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Amyloid β-Protein Toxicity and the Pathogenesis of Alzheimer Disease*[S]

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Although amyloid deposition was noted by Alzheimer in 1907 (1), it has been only 17 years since the toxicity of Aβ[2] was first described (2). The prevailing view through most of the twentieth century was that Aβ is a marker of disease progression in AD but does not play a role in the neurodegenerative process. This view changed in the 1990s with the articulation of the amyloid hypothesis, which posits that abnormal accumulation of Aβ in the brain is a direct cause of neurodegeneration and cognitive decline in AD. The hypothesis is supported by the identification of mutations in APP (3) and presenilins 1 and 2 (4–7) that increase Aβ generation or, more importantly, the generation of a minor 42-amino acid form (Aβ42) with an increased propensity for aggregation (8). This review sets forth the major lines of evidence for Aβ toxicity and focuses on the interface between Aβ toxicity and molecular mechanisms of synaptic plasticity.

Do Plaques Matter?

The early studies of Blessed and co-workers (9) suggested that plaque numbers were directly related to quantitative measures of cognitive decline in the aged population. However, subsequent studies carried out by Terry *et al.* (10) cast doubt on the predictive value of plaque numbers, suggesting instead that NFTs and synapse loss were more reliable predictors of cognitive decline. Moreover, plaque formation is a common feature of the aging human brain that can occur in the absence of cognitive decline (11). More recently, it has been suggested that accumulation of toxic oligomers of Aβ may be more relevant than plaques to mechanisms involved in cognitive decline.

Transgenic mouse models expressing APP and presenilin variants associated with FAD have provided important insights into structural, neurophysiological, and behavioral effects of Aβ accumulation in the brain (12). Multiphoton imaging studies have demonstrated disrupted neurites and decreased spine density in association with fibrillar Aβ deposits in the Tg2576 transgenic mouse model that expresses the APPsw mutation (13, 14). In addition, stereologic mapping of neuronal cell density showed some degree of neuronal loss in the immediate vicinity of Aβ deposits (15). The neuritic dystrophy observed in APP transgenic mice appears to be directly related to the fibrillar component of Aβ deposits. When the APP transgenic was placed on an apoE-deficient background, Aβ deposition still occurred, but fibrillar deposits were absent, and neuritic dystrophy was markedly reduced. When apoE3 or apoE4 was expressed, fibrillar Aβ deposits appeared with concomitant neuritic degeneration that was greater for apoE4 than for apoE3 (16, 17). However, it was unclear from these studies which came first, neuritic degeneration or deposition of fibrillar Aβ. Another study suggested that axonal dystrophy and altered axonal transport occur early in AD and may lead to amyloid deposition (18). The question of which comes first, amyloid or neuritic dystrophy, was recently addressed by *in vivo* multiphoton microscopy in an APPswe/PS1d9XYFP transgenic mouse in which the onset of plaque formation could be accurately dated. Plaque formation was followed by progressive neuritic abnormalities that appeared in direct contiguity to the plaque, establishing a causal relationship between amyloid deposition and neuritic dystrophy (19). In addition, plaques could form quickly, within 24 h, suggesting that amyloid deposition is a more dynamic process than previously appreciated. Although these findings suggest that neuritic dystrophy can be induced by fibrillar Aβ deposition, it remains to be determined whether this is mediated by Aβ fibrils or by oligomeric intermediates associated with fibrils (20).

A limitation of APP transgenic mouse models is the paucity of neuronal cell death and tau-related pathology characteristic of human AD (21, 22). Two potential explanations have been posited: either Aβ is not sufficient to account for the neurodegenerative process in AD, or rodent models do not accurately recapitulate the aging human brain. Evidence for the latter explanation comes from the introduction of plaque-equivalent concentrations of pre-fibrillized Aβ into the brains of aging rhesus monkeys, which induced neuronal cell death, tau pathology, and microglial activation (23). These toxic effects of Aβ were age-dependent in rhesus macaques but did not appear in aging rats. Thus, aging primates may be more vulnerable to Aβ toxicity than aging rodents, possibly accounting for the relative absence of AD-type pathology in APP transgenic mouse models.

