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Prion-like Mechanisms in Alzheimer Disease

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Abstract

Senile plaques and neurofibrillary tangles are the principal histopathologic hallmarks of Alzheimer disease. The essential constituents of these lesions are structurally abnormal variants of normally generated proteins: Aβ protein in plaques and tau protein in tangles. At the molecular level, both proteins in a pathogenic state share key properties with classic prions, i.e., they consist of alternatively folded, β-sheet-rich forms of the proteins that autopropagate by the seeded corruption and self-assembly of like proteins. Other similarities with prions include the ability to manifest as polymorphic and polyfunctional strains, resistance to chemical and enzymatic destruction, and the ability to spread within the brain and from the periphery to the brain. In AD, current evidence indicates that the pathogenic cascade follows from the endogenous, sequential corruption of Aβ and then tau. Therapeutic options include reducing the production or multimerization of the proteins, uncoupling the Aβ-tauopathy connection, or promoting the inactivation or removal of anomalous assemblies from the brain. Although aberrant Aβ appears to be the prime mover of AD pathogenesis, once set in motion by Aβ, the prion-like propagation of tauopathy may proceed independently of Aβ; if so, Aβ might be solely targeted as an early preventive measure, but optimal treatment of Alzheimer disease at later stages of the cascade will require intervention in both pathways.

Keywords

Abeta; Alzheimer; amyloid; aging; dementia; neurodegeneration; prion; proteopathy; seeding; tau

Alzheimer disease

Epidemiology, signs and symptoms.

One of the most feared hazards of growing old is the profound deterioration of mental faculties known as dementia. More than 50 different conditions are associated with dementia (Vonsattel and Hedley-White, 2001), but of these, Alzheimer disease (AD) is the most common, with a world-wide prevalence in 2010 of approximately 35 million people (Dartigues, 2009; Holtzman et al., 2011; Reitz et al., 2011). The incidence and prevalence of AD double every 5 years between the ages of 65 and 95 (Kawas and Katzman, 1999). As the average life expectancy of populations grows in many parts of the world, and in the absence

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of an effective preventive or treatment, as many as 115 million people are expected to have AD in the year 2050 (Dartigues, 2009). The social and economic costs of the disease will rise accordingly (Wimo et al., 2013), with an ever greater burden of caring for afflicted persons falling on younger generations. Disease-modifying treatments are urgently needed, but these can only emerge from a deep understanding of Alzheimer disease itself. A defining pathologic feature of AD is the abnormal accumulation in the brain of two proteins - Aβ and tau; recent evidence shows that this process is initiated and sustained by a prion-like mechanism of seeded protein aggregation.

AD typically begins with the gradual onset of mild cognitive impairment, progressing inexorably to dementia with an average clinical duration of 7–10 years (Holtzman et al., 2011) (although the timecourse is variable [see Chapter 24]). The signs and symptoms shown by individual patients also can vary substantially, but the diagnosis of AD is established by the universal presence of core attributes, specifically progressive dementia in the context of characteristic lesions in the brain: senile (Aβ) plaques and neurofibrillary (tau) tangles.

Dementia can be defined as “a decline from a person’s previously established level of intellectual function that is sufficient to interfere with the everyday performance of that individual” (Holtzman et al., 2011). Based on the criteria set forth in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) dementia *due to AD* is defined as “the insidious onset and gradual progression of substantial impairment in learning and memory and at least one other cognitive domain (complex attention, executive function, language, perceptual-motor, or social cognition) that interferes with independence in everyday activities” (Walker and Jucker, 2017). An important feature of these definitions is that the impairments are substantial, and thus become incapacitating even under ordinary circumstances.

Differential diagnosis and biomarkers.

Until recently, senile plaques and neurofibrillary tangles could only be identified by microscopic analysis of brain samples, but increasingly sensitive and specific diagnostic tests are emerging that enable the detection of proteopathic abnormalities in living subjects. These include radiolabeled imaging agents for Aβ and tau in the brain, and assays for quantitation of the proteins in CSF (Lewczuk et al., 2015; Olsson et al., 2016; Villemagne et al., 2017). Investigations of these biomarkers indicate that the disease process begins two decades or more before the onset of demonstrable cognitive impairment (Jack et al., 2010; Jack and Holtzman, 2013). In addition, the presence of genetic risk factors such as the ε4 allele of apolipoprotein E (*APOEε4*) can reinforce the in-life diagnosis of AD.

It is important to place AD in the context of other brain changes that impair intellectual capacities in the elderly. In younger patients with autosomal dominant causes of AD (below), the disease is relatively unambiguous histopathologically, i.e., lesions other than plaques and tangles are rare. With advancing age, additional disorders are increasingly likely to contribute to dementia, including cerebrovascular disease, hippocampal sclerosis, and such cerebral proteopathies as α-synucleinopathy, TDP-43 proteopathy, and others (Vonsattel and Hedley-White, 2001; Nelson et al., 2012). These maladies can cause

dementia on their own, but they also sometimes co-exist with AD, complicating diagnosis, exacerbating the clinical course, and likely diminishing the effectiveness of treatments directed at only one of the conditions. In addition, potentially reversible causes of a dementia-like state must be ruled out, such as depression, infections, drugs and drug interactions, thyroid dysfunction, tumors, and vitamin B12 deficiency, as intervention in these instances might at least partially restore cognitive function (Tripathi and Vibha, 2009; Holtzman et al., 2011).

Genetics.

The probability of developing AD is influenced by certain genetic risk factors, which include rare causative, autosomal dominant mutations with essentially complete penetrance, as well as diverse genetic polymorphisms that modulate risk to varying degrees (Tanzi, 2012; Wingo et al., 2012). Autosomal dominant mutations associated with AD all occur in the genes that code for the Aβ-precursor protein (APP) or for presenilin-1 or presenilin-2 (the presenilins being key components of intramembranous protease complexes that liberate Aβ from APP (Hardy, 2006; Holtzman et al., 2011)). The gene encoding APP is on chromosome 21, and the genes encoding presenilin-1 and presenilin-2 are on chromosomes 14 and 1, respectively.

AD-linked mutations in the presenilins and in the APP regions flanking Aβ alter the processing of APP, but mutations within the Aβ segment of APP often modify its potential to aggregate and its tissue-specificity (Holtzman et al., 2011; Haass et al., 2012). An unusual variant in the APP gene that results in an alanine to threonine substitution at position 2 of Aβ reduces the production (Jonsson et al., 2012) and aggregation proclivity (Benilova et al., 2014) of Aβ, thereby lowering the risk of AD (Jonsson et al., 2012). In contrast, an alanine to valine replacement at this position *increases* the production and aggregability of Aβ, causing an autosomal recessive type of AD (Di Fede et al., 2009) with unusual neuropathologic features (Giaccone et al., 2010). Furthermore, because most patients with Down syndrome (trisomy 21) have an extra copy of the APP gene on chromosome 21, they are at greatly increased risk of developing AD as they age (Head et al., 2016). Together, these genetic data consistently implicate Aβ in the ontogeny of heredofamilial forms of AD.

