

Neurodegenerative Diseases: New Concepts of Pathogenesis and Their Therapeutic Implications

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Key Words

amyloid, Alzheimer's disease, Parkinson's disease, neurodegeneration, misfolding

Abstract

Neurodegenerative diseases as diverse as Alzheimer's, Parkinson's, and Creutzfeldt-Jakob disease share a common pathogenetic mechanism involving aggregation and deposition of misfolded proteins, which leads to progressive central nervous system disease. Although the type of aggregated protein and the regional and cellular distribution of deposition vary from disease to disease, these disorders may all be linked by similar pathways of protein aggregation with fibril formation and amyloid deposition. This perspective on pathogenesis suggests that a wide variety of neurodegenerative diseases can be grouped mechanistically as brain amyloidoses, an outlook that yields novel insights into potential therapeutic approaches that may be applicable across the broad spectrum of neurodegenerative disease.

Amyloid: protein aggregates that share specific traits, including cross β -sheet quaternary structure

AMYLOID AS A COMMON THEME IN NEURODEGENERATIVE DISEASE

Neurodegenerative disorders such as Alzheimer's and Parkinson's disease account for a significant and increasing proportion of morbidity and mortality in the developed world (1, 2). Largely as a result of increased life expectancy and changing population demographics (i.e., the aging of baby boomers), neurodegenerative dementias and neurodegenerative movement disorders are becoming more common (3, 4). As our population ages, an improved understanding of these diseases will be vital to developing more effective therapies and combating the staggering personal, social, and economic costs of these diseases (5). Unifying theories of pathogenesis in neurodegenerative disease provide an avenue for developing therapeutic strategies with broad applicability for disease prevention and an opportunity for decreasing morbidity and mortality from these disorders in the elderly population (6).

Converging lines of investigation have revealed a potential single common pathogenic mechanism underlying many diverse neurodegenerative disorders, i.e., the aggrega-

tion and deposition of misfolded proteins. As summarized in **Table 1**, nearly every major neurodegenerative disease is characterized pathologically by the insidious accumulation of insoluble filamentous aggregates of normally soluble proteins in the central nervous system (CNS). Because these filamentous aggregates display the ultrastructural and tinctorial properties of amyloid (i.e., ~ 10 -nm-wide fibrils with crossed β -pleated sheet structures that stain with Congo red, thioflavin-S, or other related dyes), these diseases can be grouped together as brain amyloidoses.

What, then, accounts for the striking phenotypic diversity seen in these diseases? Each of the related brain amyloidoses is distinguished by (a) distinct temporal and regional patterns of deposition of aggregates, (b) varying cellular hosts or extracellular locales of the aggregates, and (c) different protein constituents of the aggregates (**Table 1**). Each of these characteristics, combined with the patient's own innate and variable response to the aggregates, may in turn alter the cascade of events leading to a particular temporal and regional pattern of neuronal dysfunction and death, which manifests as a specific clinical syndrome such as dementia in Alzheimer's disease or a movement disorder in Parkinson's disease. Thus, from a pathological standpoint, neurodegenerative entities are defined by the type and pattern of amyloid deposition in the brain. Unfortunately, the type and pattern of brain amyloidosis does not always correlate well with the observed clinical phenotype. This disconnect has led to a perplexing nosology that sometimes requires clinicians to describe phenotypes on the basis of the presumed presence of pathological lesions (e.g., dementia with Lewy bodies) and sometimes requires pathologists to describe lesions using clinical language regardless of the patient's actual clinical presentation (e.g., progressive supranuclear palsy, PSP). The best way to circumvent this morass may be the use some day of chemical analytes of biological fluids and neuroimaging biomarkers that allow clinicians to distinguish between

COMMON MOTIFS IN NEURODEGENERATIVE DISEASE

The major pathological lesions are accumulations of insoluble filamentous aggregates that take the form of amyloid. The aggregates are composed of a normal, soluble protein or peptide that has been misfolded. This amyloidogenic protein constituent differs among various neurodegenerative diseases. The amyloidogenic protein is typically expressed systemically, but accumulates only in the CNS. The aggregates accumulate early in the lifetime of the individual, but only manifest clinically in middle or late life. Most cases are sporadic, but genetic forms can be caused by mutations in the gene encoding the amyloidogenic protein that make it more prone to misfold and aggregate.

TABLE 1 Common neurodegenerative diseases characterized by deposition of aggregated proteins

| Disease | Microscopic lesion | Location | Aggregated protein |
|---|---|--|--|
| Alzheimer's disease | Amyloid plaque | Extracellular | Amyloid- β (A β) |
| | Neurofibrillary tangle | Intracytoplasmic (neurons) | Tau |
| | Lewy bodies (seen in Lewy body variant) | Intracytoplasmic (neurons) | α -synuclein |
| Amotrophic lateral sclerosis | Hyaline inclusions | Intracytoplasmic (neurons) | Superoxide dismutase-1 (SOD1) |
| Cortical basal degeneration/ progressive supranuclear palsy | Tau positive inclusions | Intracytoplasmic (neurons, oligodendroglia and astrocytes) | Tau |
| Dementia with Lewy bodies | Lewy bodies | Intracytoplasmic (neurons) | α -synuclein |
| Huntington disease | Neuronal inclusions | Intranuclear (neurons) | Huntington (containing polyglutamine repeat expansion) |
| Multiple system atrophy | Glial cytoplasmic inclusions | Intracytoplasmic (oligodendroglia) | α -synuclein |
| Parkinson's disease | Lewy bodies | Intracytoplasmic (neurons) | α -synuclein |
| Pick's disease | Pick bodies | Intracytoplasmic (neurons) | Tau |
| Prion diseases | Prion plaques | Extracellular | Protease-resistant prion protein (PrP) |
| Spinocerebellar ataxia | Neuronal inclusions | Intranuclear (neurons) | Ataxin (containing polyglutamine repeat expansion) |

these related brain amyloidoses on the basis of the nature and extent of the brain pathology as well as the specific amyloidogenic protein(s) involved in disease pathogenesis.

