Rapoport et al,[11] 2002	1° Neurons	Aβ fibrils are cytotoxic
King et al,[12] 2006	1° Neurons	AβOs cause tau-dependent MT loss
Nussbaum et al,[13] 2012	1° Neurons	Pyroglutamylated AβOs cause tau-dependent cytotoxicity
Seward et al,[14] 2013	1° Neurons	AβOs cause tau-dependent, ectopic cell cycle reentry
Shipton et al,[15] 2011	Brain slice	AβOs cause tau-dependent impairment of long-term potentiation
Vossel et al,[16] 2010	1° Neurons	AβOs cause tau-dependent inhibition of mitochondrial transport on MTs
Zempel et al,[17] 2013	1° Neurons	AβOs cause tau-dependent MT severing and synaptic damage in dendrites

Abbreviations: Aβ, amyloid-β; AβO, amyloid-β oligomer; APP, amyloid precursor protein; MT, microtubule; NMDA, *N*-methyl-D-aspartate.

Figure. Signaling From Amyloid-β (Aβ) Through Tau Drives Alzheimer Disease (AD) Progression



Pathological Aβ species accumulate in the brain because of simple genetic insults, such as the rare amyloid precursor protein (APP) and presenilin mutations that cause familial early-onset AD, and the presence of apolipoprotein E4 (ApoE4), the protein product of the ε4 allele of the *APOE* gene, which is the strongest genetic risk factor for late-onset AD. Complex genetic interactions and environmental risks, indicated here as other factors, also contribute to the accumulation of toxic Aβ species in late-onset AD. Toxic Aβ species stimulate formation of pathological tau by modulating protein kinases and phosphatases that regulate tau phosphorylation and by inducing tau misfolding. Toxic forms of tau mediate the synaptic dysfunction and neuron death that underlie memory and cognitive impairment in AD, so the signature adverse effects of Aβ require tau.

plaque deposition in PDAPP mice, which overexpress the human APP_{V717F} mutant that causes familial early-onset AD, and PS19:PDAPP hybrids revealed that the hybrids had accelerated tangle deposition, but plaque formation was unaffected.[7] Together, these studies demonstrated enhanced tau pathology caused by Aβ in the absence of any demonstrable effects on Aβ caused by excess mutant tau. Thus, Aβ was concluded to function upstream of tau, albeit by pathways that remained to be defined.

Evidence that tau pathology is not just an epiphenomenon of Aβ pathology, but instead that tau is required for Aβ toxicity in vivo, emerged from crossing tau knockout mice with hAPPJ20 mice that overexpress human APP containing 2 mutations, either of which causes familial early-onset AD on its own. Plaque accumulation in hybrid mice that were either tau null or contained 1 tau gene was identical to the parental APP strain that contained 2 tau genes. Remarkably, loss of either 1 or 2 tau genes protected hybrids against the learning and memory deficits and excitotoxicity characteristic of the parental APP strain.[8] These results imply that Aβ initiates a pathway that leads to tau-dependent synaptic dysfunction. Moreover, they raise the possibility that the cognitive and memory loss associated with AD can be prevented or decelerated by reducing the level of tau in the brain.

A similar, more recent study confirmed that eliminating tau from AD model mice confers protection against harmful effects of Aβ accumulation but has challenged the notion that tau functions exclusively downstream of Aβ.[9] In this case, the AD model mice overexpressed mutant forms of human APP and presenilin-1 (PS1), which individually cause familial early-onset AD. Knocking out the tau genes in the APP/PS1 mice conferred protection not only against memory impairment, but against synaptic loss, neuron loss, and premature death as well. However, in contrast to related prior studies,[6,7] APP/PS1 mice that lacked tau had lesser plaque burdens than age-matched APP/PS1 mice that expressed tau.[9] This evidence that tau influences Aβ, in combination with earlier evidence that Aβ clearly functions upstream of tau,[5-7] raises the possibility that Aβ initiates a pathological feedback loop with tau (**Figure**).

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One protein that functionally connects Aβ to tau is fyn. This nonreceptor tyrosine kinase that positively regulates *N*-methyl-D-aspartate (NMDA) receptor activity was recently shown to be targeted to postsynaptic sites in dendrites by tau,[10] which binds fyn directly.[18] Fyn was correctly targeted to dendrites in wild-type mice that expressed their endogenous tau genes, but not in otherwise identical mice that overexpressed a truncated tau that binds fyn and is excluded from dendrites or whose tau genes were eliminated. Furthermore, the memory deficits, excitotoxic seizures, and seizure-induced premature mortality of APP_{Swe} mice were relieved when fyn was not targeted to dendrites owing to transgenic expression of the aforementioned truncated tau, knocking out the endogenous tau genes or, even more effectively, by transgenically expressing truncated tau in a tau knockout background.[10]

Interpretation of these experiments must take into account tau is normally highly enriched in axons relative to dendrites[19] but in response to Aβ is extensively redistributed into the somatodendritic compartment.[20,21] Excess fyn accompanies the excess tau in AD dendrites and upregulates NMDA receptor activity there, flooding the dendrites with harmful levels of calcium. This calcium-driven excitotoxicity can damage postsynaptic sites and cause neuron death.