Dominant and recessive genetic causes account for less than 1% of all AD cases (Holtzman et al., 2011). How, then, are genetics linked to idiopathic AD? A study of twins in Sweden indicated that the heritability for AD is as high as 79% (Gatz et al., 2006), although most of the implicated polymorphisms individually have only a slight influence on risk (Humphries and Kohli, 2014). An exception is the gene that encodes apolipoprotein E (ApoE) (Yu et al., 2014), a protein that mediates lipid transport throughout the body and is the major apolipoprotein in the brain (Chouraki and Seshadri, 2014). The three major protein isoforms of ApoE in human populations are ApoE2, ApoE3 and ApoE4. The most frequent isoform is ApoE3 (~78%), followed by ApoE4 (~14%) and ApoE2 (~8%) (Liu et al., 2013). Bearers of the *APOEε4* allele have an allele-dose-dependent increase in the risk of AD, with heterozygotes having a 2- to 5-fold increase in risk, and homozygotes a 12- to 15-fold increase (Chouraki and Seshadri, 2014). The mechanism by which *APOEε4* predisposes carriers to AD is probably multifaceted (Potter and Wisniewski, 2012; Yu et al., 2014;

Huang et al., 2017), but it is known that bearers of *APOEε4* begin to accumulate Aβ in the brain at least a decade earlier in life than do non-bearers (Warzok et al., 1998; Walker et al., 2000; Resnick et al., 2015). Thus, *APOEε4*, like the known dominant and recessive genetic risk factors (above), appears to augment the probability of developing AD by advancing the onset of the Aβ cascade. Indeed, all known AD-linked mutations affect the production, removal, trafficking, or tendency to aggregate of Aβ (Hardy and Selkoe, 2002).

Other risk factors.

In addition to the genetic risk factors for AD, numerous environmental and endogenous risk factors have been identified. These include advancing age, traumatic brain injury, diabetes and metabolic disorders, inflammation, vascular disorders, gender, and lifestyle (Holtzman et al., 2011; Killin et al., 2016; Lafortune et al., 2016; Pike, 2017). In some instances these should be considered as risk factors for *dementia*, broadly defined, rather than for AD *per se*. For example, multiple small infarcts might raise the likelihood of dementia independently of AD, or they may advance the onset of dementia in people who also are incubating AD pathology in the brain.

The neuropathology of AD in the context of the prion paradigm

Amyloid.

As in the case of most proteopathies (including the prionoses), the proteins that are implicated in the development of AD are structurally abnormal manifestations of proteins that are normally generated by cells. The abnormalities often involve an altered 3-dimensional architecture (misfolding), which can be promoted by amino acid substitutions, post-translational modifications, sequence expansions or truncations, and such characteristics of the local milieu as temperature and pH (Eisenberg and Jucker, 2012). In addition, factors that increase the concentration of certain proteins (e.g., by raising their production or impairing their removal/degradation) can elevate the risk of disease (Jucker and Walker, 2013).

A frequent indication that a protein is structurally corrupted at the molecular level is its enhanced tendency to form amyloid. In general, amyloid is a state in which a protein accumulates in tissues as masses of ~10nm-diameter fibrils with a characteristic cross-β X-ray diffraction pattern and cross-polarization-induced birefringence after staining with the dye Congo red (Sipe et al., 2016), indicative of increased β-sheet molecular structure (Eisenberg and Jucker, 2012). In some biological circumstances the amyloid state is functionally advantageous, particularly in prokaryotes (Fowler et al., 2007; Greenwald and Riek, 2010) (amyloid-like fibrils consisting of stacked, cross-α helices have been identified in the bacterium *Staphylococcus aureus*(Tayeb-Fligelman et al., 2017), but α-helix-based amyloid has not been described in eukaryotes). In mammals, amyloid is often pathogenic; more than 30 different amyloidoses have been reported (Sipe et al., 2016), many of which occur outside the central nervous system (Westermark et al., 2017).

Within the brain, it is not uncommon to find some degree of Aβ-amyloidosis and tauopathy in the elderly; in those with dementia, abundant Aβ plaques and tau tangles are the two types

of amyloid that are pathognomonic for AD (Holtzman et al., 2011; Nelson et al., 2012) (Figure 1). The formation of amyloid by Aβ and tau is an obvious sign of a proteopathic process, but small oligomeric assemblies may actually be the more toxic form of the proteins (Lambert et al., 1998; Haass and Selkoe, 2007; Gerson and Kayed, 2016; Yang et al., 2017). Aβ in the amyloid state is virtually always present in AD, but an instructive exception is a rare hereditary type of AD caused by a mutation that changes glutamate to glycine at position 22 of Aβ (E22G; the 'arctic' mutation). This mutation results in early-onset AD in which Aβ plaques lack the prototypical amyloid cores (Kalimo et al., 2013), indicating that 'amyloid' in the strict sense is not required to drive the Aβ-cascade. Similarly, even though misfolded prion protein (PrP) has an enhanced ability to form amyloid, PrP-amyloid *per se* is not obligatory for the expression of prion disease (DeArmond and Prusiner, 1995).

This point bears emphasis because of the unproductive controversy (Drachman, 2014) that still bedevils the "amyloid cascade hypothesis" (aka the "amyloid hypothesis") of AD (Hardy and Selkoe, 2002; Selkoe and Hardy, 2016). The 'amyloid' in the original formulation of this concept refers to β-amyloid (i.e., Aβ in a β-sheet-rich, polymerized state). There can be little doubt that Aβ is a driving force in the genesis of AD (Jack et al., 2010; Selkoe, 2011; Bateman et al., 2012; Walker and Jucker, 2015), or that β-amyloid accumulation *per se* is detrimental to cognition, particularly when embodied as neuritic plaques (Nelson et al., 2012). However, tauopathy is an essential downstream consequence that correlates more strongly with the degree of dementia than does the number of Aβ plaques (Wilcock and Esiri, 1982; Crystal et al., 1988; Bierer et al., 1995). This apparent inconsistency mainly reflects the importance of tauopathy for the clinical expression of the disease, but it does not invalidate the instigating role of multimeric Aβ in AD. A review of published work by the Alzheimer's Disease Neuroimaging Initiative (ADNI) concluded that "CSF biomarkers are consistent with disease trajectories predicted by β-amyloid cascade … and tau-mediated neurodegeneration hypotheses for AD" (Weiner et al., 2013). Because tau and Aβ both self-aggregate by the templated corruption of like proteins by misfolded seeds, once tauopathy is set in motion, it is possible that the two proteopathies progress along separate paths, both temporally and spatially.