Recognizing that all these related neurodegenerative diseases share common mechanisms involving CNS accumulation of misfolded proteins suggests that these disorders may have similar targets for the development of diagnostic and therapeutic agents. This review highlights these potential targets, focusing on three prototypical and common amyloidogenic proteins: A β , tau, and synuclein. Within this context, Alzheimer's disease, the tauopathies (Pick's disease, cortical basal degeneration, and PSP), and the synucleinopathies (dementia with Lewy bodies, Parkinson's disease, and multiple system atrophy) are discussed as exemplars or models of the brain amyloidoses that occur in many aging-related neurodegenerative disorders.

General Mechanisms of Brain Amyloid Formation

Brain amyloidosis begins with the production of a soluble native protein that is misfolded to yield the precursor for fibril formation (**Figure 1**). The misfolded protein can self-associate to form oligomers, protofibrils, or other intermediates en route to fibril formation (reviewed in Reference 7). Oligomers of A β can be detected in vitro (8), in cell culture and transgenic mouse models of Alzheimer's disease (9–11), and in postmortem Alzheimer's disease brain specimens (12). Although oligomers of A β have been the most well studied, it is apparent that other amyloidogenic proteins such as α -synuclein or polyglutamine-containing proteins can also form oligomers. Remarkably, oligomers composed of each of these amyloidogenic proteins (which share no primary sequence homology) show a similar

Amyloidogenic:

property of being prone to aggregation and amyloid formation

A β (also amyloid- β or β -amyloid):

39–43 amino acid peptide generated by proteolytic cleavage of the amyloid precursor protein, which is prone to aggregating as amyloid

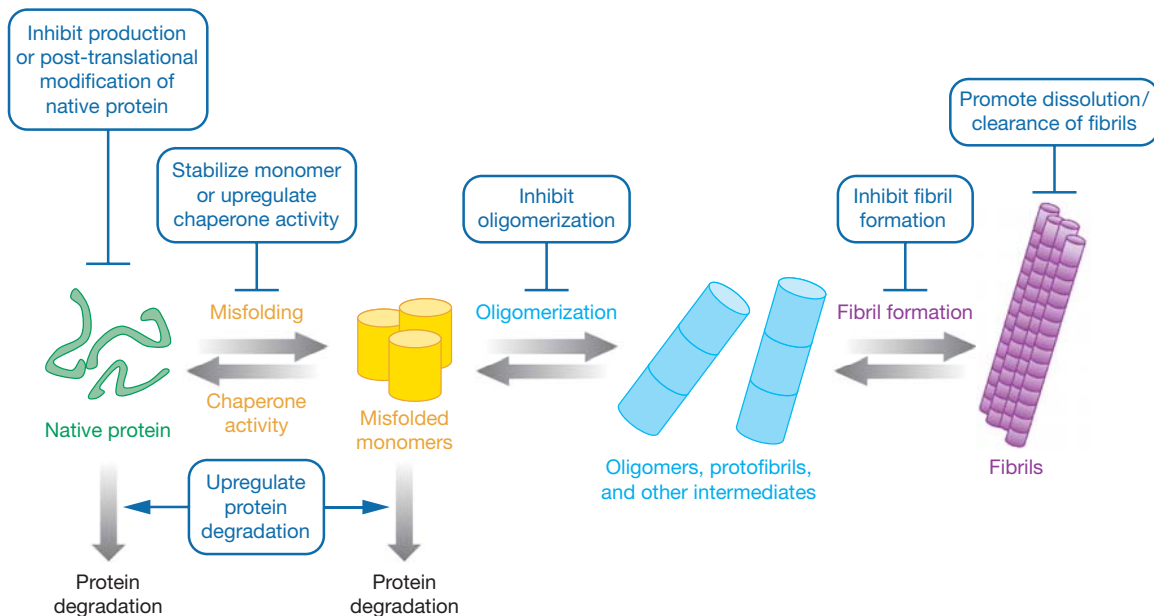


Figure 1

Model for protein misfolding and fibrillization. Soluble native protein is misfolded and associates in the form of oligomers and other intermediates that eventually give rise to fibrils. Potential opportunities for therapeutic intervention are shown in blue boxes.

conformation-dependent structure (12). These studies may suggest a common mechanism of amyloid formation that depends upon structural determinants within the oligomers. Further support for this hypothesis comes from the observation that different forms of amyloid interact with one another in vitro. For example, α -synuclein can initiate fibrillization of tau, and coincubation of tau and α -synuclein synergistically promotes fibrillization of both proteins (13).

In vivo, various factors may influence the balance between native protein, misfolded protein, oligomers, and fibrils. For example, in the disease state, overproduction of the amyloidogenic protein constituent, inappropriate covalent modification or cleavage, failed degradation, or insufficient molecular chaperone activity may all contribute in shifting the balance towards misfolded protein and oligomer formation. Each of these steps represents a potential target for therapeutic intervention, with therapies being

developed currently for different forms of amyloid.