Aβ Oligomers

The importance of Aβ aggregation in the mechanism of Aβ toxicity was noted in early cell culture studies (24, 25) and was supported by the finding that FAD mutations in APP increase generation of the highly aggregable Aβ42 peptide (8). Recent studies suggest that low molecular weight oligomers are more toxic than the larger Aβ fibrils (26). The toxicity of Aβ oli-

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[2] The abbreviations used are: Aβ, amyloid β-protein; AD, Alzheimer disease; APP, amyloid precursor protein; NFTs, neurofibrillary tangles; FAD, familial AD; ADDLs, Aβ-derived diffusible ligands; LTD, long-term depression; MAPK, mitogen-activated protein kinase; NMDA, *N*-methyl-D-aspartate; GABA, γ-aminobutyric acid.

gomers was described by Klein and co-workers (27) in studies of small diffusible Aβ oligomers that they named ADDLs, which cause neuronal cell death in hippocampal slice cultures at nanomolar concentrations. Notably, ADDLs could inhibit hippocampal long-term potentiation, suggesting a potential role in memory impairment in AD.

Evidence that Aβ oligomers could impair synaptic physiology *in vivo* came from experiments in which Aβ oligomers generated by APP-transfected Chinese hamster ovary cells were injected into the rat brain and impaired hippocampal long-term potentiation *in vivo* (28). Injection of preparations enriched in Aβ dimers and trimers, but not monomers or fibrils, resulted in behavioral deficits in a food-related reinforcement learning paradigm. Rats that received multiple oligomer injections improved and did not show a deficit, suggesting that oligomers transiently impaired synaptic physiology but did not induce neurodegeneration. Whether the low molecular mass dimers and trimers were active or aggregated further to higher molecular mass forms upon injection into the brain was not resolved. Another study showed that a 56-kDa Aβ-immunoreactive species, a putative Aβ dodecamer, correlated with memory impairment in Tg2576 transgenic mice (29). This species, referred to by the authors as Aβ*56, was isolated from the transgenic mouse cortex and injected into the adult rat brain, resulting in transient deficits in memory retention. In aged transgenic mice, however, cognitive deficits did not clearly correlate with Aβ*56 levels, leading the authors to suggest that Aβ*56 may contribute to early cognitive deficits similar to those that occur in patients with mild cognitive impairment (29). Moreover, in APP transgenic mice carrying the Arctic mutation, which augments neuritic plaque formation but reduces Aβ*56, behavioral deficits more closely paralleled Aβ*56 levels than plaque loads (30).

Despite evidence that Aβ oligomers can interfere with normal synaptic physiology and contribute to cognitive deficits in APP transgenic mice, it remains to be determined whether Aβ oligomers contribute to cognitive decline in AD. The ADDL-type of Aβ oligomer is elevated in cerebrospinal fluid and cortex in AD (31, 32). However, a covariant analysis relating Aβ oligomer levels to cognitive test scores has not yet been performed. It also remains to be determined whether oligomers are causally related to other pathological features of AD, including NFTs, microglial activation, synapse loss, and neuronal cell death.

Aβ and Mechanisms of Synaptic Plasticity

The role of Aβ in synaptic dysfunction has emerged as a central area of investigation in the pathophysiology of AD. APP transgenic mouse models have provided evidence that Aβ-related synaptic dysfunction can give rise to deficits in learning and memory (33–35) and that these deficits can be dissociated from amyloid plaque formation (14, 36, 37). Compelling evidence for direct effects of Aβ on receptor-mediated mechanisms of synaptic plasticity came from the study of Kamenetz *et al.* (38) demonstrating that neuronal activity can induce the cleavage of APP to Aβ and that Aβ can in turn depress excitatory synaptic transmission. This required both BACE and γ-secretase cleavage and was mimicked by application of synthetic Aβ peptides to cultured neurons. A physiological role for APP was also supported by studies of neuronal cultures from APP knock-out mice (39). Furthermore, the endogenous level of Aβ in the brain was regulated by synaptic activity *in vivo* (40), suggesting a dynamic feedback loop involving APP metabolism and Aβ that may modulate synaptic activity (supplemental Fig. 1).