The tau protein normally is involved in the stabilization of cellular microtubules (Spillantini and Goedert, 2013). In AD and other tauopathies, tau misfolds and becomes hyperphosphorylated; like Aβ, the altered tau molecules aggregate to form soluble oligomers and long, β-sheet-rich polymers that have the characteristics that define amyloid. The tau fibrils bundle together as neurofibrillary tangles in neurons (Figure 1), although tauopathy also can afflict glial cells (Kovacs, 2015).

Tauopathy occurs in association with many brain disorders besides AD (Nelson et al., 2012). The primary tauopathies are disorders in which tau aggregation is the major abnormality (Spillantini and Goedert, 2013; Crary et al., 2014; Kovacs, 2015); in many conditions however, tauopathy is secondary to various types of injury or stress to the brain (Nelson et al., 2012). In human prion diseases, tauopathy is variable in appearance and degree (DeArmond et al., 2004; Kovacs et al., 2016b), and in instances where it is relatively prominent (such as Gerstmann-Sträussler-Scheinker disease and variant Creutzfeldt-Jakob

disease [vCJD]) the cytology and anatomic distribution often differ from those seen in AD (Giaccone et al., 2008; Kovacs et al., 2016b).

The extended neuropathology of AD.

In addition to the canonical lesions that define AD – Aβ plaques and tau tangles – other changes are present in the brain that complicate the disease phenotype. One is the accumulation of Aβ in and around the walls of cerebral blood vessels, a condition known as Aβ-type cerebral amyloid angiopathy (Aβ-CAA). Aβ-CAA weakens the vascular wall and elevates the risk of intracranial hemorrhage (Biffi and Greenberg, 2011). Like Aβ plaques and tauopathy, Aβ-CAA is not specific to AD, and its prevalence increases with advancing age (Revesz et al., 2003; Biffi and Greenberg, 2011). However, some degree of Aβ-CAA is almost always present in AD (Attems and Jellinger, 2014; Vinters, 2015; Kapasi and Schneider, 2016), and it is severe in around 25% of cases (Charidimou et al., 2012). The factors that drive the inconsistent occurrence of Aβ-CAA in different people remain uncertain.

Other alterations are found to variable extents among end-stage AD cases, and most of these anomalies lack diagnostic specificity for the disease. Macroscopically, loss of brain tissue and concomitant expansion of the ventricles are common, but this varies among regions and among patients (Hauw and Duyckaerts, 2001). Evidence of inflammation includes reactive microglia and astrocytes, especially in association with Aβ plaques, as well as increased inflammatory mediators such as cytokines (Duyckaerts et al., 2009). Granulovacuolar degeneration, perisomatic granules and Hirano bodies may be present (Duyckaerts et al., 2009), but their significance for AD *per se* is uncertain. Many different neuronal systems are compromised in AD (Mann and Yates, 1986; Hauw and Duyckaerts, 2001), some more markedly than others, and synapses are regionally depleted (Terry et al., 1999; Duyckaerts et al., 2009). In some cases of AD, spongiform change is evident that, though generally less severe, can resemble that seen in CJD (Smith et al., 1987; Sherzai et al., 2013) (Figure 2). As noted above, other neurodegenerative conditions might be present in the brain along with the lesions of AD, particularly in older patients.

Regardless of the complexity of damage to the brain, the essential and unifying feature of AD is the obligatory presence of aggregated Aβ and tau proteins. For this reason, extensive research has been directed toward determining how the proteins misfold, self-assemble, and propagate their pathogenic features, a process that shares important commonalities with the molecular pathogenesis of prion diseases (Walker and LeVine, 2000; Walker et al., 2006; Jucker and Walker, 2013; Prusiner, 2013; Goedert, 2015; Walker and Jucker, 2015; Walker et al., 2016).

The prion-like properties of aggregated Aβ

The idea that Alzheimer disease might arise by a pathogenic mechanism similar to that of prion diseases has a fairly long history (Farquhar and Gajdusek, 1981; Prusiner, 1984). Based on their success in transmitting kuru and Creutzfeldt-Jakob disease to nonhuman primates (Gajdusek et al., 1966; Gajdusek et al., 1968; Gibbs et al., 1968), and on the hypothesis that a ‘slow virus’ might be involved in other neurodegenerative disorders

(Gajdusek, 1977), D. Carleton Gajdusek's group attempted to experimentally transmit AD to several species of nonhuman primates via intracerebral injection of AD brain homogenates. They tentatively reported that the attempt was unsuccessful (Goudsmit et al., 1980). In Great Britain, Ridley and Baker undertook similar transmission experiments in marmosets (*Callithrix jacchus*). After an incubation period of more than 5 years, they detected a significant increase in the senile plaque load of the host animals (Baker et al., 1994). The causative agent, however, remained uncertain.

When transgenic mouse models expressing human-type APP became available, experiments were initiated to explicitly test the hypothesis that Aβ can be induced to aggregate in the living brain by a prion-like mechanism (Kane et al., 2000). These studies showed that Aβ plaques and CAA are seedable by brain extracts from AD patients, but not by extracts derived from control brains that were devoid of aggregated Aβ (Kane et al., 2000; Walker et al., 2002; Meyer-Luehmann et al., 2006) (Figure 3). AD brain extracts infused into the brains of wild-type mice (which express an aggregation-resistant sequence of Aβ) did not yield Aβ deposits.