Consequences of Brain Amyloidosis

Although accumulation of brain amyloid is clearly a unifying characteristic of many neurodegenerative diseases, the mechanisms by which brain amyloid leads to neuronal death or dysfunction are ill defined, but likely to be numerous and diverse. For example, evidence suggests that brain amyloid is linked mechanistically to impairments in axonal transport (14–17), inhibition of proteasomal activity (18, 19), defects in DNA transcription (20), increased levels of oxidative stress (21, 22), and apoptosis (23, 24). Despite a wealth of experimental data, there is still no consensus on whether oligomers, protofibrils, or mature fibrils (or some combination of these) are the important toxic species that mediate neurodegeneration, nor do we understand the mechanisms by which they compromise the

function and viability of selectively vulnerable CNS cells.

A β : THE EXTRACELLULAR AMYLOID OF ALZHEIMER'S DISEASE

Alzheimer's Disease: The Prototype A β Amyloidosis

The *sine qua non* of Alzheimer's disease, as defined originally by Alois Alzheimer, is the presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles (NFTs). In addition to these two cardinal lesions, >50% of sporadic and familial Alzheimer's patients have coexisting cortical Lewy bodies (25–28). Indeed, these three types of amyloid lesions define the Lewy body variant of Alzheimer's disease, the most common pathological subtype of this widespread dementia disorder. Because each of these three lesions is composed of filamentous aggregates of distinctly different misfolded proteins, the Lewy body variant of Alzheimer's disease is a triple amyloidosis. Specifically, amyloid plaques are comprised of fibrils formed by 39–42 amino acid long A β peptides, tangles are comprised of fibrils of hyperphosphorylated tau protein, and Lewy bodies are comprised of filamentous α -synuclein.

Other triple brain amyloidoses that can display A β , tau, and α -synuclein pathology include Down's syndrome (29) and Guam Parkinson's dementia complex (30). Examples of double amyloidoses (two forms of brain amyloid) include the majority of Alzheimer's disease patients (A β and tau), certain Parkinson's disease patients (e.g., patients of the Contursi kindred, who show both abundant tau and α -synuclein pathology) (31), and subsets of patients with Niemann-Pick type C disease (some have tau and A β pathology, whereas others have tau and α -synuclein pathology) (32, 33). Notably, A β pathology is accompanied by other forms of amyloidosis in all neurodegenerative dementias, but pure A β amyloidosis is seen in cerebral amyloid an-

giopathy, which manifests clinically as a stroke syndrome.

The Role of A β Pathology in Alzheimer's Disease

Amyloid plaques are not only a histopathological hallmark of Alzheimer's disease, but the aggregated A β of which they are composed likely plays a key role in the pathogenesis of Alzheimer's disease (summarized by the amyloid cascade hypothesis) (34). The most direct evidence supporting this hypothesis stems from studies of gene mutations that cause autosomal-dominant inherited forms of Alzheimer's disease. As illustrated in **Figure 2**, most but not all of these mutations lead to increased production and accumulation of specific A β species (A β 42), either through effects on the amyloid precursor protein (APP) itself (35) or through effects on presenilin 1 or 2 (36), which form part of γ -secretase, one of the proteolytic complexes that cleaves APP to generate A β (37). Aggregated amyloid (in the form of oligomers, protofibrils, or fibrils) is toxic to neurons in most but not all culture conditions (38, 39), and in primary neuronal culture and mouse models, A β may act synergistically with neurofibrillary tangle pathology (40, 41). These observations have led to the hypothesis that increased production, aggregation, and accumulation of A β initiates a cascade of events leading to neurotoxicity and eventually to clinical symptoms of Alzheimer's disease (34), as summarized in **Figure 3**. Autopsy studies of patients with genetic forms of Alzheimer's disease, Down's syndrome, or mild cognitive impairment (which appears to be a prodromal phase of Alzheimer's disease) have shown that accumulation of A β may precede clinical development of Alzheimer's disease by as many as 10 years (42–45); importantly, the increased presence of A β correlates well with cognitive decline early in the course of the disease (46).

Thus, A β pathology (*a*) is required for the diagnosis of Alzheimer's disease, (*b*) plays a key role in the pathogenesis of Alzheimer's