Aβ can depress synaptic transmission through mechanisms similar to the physiological phenomenon of LTD (41). Aβ-mediated synaptic depression may require p38 MAPK, leading to phosphorylation of the AMPA receptor at the site phosphorylated in LTD that results in receptor endocytosis (supplemental Fig. 1) (41). Synaptic removal of NMDA receptors may also be mediated by binding of Aβ to the α7 nicotinic receptor, leading to activation of two phosphatases, PP2B and the striatal enriched tyrosine phosphatase (STEP). STEP may induce NMDA receptor endocytosis by dephosphorylating the NR2B subunit (42). Another study suggested that sustained application of naturally secreted Aβ dimers and trimers to hippocampal slice cultures reduces synapse and spine numbers (43). This also resembled LTD in its requirement for NMDA receptor activity and the action of calcineurin and the actin cytoskeletal protein cofilin. Synapse loss associated with low molecular weight Aβ oligomers was unaffected by blockade of nicotinic acetylcholine receptors with α-bungarotoxin, suggesting a different pathway than that described by Snyder *et al.* (42). It is unclear whether this difference relates to different aggregated forms of Aβ or experimental paradigms. Nonetheless, these observations suggest that Aβ can affect multiple synaptic signaling mechanisms, resulting in reduced excitatory synaptic transmission and structural changes such as dendritic spine loss (supplemental Fig. 1).

In contrast to the inhibitory effects of Aβ on synaptic activity *in vitro*, a recent study demonstrated spontaneous nonconvulsive seizure activity in APP transgenic mice consistent with increased excitation (44). Altered glutamate receptor regulation was suggested by changes in the phosphorylation state of the NR2B subunit of the NMDA receptor and reduced levels of the GluR1 and GluR2 AMPA receptor subunits. These findings are intriguing in light of recent evidence for increased seizure activity in AD patients (45). In addition, deleterious overexcitation of cortical networks would suggest a context for the clinical efficacy of the NMDA receptor antagonist memantine, a drug that slows disease progression in AD. However, the overexcitation observed in this APP transgenic model is difficult to reconcile with electrophysiological observations suggesting a primary inhibitory effect of Aβ on synaptic transmission (38, 41, 42).

Depressive effects of Aβ on synaptic transmission in the GABAergic inhibitory system could potentially reconcile these seemingly disparate observations. The J20 APP transgenic mouse exhibits markedly reduced calbindin 1 levels in hippocampal dentate granule cells that correlate closely with cognitive deficits (46). Calbindin is also reduced in AD and to a lesser extent during normal aging (47, 48). Calbindin is a calcium-buffering cytosolic protein specifically expressed in GABAergic inhibitory neurons that can protect against excitotoxicity (49). Hence, loss of calbindin in APP transgenic mice might be indicative of impaired inhibitory neuronal function. Moreover, functional imaging studies in AD patients suggest

that impaired inhibitory network function may lead to cortical overactivation at an early stage (50).

Aβ-APP Interactions and Toxicity

Aggregation of Aβ can induce binding to a variety of neuronal cell-surface proteins, including APP (51). Moreover, cortical neurons cultured from APP knock-out mice are partially resistant to Aβ toxicity, implicating APP in the mechanism of toxicity (51). Aβ can induce APP oligomerization and caspase cleavage at Asp^{664}, liberating an APP fragment containing the C-terminal 31 amino acids (52, 53). This APP C-terminal fragment is neurotoxic when overexpressed (54) and may activate a G-protein signaling cascade (55).

Evidence that APP may be directly involved in pathological and behavioral changes in APP transgenic mice was suggested by a transgenic mouse model expressing APP with the Swedish and Indiana FAD mutations together with an additional mutation at Asp^{664}, a C-terminal caspase cleavage site. The Asp^{664} mutation did not affect Aβ generation or plaque number but prevented synapse loss, astrogliosis, and spatial memory deficits (56). Cleavage of APP at Asp^{664} might promote these pathological changes by generating a toxic C-terminal fragment (54) or by altering physiological interactions between APP and signaling proteins such as Fe65. These findings also call into question the role of Aβ *per se* as a primary cause of cognitive deficits in APP transgenic mice. However, a causal role for Aβ is supported by Aβ immunotherapy experiments that reduce plaque load and soluble Aβ levels without any known effects on the APP holoprotein (57, 58). An interaction of Aβ with APP, either by direct binding or through convergent signaling pathways, may at this point be the most parsimonious working model.