Subsequent experiments showed unequivocally that the active agent is aggregated Aβ, and that the ability of Aβ to seed as well as the characteristics of the resulting deposits are governed by both the agent and the host (Meyer-Luehmann et al., 2006). These findings have been confirmed and extended by other laboratories (Watts et al., 2011; Morales et al., 2012; Stohr et al., 2012; Duran-Aniotz et al., 2013; Stohr et al., 2014; Duran-Aniotz et al., 2014; Watts et al., 2014; Morales et al., 2015a; Burwinkel et al., 2018), and the collective experiments have established that the molecular features of Aβ seeds are essentially the same as those that define the pathogenicity of prions (Jucker and Walker, 2013; Morales et al., 2015b; Walker and Jucker, 2015; Walker et al., 2016). Key commonalities between Aβ seeds and PrP-prions are summarized as follows:

1. *The active seeding agent is a form of the protein itself*. In addition to brain extracts from AD patients, extracts from APP-transgenic mice (Meyer-Luehmann et al., 2006) and aged monkeys (Rosen et al., 2016) can seed Aβ deposition as long as aggregated Aβ is present in the donor brain. The degree of Aβ-seeding is directly related to the concentration of Aβ in the brain extract (Meyer-Luehmann et al., 2006; Fritschi et al., 2014b), and even extremely small amounts of Aβ seeds are capable of stimulating aggregation in the brain (Fritschi et al., 2014b; Morales et al., 2015a). Immunodepletion of Aβ from the donor extract prior to injection nullifies the seeding effect (Meyer-Luehmann et al., 2006; Duran-Aniotz et al., 2014). Synthetic, pre-aggregated Aβ is capable of seeding deposition *in vivo* (Stohr et al., 2012), albeit relatively weakly (see below).

2. *Aβ seeds are rich in β-sheet secondary structure*. Amyloid fibrils of all types, including Aβ-amyloid and PrP-amyloid, are rich in β-sheets in which the individual β-strands run approximately perpendicular to the long axis of the fibrils (Eisenberg and Jucker, 2012). *In vitro* studies by Lansbury and colleagues demonstrated that pre-aggregated, β-sheet-rich seeds of synthetic Aβ efficiently induce monomeric Aβ to acquire β-sheet and assemble into amyloid (Harper and

Lansbury, 1997). In addition, *in vivo* seeding experiments have shown that denaturation of Aβ-seed-rich brain extracts with formic acid (which disrupts the 3-dimensional architecture of proteins) negates the ability of the extracts to induce plaque formation (Meyer-Luehmann et al., 2006).

3. *Misfolded Aβ can manifest as structurally and functionally variant strains*. In the canonical (PrP) prion diseases, prion traits and the host response vary in ways that suggest alternative structural and functional 'strains' of the agent. Strain differences, in turn, have been linked to dissimilarities in PrP amino acid sequence, protease sensitivity, resistance to denaturants, and glycosylation patterns (McKintosh et al., 2003; Weissmann, 2004; Wiseman et al., 2015). However, a critical factor governing prion infectivity and disease phenotype is the molecular conformation of pathogenic PrP (PrP^{TSE}, or PrP^{Sc}]) (Peretz et al., 2002; Tanaka et al., 2006; Gambetti et al., 2011). Distinct strains of PrP^{Sc} often yield characteristic patterns of lesion structure and distribution in the brain (Peretz et al., 2002; DeArmond et al., 2004). An important indication that variant CJD (the human prionosis that is linked to bovine spongiform encephalopathy) is caused by a novel prion strain was the discovery of atypical lesions termed florid plaques in affected humans (Ironside et al., 2000).

   As in the case of PrP-prions, Aβ can fold into strain-like variants both *in vitro* (Petkova et al., 2005; Nilsson et al., 2007; Yagi et al., 2007; Paravastu et al., 2008; Meinhardt et al., 2009; Miller et al., 2010; Kodali et al., 2010; Agopian and Guo, 2012; Spirig et al., 2014; Tycko, 2015; Tycko, 2016) and *in vivo* (Meyer-Luehmann et al., 2006; Rosen et al., 2010; Rosen et al., 2011; Lu et al., 2013; Heilbronner et al., 2013; Watts et al., 2014; Stohr et al., 2014; Cohen et al., 2015; Condello et al., 2018; Rasmussen et al., 2017). Cerebral Aβ assemblies in humans with AD vary in terms of plaque morphology (Wisniewski et al., 1989; Thal et al., 2006), ligand binding characteristics (Rosen et al., 2010; Condello et al., 2018; Rasmussen et al., 2017), solid-state nuclear magnetic resonance features (Qiang et al., 2017), as well as conformational stability and other biophysical characteristics (Cohen et al., 2015). Interestingly, Aβ extracted from the autopsied brains of nondemented elderly subjects exhibits molecular-level features that differ in some ways from AD-derived Aβ (Piccini et al., 2005; Portelius et al., 2015). Whether these differences are indicative of fundamentally distinctive strains of Aβ, or whether they reflect early versus late stages in the pathogenesis of AD is not certain.

   Experimental studies in transgenic mice have shown that strain-like features of aggregated Aβ can be transferred from donor to host by exogenous seeding. Specifically, in the absence of seeding, APP23 mice and APP/PS1 mice develop Aβ plaques with different morphologies and ratios of the 40- and 42-amino acid lengths of Aβ (Aβ40 and Aβ42); when Aβ seeds from one transgenic mouse model were infused intracerebrally into the other, the plaque morphology (Meyer-Luehmann et al., 2006), spectral signature of bound conformation-sensitive thiophene ligands, and the Aβ40:42 ratio (Heilbronner et al., 2013) were influenced both by the source of the seeds and the type of murine host. In

addition, strain-like features of Aβ from human AD cases can be at least partially replicated in mouse models (Condello et al., 2018; Rasmussen et al., 2017).

4. *Aβ seeds vary in size and sensitivity to proteinase K*. Infectious PrP-prions exist in a wide range of sizes, the most potent of which are small and soluble (Silveira et al., 2005). Similarly, Aβ seeds can range from large fibrils to small, oligomeric seeds with high biologic potency (Langer et al., 2011). Large Aβ seeds are relatively resistant to inactivation by proteinase K, whereas - like PrP-prions - oligomeric Aβ seeds are readily inactivated by the enzyme (Langer et al., 2011).

5. *Some Aβ seeds are durable*. When Aβ-rich brain extracts are boiled for 5 minutes prior to infusion into host mice, a significant fraction of bioactive Aβ seeds remain (Meyer-Luehmann et al., 2006). In addition, similar to PrP-prions, Aβ seeds retain their potency in donor brain tissue that has been in formaldehyde for years (Fritschi et al., 2014a). Aβ seeds also are durable within the living brain; they retain some bioactivity (albeit with progressively diminishing potency) for at least 6-months after infusion into the brains of mice engineered to lack APP, and which therefore are incapable of replicating Aβ in any form (Ye et al., 2015a). Analogously, PrP-prions have been reported to persist in the brains of PrP-deficient mice for up to 600 days (Diack et al., 2016). Likewise, AA amyloidosis in systemic organs can be promoted by fibrillar AA seeds (‘amyloid enhancing factor’) that persist in mice for at least 6 months (Lundmark et al., 2002). The endurance of some proteopathic seeds may result from their ability to adopt the highly stable, β-sheet-rich amyloid state (above).