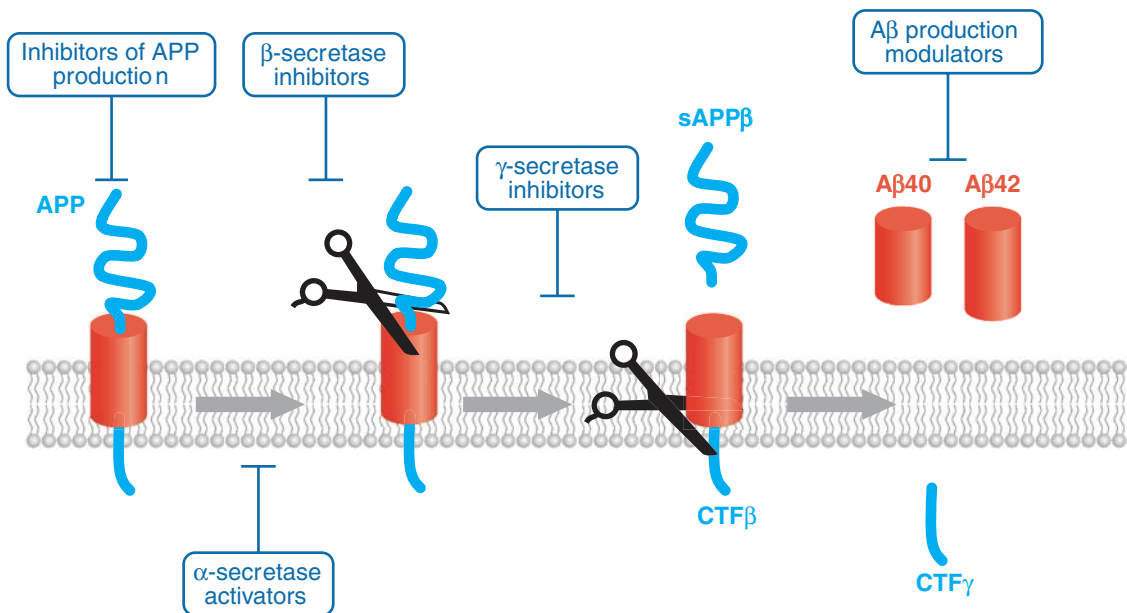


Figure 2

Aβ production. The integral membrane protein amyloid precursor protein (APP) is cleaved by the beta-site APP-cleaving enzyme (BACE, or β-secretase) to yield a secreted fragment of APP (sAPPβ) and a C-terminal fragment of APP (CTFβ). CTFβ is then cleaved by γ-secretase within the membrane to yield a smaller C-terminal fragment (CTFγ) and Aβ fragments of various lengths (shown in red). An alternate cleavage by α-secretase (not shown) cuts within the Aβ domain and thus precludes Aβ production. Potential opportunities for therapeutic intervention are shown in the blue boxes.

disease, and (c) develops prior to symptomatic manifestations of Alzheimer's disease. For these reasons, there has been great interest in developing therapies and diagnostic tools aimed at Aβ. Of the 66 drugs that are known currently to be in clinical trials for Alzheimer's disease, more than 40% target amyloid plaques or Aβ production.

Potential Therapeutic Interventions Suggested by Current Understanding of Aβ Amyloidosis

β-secretase inhibitors. The proteases that cleave APP to generate Aβ (Figure 2) provide some of the most alluring targets for drug development (47). The β-secretase protein referred to as beta-site APP-cleaving enzyme (BACE) may be a particularly good drug target because (a) knock-out of BACE in mice eliminates Aβ production without side effects

(48), (b) BACE belongs to a well-studied class of proteases (aspartic proteases) for which inhibitors have been developed successfully for human use (i.e., renin and HIV protease inhibitors) (49), (c) the X-ray crystal structure of BACE has been published (50), and (d) peptidomimetic inhibitors of BACE with nanomolar activity have been generated (51). However, the development of small-molecule BACE inhibitors is complicated by the fact that the active-site cleft of the enzyme is larger and more open than other aspartic proteases (50).

γ-secretase inhibitors. The APP γ-secretase has been an active target for drug development, with multiple classes of potent inhibitors described (52–54). At the 2004 International Conference on Alzheimer's Disease and Related Disorders, investigators