Modulation of Aβ Toxicity by Tau

NFTs are composed predominantly of hyperphosphorylated forms of the microtubule-associated protein tau, a set of post-translational modifications that can dissociate tau from microtubules and potentially disrupt axonal transport. A long-standing issue is whether amyloid- and tau-related changes are causally related or represent parallel pathogenic pathways. Initial studies of primary neuronal cultures showed that aggregated forms of Aβ induce tau phosphorylation at the same sites that are hyperphosphorylated in AD (59). APP transgenic mice exhibit focally increased tau phosphorylation in dystrophic neurites surrounding neuritic plaques but do not develop NFTs (21, 60). Tangle formation was observed in a triple transgenic mouse expressing FAD variants of APP and presenilin 1 and a tau variant associated with frontotemporal dementia. Cognitive deficits appeared in these mice before plaques and tangles and correlated with intraneuronal Aβ (34). These cognitive deficits could be reversed by administration of an anti-Aβ antibody but only under conditions in which both Aβ and tau were reduced, consistent with a mechanism requiring both proteins. Moreover, cell culture studies suggest that tau-deficient neurons may be resistant to Aβ toxicity and that Aβ toxicity is accompanied by proteolytic generation of a 17-kDa tau fragment (61–63).

A dramatic effect of endogenous tau on cognitive deficits was observed in APP transgenic mice crossed with tau knock-out mice (60). Spatial memory deficits were absent in animals with complete deletion of tau and partially prevented by deletion of a single tau allele. These behavioral effects occurred without any change in Aβ levels, plaque load, or dystrophic neurites and were attributed to a protective dampening effect of tau on excitatory neurotransmission. These intriguing observations provide a potentially novel link between neurofibrillary pathology and excitotoxic neurodegeneration.

Signaling Mechanisms Associated with Aβ Toxicity

The literature on Aβ biology is replete with a variety of different mechanisms of action, some of which may relate to varying structural states of the peptide. In primary neuronal cultures, Aβ oligomers and ADDLs can bind avidly to neuronal membranes and induce rapid cell death through the mitochondrial apoptotic pathway (64). In contrast, Aβ fibrils appear to induce a more chronic form of neuritic dystrophy and neuronal cell death. Rapid toxic effects of Aβ have been associated with a pro-oxidant effect of the peptide (65) and may be mediated in part through RAGE (receptor for advanced glycation end products) (66). Aβ can also induce apoptosis through activation of caspases and calpain (67–70). Caspase-7 and -8 levels are elevated in the AD brain, and caspase-8 levels correlate with formic acid-extractable Aβ42 (71). In addition, activated caspase-6 is associated with neuritic plaques and NFTs in mild cognitive impairment and AD (72). Another mechanism of toxicity may involve aberrant activation of cell cycle reentry in neurons, which has been observed in Aβ-treated neuronal cultures and in AD (73, 74). Little is known about the factors that regulate the generation of toxic Aβ aggregates in the aging brain, although recent studies suggest potential roles for insulin/insulin-like growth factor-1 signaling (75) and calcium homeostasis (76).

Another class of signaling pathways activated by Aβ is involved in the microglial inflammatory response. Amyloid deposits are closely associated with activation of microglia in AD and in APP transgenic mice. Fibrillar Aβ can bind to class A and B scavenger receptors on microglia, leading to an inflammatory response characterized by release of reactive oxygen species and chemokines (77–79). Binding of Aβ to the scavenger receptor CD36 activates signaling through the Src family kinase members Lyn and Fyn and p44/42 MAPK. Targeted disruption of this signaling pathway inhibits Aβ-induced secretion of reactive oxygen species and chemokines (79). Microglial activation also results in clearance of Aβ deposits (80), and loss of the microglial signaling response through blockade of chemokine receptors results in increased Aβ deposition and premature death in APP transgenic mice (81). An unresolved issue is the relative contributions of microglial clearance of Aβ *versus* microglial elaboration of toxic cytokines and reactive oxygen species in AD (82).

Conclusion

Recent studies suggest that Aβ can impair synaptic plasticity through mechanisms that might contribute to cognitive decline in AD. Evidence is mounting that Aβ oligomers can mediate these effects, possibly accounting for why plaque number is a poor predictor of cognitive status. It will be important, how-

ever, to determine whether there is a clear relationship between Aβ oligomers and cognitive status in patients at different stages of cognitive decline. A related question is whether Aβ pathology is linked to mechanisms of human brain aging (11) and whether mechanisms related to aging, such as oxidative stress, reduced mitochondrial energy metabolism, and altered protein turnover, are necessary cofactors for Aβ toxicity to become manifest.

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