6. *Aβ seeds spread systematically within the brain*. As with PrP-prions (Fraser, 1982; Buyukmihci et al., 1983; Kimberlin and Walker, 1986; Liberski et al., 2012; Rangel et al., 2014) and other proteopathic seeds (Clavaguera et al., 2009; Clavaguera et al., 2013; Ahmed et al., 2014; Iba et al., 2015; Boluda et al., 2015; Rey et al., 2016; Hock and Polymenidou, 2016)), Aβ seeds introduced into one part of the brain induce protein aggregation that spreads systematically to interconnected regions (Hamaguchi et al., 2012; Ye et al., 2015b). In APP-transgenic mouse models, Aβ seeds injected into the peritoneal cavity (Eisele et al., 2010; Eisele et al., 2014) or intravenously (Burwinkel et al., 2018) travel to the brain, where many of the induced deposits are associated with cerebral blood vessels.

   The cellular mechanisms involved in the trafficking of Aβ seeds remain uncertain. Extracellular, soluble Aβ is taken up by cultured cells and concentrated in the acidic environment of endosomes/lysosomes, where the Aβ assembles into higher molecular weight seeds (Hu et al., 2009). Oligomeric Aβ seeds have been described that are bound to intracellular membranes and that strongly stimulate Aβ aggregation *in vitro* and *in vivo* (Marzesco et al., 2016). In cell culture experiments, Aβ seeds were demonstrated to spread by transfer from neuron to neuron (Nath et al., 2012; Domert et al., 2014), and neuroanatomical patterns of deposition are consistent with spread along neuronal pathways (Hamaguchi et al., 2012; Ronnback et al., 2012; Ye et al., 2015b) by active

cellular transport and/or diffusion (Eisele and Duyckaerts, 2016). In addition, there is evidence that macrophages can phagocytose and translocate Aβ seeds (Eisele et al., 2014; Cintron et al., 2015).

Small, cell-derived extracellular vesicles such as exosomes have been linked to the transmissibility of PrP-prions (Fevrier et al., 2004; Properzi et al., 2015; Guo et al., 2016a). Extracellular vesicles also have been suggested to ferry Aβ between cells (Rajendran et al., 2006), although their influence on the pathogenesis of AD – positive or negative - remains uncertain (Joshi et al., 2015).

7. *Aβ aggregation can be instigated de novo*. PrP-prions induce prion disease in animals that are unlikely to have acquired the disease without exposure to exogenous prions. In contrast, many of the experiments showing seeding of Aβ have been undertaken in transgenic mouse models that, with age, eventually develop Aβ-plaques and CAA spontaneously. To determine whether Aβ deposition can be seeded in normally resistant animals, Aβ-seed-rich brain extracts were injected intracerebrally into transgenic rodent models that do not generate Aβ lesions within their average lifespans; these studies indicate that Aβ deposition is inducible *de novo*, and in this paradigm is not simply an acceleration of an ongoing process (Morales et al., 2012; Rosen et al., 2012).

8. *Aβ proteopathy is serially transmissible*. Similar to PrP-prions, different strains of Aβ seeds can be successively transmitted from the initially seeded mice to subsequent hosts (Watts et al., 2014).

Prion-like properties of Aβ: Open questions

Pure, pre-aggregated synthetic Aβ is able to seed deposition *in vivo*, but synthetic Aβ seeds are much weaker than are Aβ seeds derived from the brain (Stohr et al., 2012). Correspondingly, generating infectious prions from purified, recombinant PrP has long been a challenge (Legname et al., 2004). Both Aβ seeds and PrP-prions thus are most potent when they are generated within living tissues. The infectivity of recombinant PrP-prions can be augmented by adding certain cofactors to the medium during aggregation (Wang et al., 2010; Deleault et al., 2012; Zhang et al., 2014). It is possible that specific cofactors also are required to optimize the bioactivity of Aβ seeds *in vivo*. The lipid environment, for instance, influences the pathobiology of Aβ (Morgado and Garvey, 2015), and lipids are essential for the high-affinity binding of the β-amyloid imaging agent Pittsburgh Compound B (PiB) to cerebral Aβ (Matveev et al., 2014). Potent, *in vivo*–active Aβ seeds recently have been generated by the seeded conversion of synthetic Aβ in a hippocampal slice culture model (Novotny et al., 2016). Clarifying the conditions that influence protein aggregation, seeding, and toxicity in living systems could disclose new therapeutic objectives for multiple proteopathies. Insights might also emerge from an analysis of senescent nonhuman primates which, despite substantial accumulation of human-sequence Aβ with age, exhibit neither significant tauopathy nor dementia (Rosen et al., 2016). A possible parallel in the prion field is the dissociation of PrP-amyloid seeding and transmission of spongiform encephalopathy in a mouse model (Piccardo et al., 2013).

Another open question is why the Aβ that is present in the CSF of AD patients only weakly seeds the aggregation of synthetic Aβ *in vitro*, and fails to seed deposition in the brains of APP-transgenic mice even at Aβ concentrations that exceed the levels in brain extracts by a factor of ten (Fritschi et al., 2014b). The reasons for the poor seeding efficiency of CSF Aβ are unknown, but the Aβ assemblies in CSF were found to be smaller and mostly devoid of N-terminally truncated variants compared to brain-derived Aβ (Fritschi et al., 2014b). Additionally, other substances in the CSF, such as cystatin C (Kaeser et al., 2007), might interfere with the seeding capacity of multimeric Aβ.

Finally, in an intriguing intersection of disease-related proteins, the normal, cellular form of the prion protein (PrP^{C}) was discovered to be a cell-surface receptor for oligomeric Aβ (Salazar and Strittmatter, 2016). The implications of the Aβ-PrP interaction for AD appear to be complex, as its impact on Aβ toxicity or aggregation may be either deleterious (Um et al., 2012; Rushworth et al., 2013; Hu et al., 2014; Lauren, 2014) or beneficial (when it occurs in extracellular vesicles (Falker et al., 2016) or between Aβ and soluble (glycophosphatidylinositol anchor-free) PrP (Nieznanski et al., 2012)).

The prion-like properties of aggregated tau

At the ultrastructural level, neurofibrillary tangles in AD consist predominantly of characteristic paired helical filaments (Crowther, 1991) that result from the ectopic polymerization of hyperphosphorylated tau protein (Lee et al., 2001; Spillantini and Goedert, 2013). Tau hyperphosphorylation is thought to be an early stage in the formation of tangles (although it can occur as a reversible phenomenon under such conditions as fetal development, hibernation, and hypothermia (Spillantini and Goedert, 2013)).