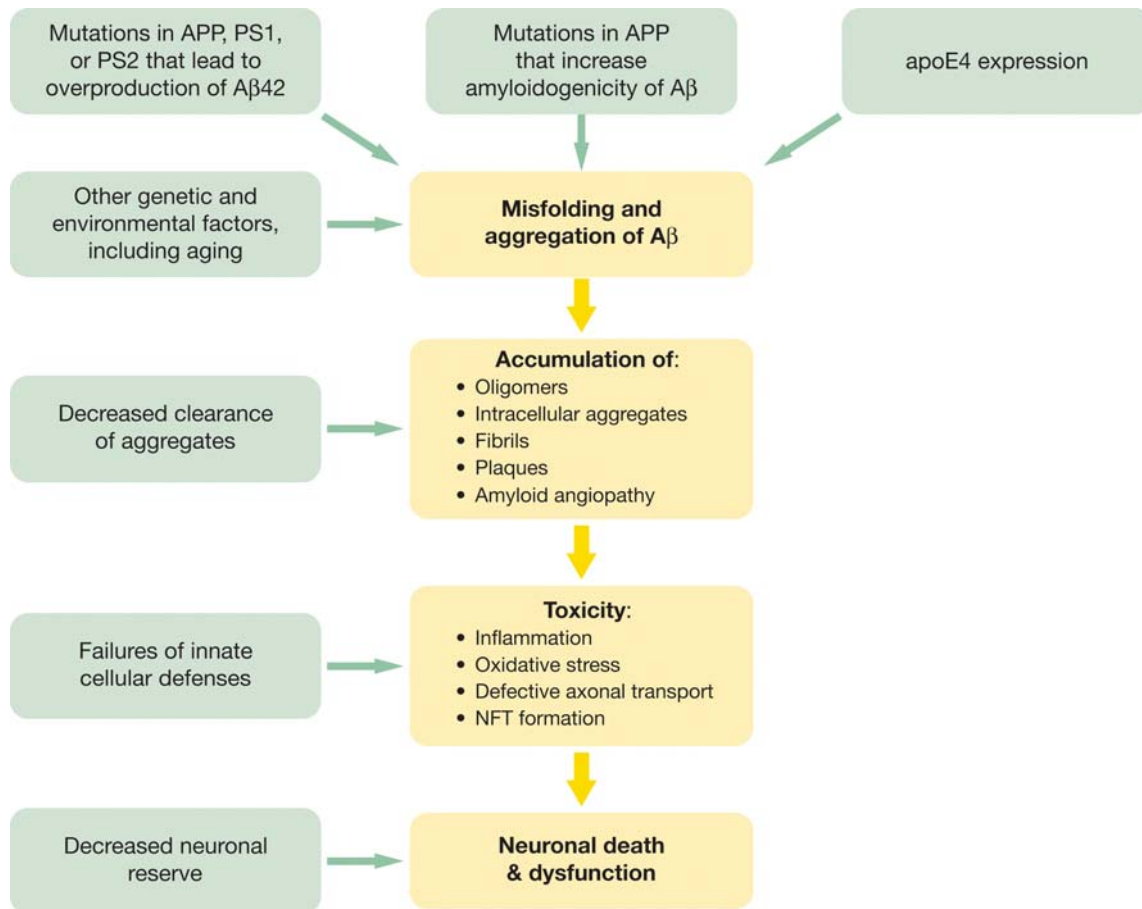


Figure 3

Amyloid cascade hypothesis. Increased aggregation of A β can occur as a result of (a) overproduction of A β 42 [as in the case of most amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) gene mutations], (b) expression of mutations in the A β domain of APP that increases its propensity for aggregation, (c) Apolipoprotein E4 (apoE4) expression, and (d) other genetic and environmental factors, including aging. Aggregated A β accumulates in various forms and locations, some or all of which may result in cellular toxicities mediated by a variety of mechanisms. Decreased clearance of aggregates and failures of cellular defenses to toxicity may exacerbate this process. The toxic effects of amyloid result eventually in neuronal death and dysfunction, manifesting as dementia. Patients with decreased neuronal reserve (perhaps as a result of existing comorbidities) may show increased sensitivity to neuronal loss. NFT, neurofibrillary tangles.

from Eli Lilly reported Phase I data with a γ -secretase inhibitor (LY450139), which reduced blood levels of A β , but did not alter levels of A β in cerebral spinal fluid (CSF). However, enthusiasm for the use of γ -secretase inhibitors is tempered by concerns regarding toxicity caused by interference with γ -secretase-mediated Notch

signaling (55) or inhibition of signaling by other γ -secretase-cleaved substrates (56). Alternatively, indirect inhibition of γ -secretase may be one way to avoid this issue. For example, inhibitors of glycogen synthase kinase 3 (GSK3), such as lithium and kenpaullones as well as small interfering RNAs directed against GSK3 α , reduce A β

production in cells and transgenic mice by inhibiting γ -secretase cleavage, without altering Notch cleavage (57).

A β vaccination. A β vaccination has proven to be one of the most exciting and novel strategies for removing amyloid plaques from the brain (reviewed in Reference 58). Immunization of transgenic mice with A β peptides (active immunization) or with monoclonal antibodies directed against A β (passive immunization) results in dramatic clearance of plaques (59, 60). Immunization also results in improved cognitive performance in several different transgenic mouse models of Alzheimer's disease (61, 62). Various mechanisms for immunization have been hypothesized, including antibody-mediated microglial clearance of plaques, clearance of brain A β oligomers, and peripheral clearance of soluble A β . A combination of mechanisms may be required for maximal effect of immunization. Human studies of active A β immunization were halted because of cases of meningoencephalitis in treated patients (63, 64). However, active and passive immunization strategies that decrease the risk of this serious side effect are currently under preclinical and clinical development (58). Provocatively, preliminary analysis of the Phase II data from the first vaccination study suggested that patients who generated antiplaque antibodies showed a slower rate of cognitive decline (65).

NSAIDs. Several nonsteroidal anti-inflammatory drugs (NSAIDs) selectively lower A β 42 through a mechanism independent of cyclooxygenase but likely involves the modulation of γ -secretase (66, 67). Indeed, preclinical studies on R-flurbiprofen, the pure R enantiomer of the NSAID flurbiprofen, show that it does not inhibit cyclooxygenase enzymes, but it does reduce A β 42 levels in vitro and in vivo, and it also reduces A β amyloid pathology in the brain (68). Not surprisingly, this compound recently entered Phase III trials for Alzheimer's disease (Myriad genetics). The approach using NSAIDs and re-

lated compounds for treatment of Alzheimer's disease is bolstered by epidemiological evidence linking NSAID use to decreased risk of the disease (69).

Statins. Epidemiological studies suggest that high levels of cholesterol may contribute to the pathogenesis of Alzheimer's disease (70; reviewed in Reference 71). Retrospective studies indicate that the cholesterol-lowering drugs or statins can protect against Alzheimer's disease, in some cases reducing the relative risk of Alzheimer's by more than 70% (72, 73). These data prompted prospective studies of statins in Alzheimer's disease. Preliminary data from one such study has shown a reduction of A β 40 in the CSF and slight improvement in cognitive function (74) with simvastatin treatment. However, results from a larger-scale trial of a different design (named Prospective Study of Pravastatin in the Elderly at Risk, PROSPER) have not shown similar improvements (75). The mechanisms by which statins affect brain A β deposition remains an area of active investigation (71). Nonetheless, there is growing evidence that high cholesterol levels increase A β generation and plaque deposition (76, 77), and these effects appear to be offset or reversed by statins (78–80).

Clioquinol. The metal-protein-attenuating compound (MPAC) clioquinol (iodochlorhydroxyquin) dissociates amyloid plaques in postmortem human brain samples by a mechanism that may involve chelating Cu²⁺ and Zn²⁺ (81). Strikingly, clioquinol decreases brain A β deposition in a transgenic mouse model of Alzheimer's disease (82), and preliminary data from a Phase II study of clioquinol in Alzheimer's patients has shown decreased plasma A β 42 levels as well as slowed cognitive deterioration in clioquinol-treated patients (83).