Therefore, reducing the dendritic content of fyn might protect human neurons against the Aβ-induced, tau-dependent hyperactivity of NMDA receptors that occurs in AD. The strategies that reduced dendritic fyn in mice, knocking out the tau genes or overexpressing a tau fragment that sequesters fyn away from dendrites,[8,10] do not seem feasible in humans, but reverse genetic approaches that reduce tau expression using antisense oligonucleotides may be the answer. A major advantage of this approach is that it would target a nearly neuron-specific protein, tau, and would thereby be unlikely to harm most nonneuronal brain cells or organs other than the brain. However, to make this strategy possible, the challenge of delivering antisense oligonucleotides to the brain side of the brain-blood barrier must first be overcome.

Tau-Dependent Aβ Toxicity in Cultured Neurons

As valuable as in vivo studies such as those described here have been for revealing AD mechanisms at the whole-animal level, their ability to unravel the basic, underlying pathways at the cellular and biochemical levels are limited. This is because of the difficulty of systematically and precisely manipulating the environments of specific cell types in vivo. Those limitations have been largely overcome by numerous studies that emphasized the use of cultured cells, especially primary neurons, and cultured brain-slice preparations.

One of the first published uses of this approach to study the Aβ-tau connection involved exposure of primary mouse neurons to fibrils assembled from synthetic $Aβ_{1-40}$. Within days of initial Aβ exposure, neurite degeneration and extensive cell death was observed for wild-type neurons but not for neurons derived from tau knockout mice. However, when human tau was expressed in the tau knockout neurons, Aβ sensitivity was restored, and tau was therefore concluded to be essential for the neurodegeneration and cytotoxicity induced by Aβ.[11] Subsequent studies have implicated small Aβ oligomers (AβOs) as being much more toxic than Aβ fibrils, and synthetic $Aβ_{1-40}$ being much less potent than other Aβ variants, such as synthetic $Aβ_{1-42}$ and $Aβ_{3pE-42}$, and Aβ isolated from cultured mammalian cells or human AD brain.[12-16,22-26] It is also important to note that the cytotoxic $Aβ_{1-40}$ fibrils described here were used at a very high concentration of total peptide (20 μM) relative to more recent studies using synthetic or biologically produced AβOs (low nanomolar to low micromolar).[12-16,23-26]

Acute cytotoxicity[11,13] is not the only tau-dependent effect of Aβ on cultured dissociated brain cells or brain slices. Amyloid-β oligomers also have been found to cause tau-dependent microtubule disassembly,[12] inhibition of mitochondrial transport along microtubules,[16] impaired long-term potentiation,[15] dendritic microtubule severing,[17] and ectopic cell cycle reentry of neurons,[14] which ironically leads to massive neuron death in AD and possibly in other neurodegenerative disorders as well.[27] Because microtubules are essential for efficient delivery of presynaptic components to axon terminals and postsynaptic components to dendritic spines,[28] the Aβ-induced, tau-dependent effects on microtubules described here represent significant threats to synaptic function.

Not all effects of Aβ on neurons require tau. For example, AβO-induced neuronal cell cycle reentry involves requisite activation of 3 protein kinases—fyn, PKA, and CaMKII—that then must phosphorylate tau at specific sites. These kinases are activated by AβOs in tau knockout neurons just as effectively as in wild-type neurons that contain tau,[14] so any cellular process that requires AβO-stimulated kinase activation, but does not rely on tau, may therefore be sensitive to AβOs. One such example is inhibition of the microtubule-dependent, axonal transport of brain-derived neurotrophic factor–containing vesicles that results from AβO-induced activation of the kinase, GSK3β, but occurs independently of tau.[29] Although tau is not essential for some effects of AβOs, their many known tau-dependent effects on microtubules and neuronal viability emphasize how AβOs and tau work interdependently to impair and destroy synapses, which causes the behavioral symptoms of AD. Because tau is expressed predominantly in neurons,[19] the AβO-tau connection also helps to explain why neurons are the cell type most vulnerable to AβOs.

Prionlike Properties of Toxic Aβ and Tau

Two of the most remarkable features of AD are the stereotypic patterns by which plaques and tangles spread through the brain,[30] and the ability of toxic, misfolded AβOs and tau to serve as templates that convert their innocuous counterparts into equivalent pathological forms by a prionlike process in vitro[13,31-33] and in vivo.[34-38] Several in-depth reviews on these topics have been published recently,[39-42] so no duplication of those efforts will be made here. However, they are mentioned in this review because they raise the question of how toxic posttranslational modifications of tau, like those that cause cell cycle reentry,[14] might relate to the misfolding and acquisition of prionlike properties by tau. Amyloid-β oligomers clearly control many of tau's posttranslational modifications, but how do they also drive formation of tau prions? Do the AβOs serve as direct templates for misfolding tau into prions or do specific combinations of posttranslational modifications induced by AβOs cause the conversion of tau into prions? Regardless of how these questions may be answered eventually, they emphasize yet another dimension of the concept that Aβ and tau serve as respective trig-

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gers and bullets for AD pathogenesis. Moreover, they point to the urgent need for methods that can accurately detect AD long before toxic, prionlike forms of Aβ and tau have expanded beyond the point at which they can be controlled. The development of disease-modifying drugs for AD will likely depend on the prior development of such improved diagnostic methods.

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