Considerable evidence now supports the inclusion of tauopathy among the disorders that share a prion-like mechanism of pathogenesis. Similar to *in vivo* Aβ seeding, the accumulation of hyperphosphorylated tau is inducible in the brains of tau-transgenic host mice by infusion of aggregated tau seeds (Clavaguera et al., 2009; Guo and Lee, 2011; Holmes et al., 2014; Clavaguera et al., 2015; Peeraer et al., 2015; Polanco et al., 2016; Takeda et al., 2016; Gerson et al., 2016). The ensuing tauopathy spreads systematically from the site of injection to axonally connected regions of the brain (Clavaguera et al., 2009; Clavaguera et al., 2013; Ahmed et al., 2014; Stancu et al., 2015; Narasimhan et al., 2017), consistent with the uptake, transport, and discharge of tau seeds by neurons (Frost et al., 2009; Wu et al., 2013; Sanders et al., 2014). Neuronal activity augments the release of tau from cells *in vitro*, and also increases the amount of tauopathy *in vivo* (Wu et al., 2016). Additionally, tau antisense oligonucleotides decrease tau expression and pathology in mouse models, and also reverse pathologic tau seeding (DeVos et al., 2017). Like Aβ-proteopathy and prion disease, tauopathy can be induced in the brain by tau seeds that have been infused into the peritoneal cavity (Clavaguera et al., 2014), and bioactive tau seeds exist in a range of sizes (Lasagna-Reeves et al., 2012; Mirbaha et al., 2015; Gerson et al., 2016; Jackson et al., 2016).

Brain extracts from donors with clinicopathologically distinct human tauopathies induce tau lesions in host mice that resemble the lesions in the corresponding human disorders

(Clavaguera et al., 2013; Sanders et al., 2014; Boluda et al., 2015; Narasimhan et al., 2017), indicating that tau, like Aβ and PrP, can misfold into replicable proteopathic strains (Sanders et al., 2014). At the cellular level, multimeric tau is taken up by a heparan sulfate proteoglycan-associated mechanism (Holmes et al., 2013), and the aggregates enter cells via macropinocytosis (Holmes et al., 2013; Falcon et al., 2015). Tau strains instigate distinct regional and cellular patterns of inclusions, and the strains can be reliably propagated in cell cultures (Kaufman et al., 2016). The bioactivity of tau strains in HEK cells was shown to be governed by the isoform composition (3-repeat and/or 4-repeat) of the tau seeds along with the isoform expression by the host cells (Woerman et al., 2016). Tau seeds are present in the human brain early in the development of tauopathy, and possibly prior to the histologic appearance of hyperphosphorylated tau within neurons (Furman et al., 2017).

Tau seeding differs from Aβ seeding in that tauopathy is readily inducible by AD brain extracts in non-transgenic (wild-type) mice (Audouard et al., 2016; Guo et al., 2016b). In addition, recombinant tau fibrils can fairly efficiently instigate tauopathy in tau-transgenic mice (Lasagna-Reeves et al., 2012; Clavaguera et al., 2013; Iba et al., 2013; Peeraer et al., 2015), although the potency of recombinant tau is less than that of tau that originates in brain samples (Falcon et al., 2015). Recombinant tau fibrils did not seed tauopathy in wild-type mice, possibly due to distinct conformational differences between artificially assembled fibrils and those generated in the brain (Guo et al., 2016b).

In the CSF of AD patients and transgenic mice expressing human-type tau, seed-competent tau is present that can stimulate tauopathy in cultured cells (Takeda et al., 2016), and some tau seeds in AD CSF appear to be associated with extracellular vesicles (Wang et al., 2017). The seeding capability of CSF tau *in vivo*, however, has not been reported; because CSF Aβ does not readily seed plaques or CAA in APP-transgenic mice (Fritschi et al., 2014b) (see above), a similar analysis of *in vivo* tau seeding by CSF from patients with AD (and other tauopathies) in the appropriate models could be informative.

These experiments collectively underscore the prion-like molecular properties of aggregated tau, but current evidence indicates that tauopathy, like Aβ-proteopathy, is not infectious in the customary sense of being facilely transmissible from one organism to another (Walker and Jucker, 2015). Rather, in AD, the process of tau misfolding and propagation takes place entirely within the affected organism. To model the endogenous emergence and spread of tauopathy, genetically modified mice were studied in which the expression of a disease-associated human tau transgene is restricted principally to projection neurons of the entorhinal cortex (de Calignon et al., 2012; Liu et al., 2012). The mice developed tauopathy initially in the entorhinal cortex, as expected, but with passing time the abnormalities successively emerged in axonally connected brain areas (de Calignon et al., 2012; Liu et al., 2012). Subsequent studies have found that the tau transgene is weakly expressed in other brain regions, which could influence the pattern of lesion progression (Yetman et al., 2016). However, when considered in light of the orderly neuroanatomic localization of tau lesions in interconnected brain regions in AD (Saper et al., 1987; Arnold et al., 1991; Braak and Braak, 1995), the experiments in mouse models implicate neuronal transport and cytotic mechanisms in the propagation of tau seeds within the nervous system. This possibility is indirectly supported by evidence for the neuronal trafficking of Aβ seeds, PrP-prions and

other proteopathic seeds, as described above. Furthermore, *in vivo* imaging studies of the regional accumulation of pathogenic proteins in relation to the connectedness of the affected areas implicate the connectome in the systematic spread of seeds in AD and other neurodegenerative disorders (Bero et al., 2011; Zhou et al., 2012; Iturria-Medina et al., 2014; Raj et al., 2015).

Prion-like seeding and AD pathology in humans.

Between 1958 and 1985, approximately 30,000 children received a series of injections of cadaver-derived human growth hormone (c-hGH), in most instances to correct a deficiency in growth (Will, 2003; Brown et al., 2012). To obtain sufficient hormone for treatment, human pituitary glands were collected at autopsy, pooled into large batches, homogenized, and the c-hGH chemically extracted for injection. The treatment successfully stimulated growth, but years after treatment had ceased, a small percentage of the c-hGH recipients developed Creutzfeldt-Jakob disease (Brown et al., 2012). Subsequent studies have confirmed that the growth hormone was contaminated with PrP-prions, which presumably originated from pituitaries inadvertently obtained from patients who had died with prion disease (Jucker and Walker, 2015). In 1985, cadaver-derived hGH was replaced by recombinant growth hormone, thereby effectively eliminating the possibility that the therapeutic agent would be contaminated by prions (Brown et al., 2012).