Glycosaminoglycans mimetics. Another strategy to prevent the formation of A β fibrils in Alzheimer's disease capitalized on

the role of glycosaminoglycans (GAGs) in amyloid formation (reviewed in Reference 84). Small-molecule GAG mimetics compete with binding of GAGs to amyloid fibrils and thus prevent fibril formation. Encouragingly, the biotechnology company Neurochem reports that one such GAG mimetic is currently in Phase III clinical trials for Alzheimer's disease (reviewed in Reference 85).

TAU: A PROTOYPICAL INTRACELLULAR AMYLOID

Tauopathies

Tau pathology is not only a prominent feature of Alzheimer's disease, but it is also seen in a variety of other related neurodegenerative diseases. Indeed, Pick's disease, corticobasal degeneration (CBD), PSP, and frontal temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) are all defined by specific regional and cellular distributions of abnormally aggregated tau filaments. There is now unequivocal evidence demonstrating that abnormalities in tau are sufficient to cause neurodegenerative disease. These abnormalities include (a) the presence of causative mutations in the gene for tau in patients with FTDP-17 (86, 87), (b) the linkage of specific tau haplotypes to PSP and CBD (88), (c) the absence of other disease-specific neuropathological abnormalities in many tauopathies, and (d) the generation of tau transgenic mice that recapitulate the key phenotypic hallmarks of authentic human neurodegenerative tauopathies (89).

Although tau dysfunction alone is sufficient to induce neurodegeneration in the absence of other brain amyloids, the frequency with which tau pathology occurs in a wide variety of other neurodegenerative diseases has led to the hypothesis that tau plays a role in a final, common pathway leading to neuronal death or dysfunction, which can be activated by other initiating events. In transgenic mice expressing tau, coexpression of APP or α -synuclein results in the acceleration of tau

pathology, which suggests that neurodegeneration mediated by tau pathology may also be activated downstream of disease pathways resulting from accumulations of both A β and α -synuclein amyloidogenesis. This fits well with observations from human disease that patients with APP mutations show abundant A β and tau pathology, but patients with tau mutations show primarily tau pathology alone.

Mechanisms of Tau-Induced Pathogenesis

Tau is a microtubule-associated protein that binds to and stabilizes microtubules. There are now more than 30 distinct mutations or pathogenic nucleotide substitutions in the gene for tau that have been shown to cause FTDP-17 in more than 50 different kindreds (reviewed in Reference 90), representative examples of which are shown in **Figure 4**. These mutations may lead to neurodegenerative disease by one or more distinct mechanisms: (a) alterations in tau splicing, leading to abnormal patterns of tau-isoform expression (91), (b) compromise of tau's ability to bind to and stabilize microtubules (92, 93), and (c) enhanced fibrillization of tau (94). Thus, as illustrated in **Figure 5**, tau mutations, and by analogy tau dysfunction in sporadic disease, may be pathogenic through mechanisms involving both loss of function (decreased microtubule stabilization) and toxic gain of function (increased fibril formation). Reflecting this fundamental dichotomy, therapies targeted at both mechanisms are currently in development.

Potential Therapeutic Interventions Suggested by Current Understanding of Tau Amyloidosis

Microtubule-stabilizing drugs. Because tauopathies may be caused in part by the failure of tau to appropriately stabilize microtubules, microtubule-stabilizing drugs may be therapeutically beneficial for these diseases (95). Transgenic mice that overexpress tau