Hypothesizing that pituitaries collected from AD patients were likely to be included in the batches for hormone extraction, Jaunmuktane, Collinge and colleagues sought evidence of AD-like pathology in eight c-hGH recipients who had died of prion disease approximately 30 years after treatment (Jaunmuktane et al., 2015). The cases ranged from 36 to 51 years of age at death – well before the lesions of idiopathic AD usually are evident – and they lacked the major genetic risk factors that would have predisposed them to early-onset AD. Along with the neurodegenerative changes typical of CJD, four of the subjects had extensive Aβ deposition in the brain in the form of both Aβ plaques and CAA, and two others had sparse Aβ deposits. Such Alzheimer-like Aβ-pathology was not present in control patients of similar age who had died of other (non-c-hGH-related) prion diseases. In addition, the frequent presence of Aβ-CAA is reminiscent of the increased vascular Aβ deposition seen in APP23 transgenic mice following peripheral administration of Aβ seeds (Eisele et al., 2010; Eisele et al., 2014; Burwinkel et al., 2018).

Significant Aβ deposition also has been reported in the brains of patients who died of CJD years after receiving PrP prion-contaminated dura mater transplants (Frontzek et al., 2016; Hamaguchi et al., 2016) or in c-hGH recipients who died of causes other than CJD (Ritchie et al., 2017). The most parsimonious explanation for the presence of Aβ-proteopathy in the recipients of human-derived biologics is that some batches of growth hormone and dura mater were contaminated with Aβ seeds in tissues originating from AD (or incipient AD) donors. This possibility is supported by evidence that some pituitary glands from AD patients (Irwin et al., 2013) (Figure 4A) and also samples from implicated c-hGH (Duyckaerts et al., 2018) and dura mater (Kovacs et al., 2016a) contain Aβ.

In light of experimental work on Aβ seeding *in vivo* (above), it is likely that a prion-like seeding mechanism underlies the development of Aβ-plaques and Aβ-CAA in recipients of c-hGH and dura mater transplants. Surprisingly, few of these iatrogenic CJD patients also had evidence of significant tauopathy (Jaunmuktane et al., 2015; Kovacs et al., 2016a; Duyckaerts et al., 2018). Mild tauopathy is present in AD-derived pituitaries (Hashizume et al., 2011; Irwin et al., 2013)(Figure 4B), and, as discussed above, tauopathy is directly seedable by aggregated tau in experimental models. Some c-hGH samples have been found to contain tau (Duyckaerts et al., 2018). Furthermore, experimental studies show that tau polymerization can be cross-seeded by aggregated Aβ (Vasconcelos et al., 2016) and that tauopathy is augmented by Aβ plaques *in vivo* (Pooler et al., 2015; Li et al., 2016).

Whether the Aβ-positive recipients of c-hGH or dura transplants would have manifested the full AD phenotype had they lived longer cannot be known. An analysis of pituitary hormone recipients in the US suggests that they are not more likely to develop AD than those in the general population (Irwin et al., 2013). However, longer term follow-up and investigation of c-hGH recipients in other countries, particularly where the processing of the hormone differed from that in the US (Brown et al., 2012), will be necessary to fully gauge the transmission risk of non-prion proteopathies in these instances.

Conclusions

The seeded propagation of misfolded Aβ is an early and obligatory occurrence in the cascade of events leading to the dementia of Alzheimer's disease, but tauopathy is a critical downstream consequence that strongly impairs brain function. Both proteins have been shown to misfold, self-assemble and convey their abnormal properties to like proteins by a prion-like molecular mechanism. Therapeutic strategies for AD stemming from the prion paradigm include impeding the production or multimerization of the proteins, uncoupling the pathogenic link between abnormal Aβ and tau, and promoting the elimination of the seeds from the brain. Because Aβ-proteopathy and tauopathy each propagate by a prion-like mechanism of homologous protein corruption, it is likely that, once set in motion, the two pathologic processes advance more or less independently. If so, targeting Aβ should suffice for early prevention, but late-stage therapeutics will need to impede both branches of the cascade to be optimally effective. Another practical implication of the prion-like properties of misfolded Aβ and tau is to reinforce the importance of pristine instruments in neurosurgery. Finally, recognition of the prevalence of prionic mechanisms in neurodegenerative diseases could serve to integrate research efforts on these intractable disorders conceptually, experimentally and therapeutically.

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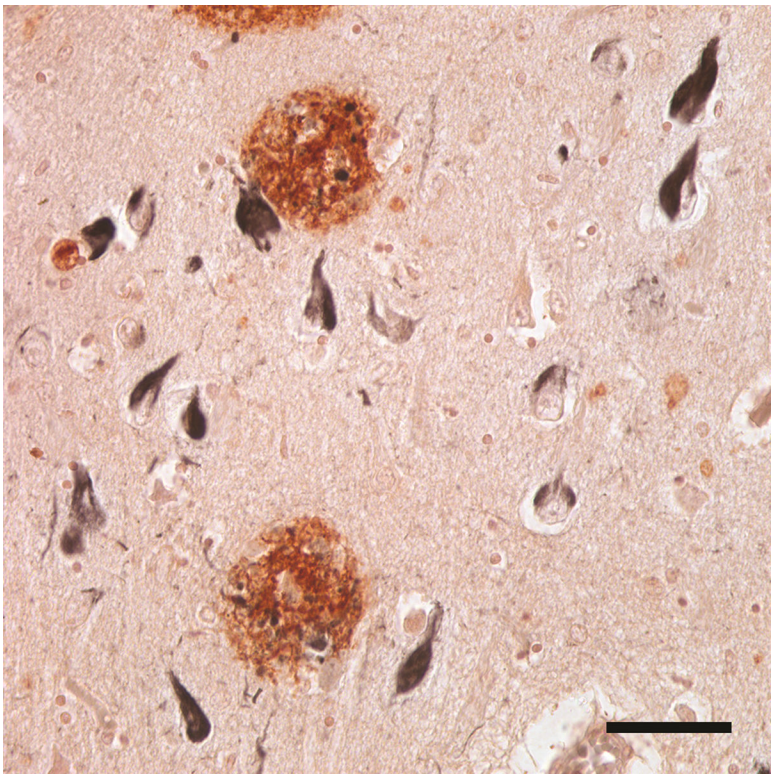

Figure 1.

The canonical neuropathologic features of AD include senile (Aβ) plaques (reddish brown) and neurofibrillary (tau) tangles (black). Aβ was immunostained with rabbit polyclonal antibody R398 to Aβ42, and tau was immunostained with mouse monoclonal antibody MC1 to paired helical filaments. CA1 field of the hippocampus. Bar = 50μm.