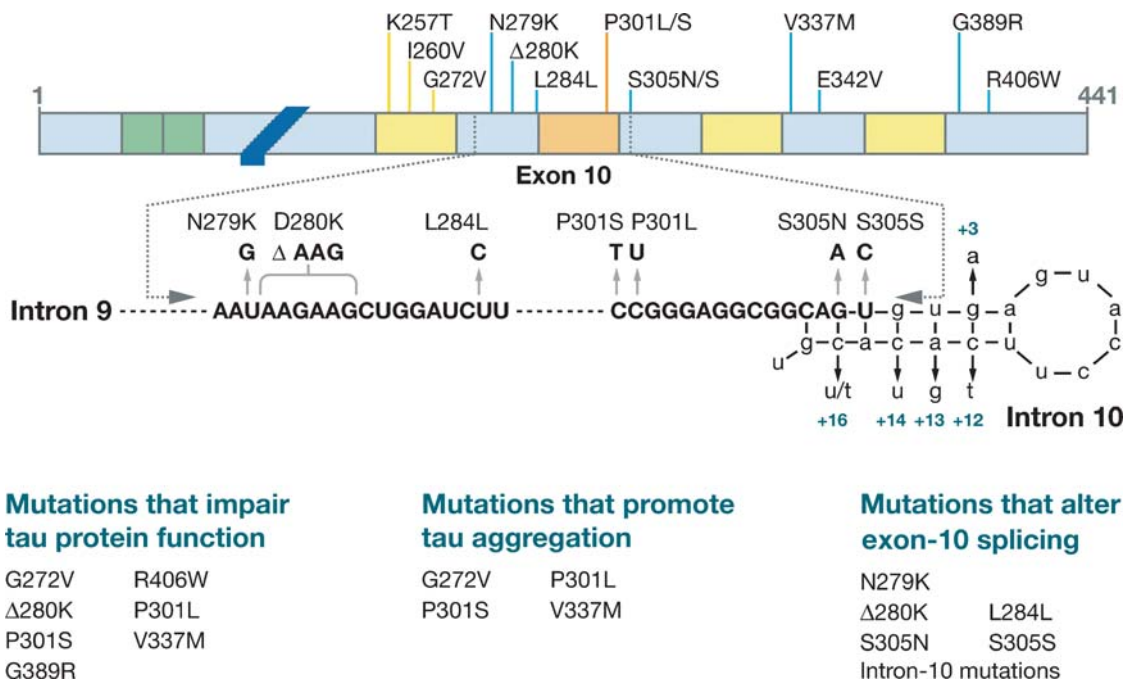


Figure 4

Tau mutations cause frontal temporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) by different mechanisms. Tau mutations may lead to neurodegenerative disease by impairing tau's ability to bind to and stabilize microtubules, promoting tau aggregation, and altering exon-10 splicing.

accumulate filamentous tau inclusions and show reductions in microtubules and impaired fast axonal transport, in addition to neurodegeneration and motor weakness (96). When these mice are treated with the microtubule-stabilizing drug paclitaxel they show improvements in microtubule numbers and fast axonal transport, accompanied by improved motor abilities, thus providing in vivo evidence that microtubule-stabilizing drugs may have a therapeutic benefit for human tauopathies (97).

Inhibitors of tau filament and tau phosphorylation. There has been a growing emphasis on designing inhibitors of tau filament formation in an attempt to generate drugs that ameliorate tau pathology in neurodegenerative diseases. Rational-design approaches and screening of small-molecule libraries have revealed a number of differ-

ent classes of inhibitors (98–101), although in vivo data are not yet available. Similarly, inhibition of tau phosphorylation has presented a tempting target for drug design, with most efforts focused on inhibiting GSK3β (reviewed in Reference 102). However difficulties generating inhibitors with appropriate specificity for GSK3β as well as issues with target-mediated toxicity complicate this approach.

α-SYNUCLEIN: THE INTRACELLULAR AMYLOID OF PARKINSON'S DISEASE

Parkinson's Disease and Other α-Synucleinopathies

Although the molecular identities of the amyloidogenic proteins that define Alzheimer's disease and tauopathies were discovered by biochemical methods, the molecular identity

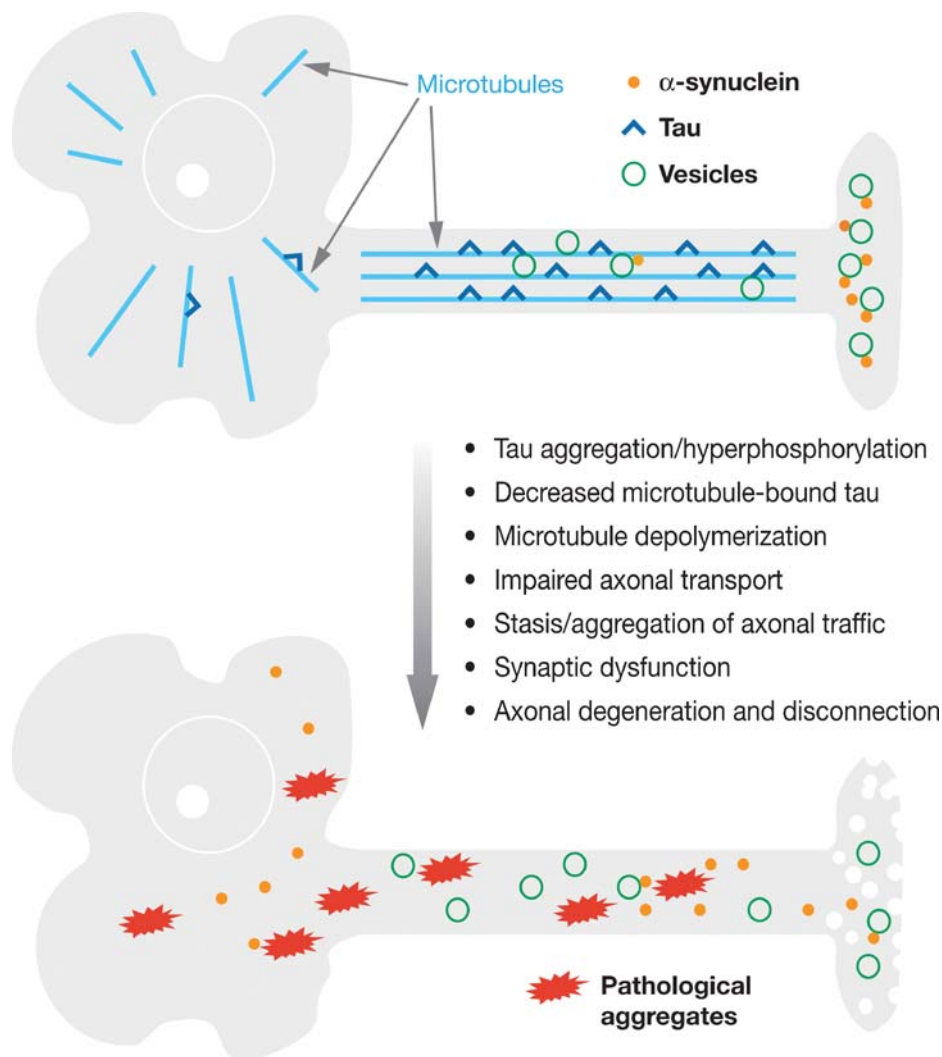


Figure 5

Deleterious effects of tau amyloidosis. Tau hyperphosphorylation and aggregation may lead to neuronal dysfunction through a variety of mechanisms, including microtubule depolymerization. This in turn may lead to impaired axonal transport, causing synaptic dysfunction and eventually axonal degeneration.

of the amyloidogenic protein in Parkinson's disease was first suggested by genetic studies. The discovery that familial forms of Parkinson's disease may be caused by mutations in the gene for α -synuclein (103) provided the rationale for studies demonstrating that the Lewy bodies that define Parkinson's disease are composed of filamentous aggregates of α -synuclein (104). Similar studies have demonstrated extensive α -synuclein pathology in dementia with Lewy bodies, multiple system atrophy, and other seemingly distinct disorders that, because they are char-

acterized by inclusions formed by the same protein, are now classified together as α -synucleinopathies (105–107).

Mechanisms of α -Synuclein-Induced Pathogenesis

Because mutations or duplications in the gene for α -synuclein lead to genetic forms of autosomal-dominantly inherited Parkinson's disease and dementia with Lewy bodies (103, 108), it has been hypothesized that increased expression, aggregation, and accumulation of

α -synuclein in the brain plays a key role in the pathogenesis of neurodegeneration (reviewed in Reference 109). Further support for the role of α -synuclein in disease has come from transgenic mice engineered to overexpress mutant forms of α -synuclein, which show both α -synuclein pathology and neurodegeneration (110–112). Importantly, in human disease, deposition of brain α -synuclein may precede disease symptoms by more than a decade, providing a window for therapeutic intervention (113, 114).

Environmental factors may also play a crucial role in the pathogenesis of synucleinopathies, and epidemiological studies suggest an association between Parkinson's disease and environmental toxins such as pesticides (115). Chronic systemic treatment of rats with rotenone, a pesticide known to inhibit mitochondria, causes selective nigrostriatal dopaminergic degeneration with associated inclusions containing fibrillar α -synuclein (116). Rotenone treatment may induce an increase in oxidative stress in the dopaminergic neurons, which in turn may facilitate fibrillization of α -synuclein, providing a link between oxidative stress and pathogenesis of synucleinopathies (117–119).

Potential Therapeutic Interventions Suggested by Current Understanding of α -Synuclein Amyloidosis

Inhibition of aggregation. Inhibition of α -synuclein aggregation is an attractive target for drug development, and several groups have identified small-molecule and peptide-based inhibitors of aggregation (120–124). A number of catecholamines, including dopamine, have been found to inhibit synuclein fibril formation (124). The inhibitory activity of dopamine depends on its oxidation and leads to accumulation of α -synuclein protofibrils (124). The link between dopamine and α -synuclein may provide insights into the potential mechanisms underlying the selective vulnerabil-

ity of dopaminergic neurons in Parkinson's disease, although many other types of neurons as well as glial cells are selectively affected by accumulations of α -synuclein inclusions.

Induction of chaperones. A complementary approach to inhibiting α -synuclein-induced toxicity has been suggested by *Drosophila* studies, which show that expression of the molecular chaperone Hsp70 prevents the dopaminergic neuron loss associated with α -synuclein expression and that interference with endogenous chaperone activity accelerates α -synuclein toxicity (125). Treatment of *Drosophila* flies with the drug geldanamycin protects neurons against α -synuclein toxicity, likely through enhanced chaperone activation (125–127).

SUMMARY

Neurodegenerative diseases have long been defined by the properties of the neuropathological lesions observed in the brain. We now know that these lesions are not just markers for neurodegenerative diseases, but are tied intrinsically to their pathogenesis. Moreover, the striking similarities between many neurodegenerative diseases suggest common mechanisms in the etiology of these disorders. The repeated theme of protein misfolding leading to amyloid formation and neurotoxicity is reinforced by a striking message from genetic studies: In each case of dominantly inherited neurodegeneration, the disease-causing mutations can be linked directly to amyloid formation. These clues have now come into sharp focus and neurodegenerative properties are better understood, and they have provided a strong rationale for the *in vitro* experiments, mouse models, and epidemiological studies that have gone a long way towards verifying this hypothesis. These experiments have laid a solid groundwork for a number of potential therapeutics that are now in preclinical and clinical development. Over the next five years the efficacy of a large

number of these drugs will be tested, and there is a growing optimism that the results of these trials will confirm current notions of the etiology of neurodegenerative diseases.

SUMMARY POINTS

1. Most neurodegenerative diseases are characterized by pathological lesions composed of accumulations of amyloid.
2. Mutations that cause familial forms of these diseases are linked to accumulation of the amyloid, and mouse models that recapitulate features of these diseases can be generated by engineering amyloid accumulation in the brain.
3. In different diseases the amyloid is composed of different protein constituents, but in each case there are likely to be quite similar pathways of misfolding, oligomerization, and fibril formation.
4. Each step in these pathways may provide targets for therapeutic drug development.

FUTURE DIRECTIONS/UNRESOLVED ISSUES

1. What causes amyloid deposition in sporadic (nonfamilial) cases of neurodegenerative disease?
2. Why does amyloid take decades to accumulate and become symptomatic?
3. Which intermediates along the pathway from misfolded protein to amyloid fibrils are the toxic species?
4. What are the mechanisms underlying the toxicity of these species?
5. What accounts for the striking selective vulnerability of different brain regions to amyloid and its effects?
6. Why is the brain so prone to amyloidosis?

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