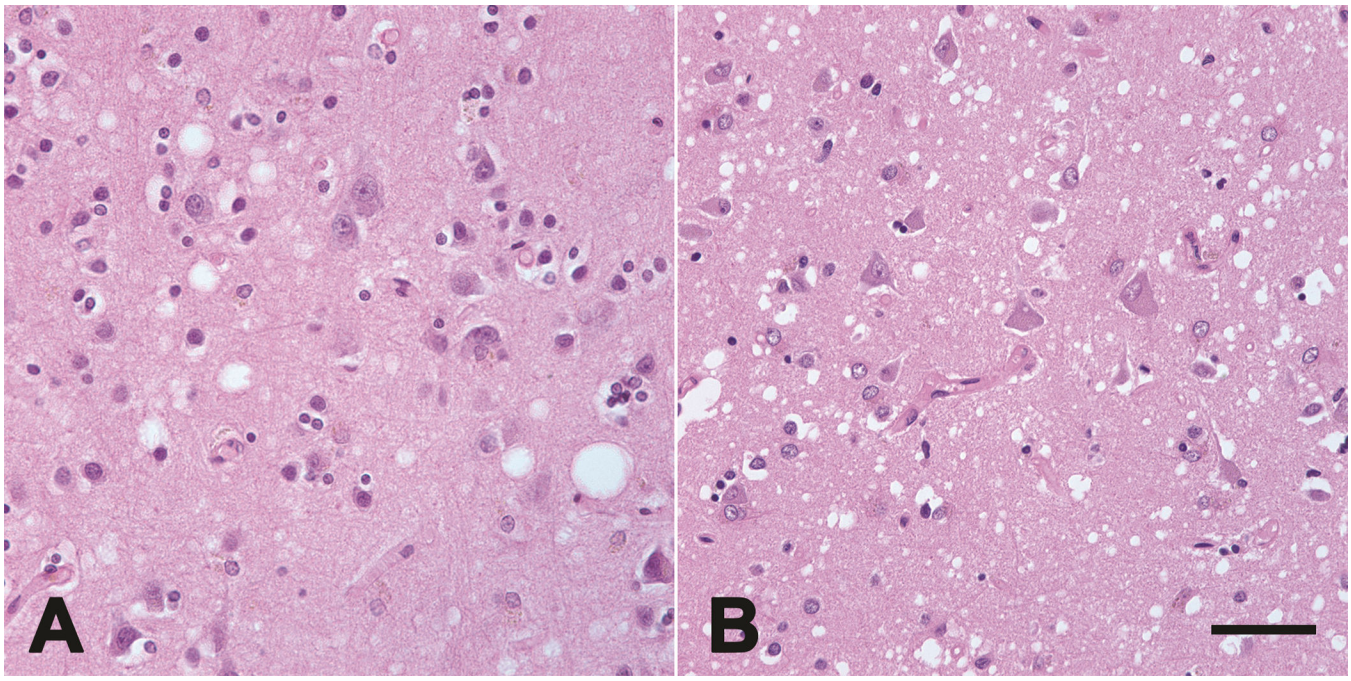

Figure 2.

Spongiform change (vacuoles, seen in these micrographs as white holes) in the neocortex of an AD patient (A) and in a patient with CJD (B). Spongiform change is not unique to prion diseases, but it is less common in AD, and when it occurs it is generally mild (Smith et al., 1987; Sherzai et al., 2013). Hematoxylin and eosin stain. Bar = 50μm.

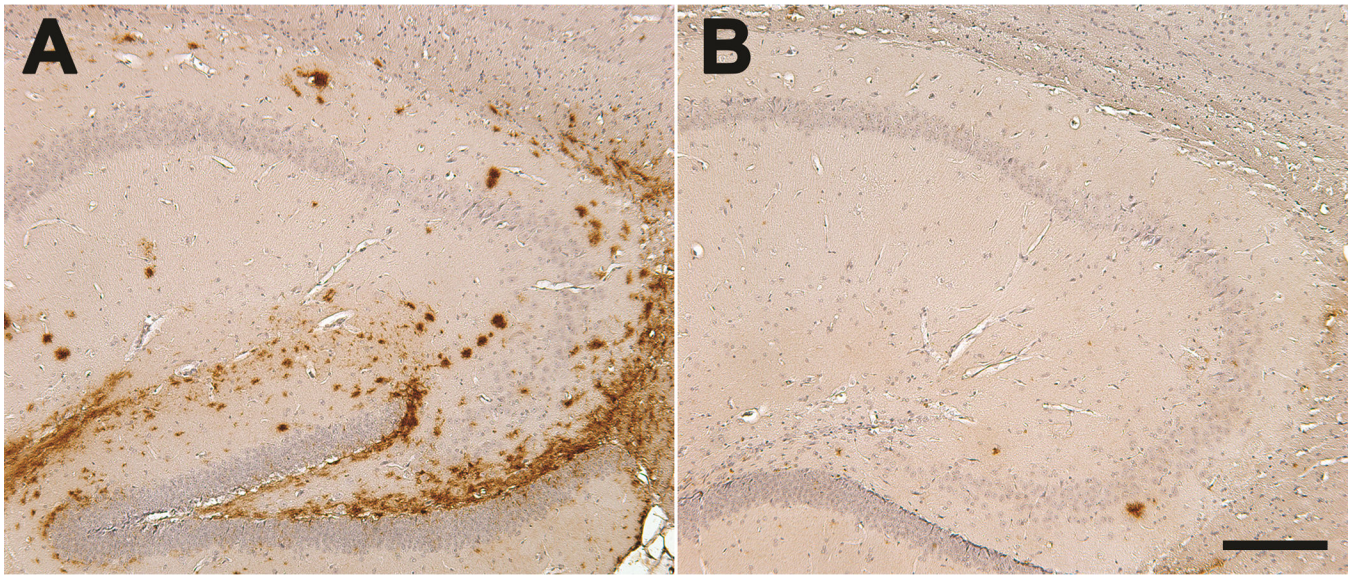

Figure 3.

Seeded Aβ deposition (brown) in the hippocampus of an 8-month-old TG2576 APP-transgenic mouse (sagittal sections; rostral is to the right). The hippocampus of one hemisphere (**A**) was injected 5 months earlier with clarified cortical extract from an AD case, and the contralateral hippocampus (**B**) received a similar amount of control brain extract lacking aggregated Aβ. The induced deposits emerge histologically in this model after around 2–3 months, and increase thereafter. Sections were incubated with polyclonal antibody R398 to Aβ42. Hematoxylin counterstain (blue). Bar = 200μm.

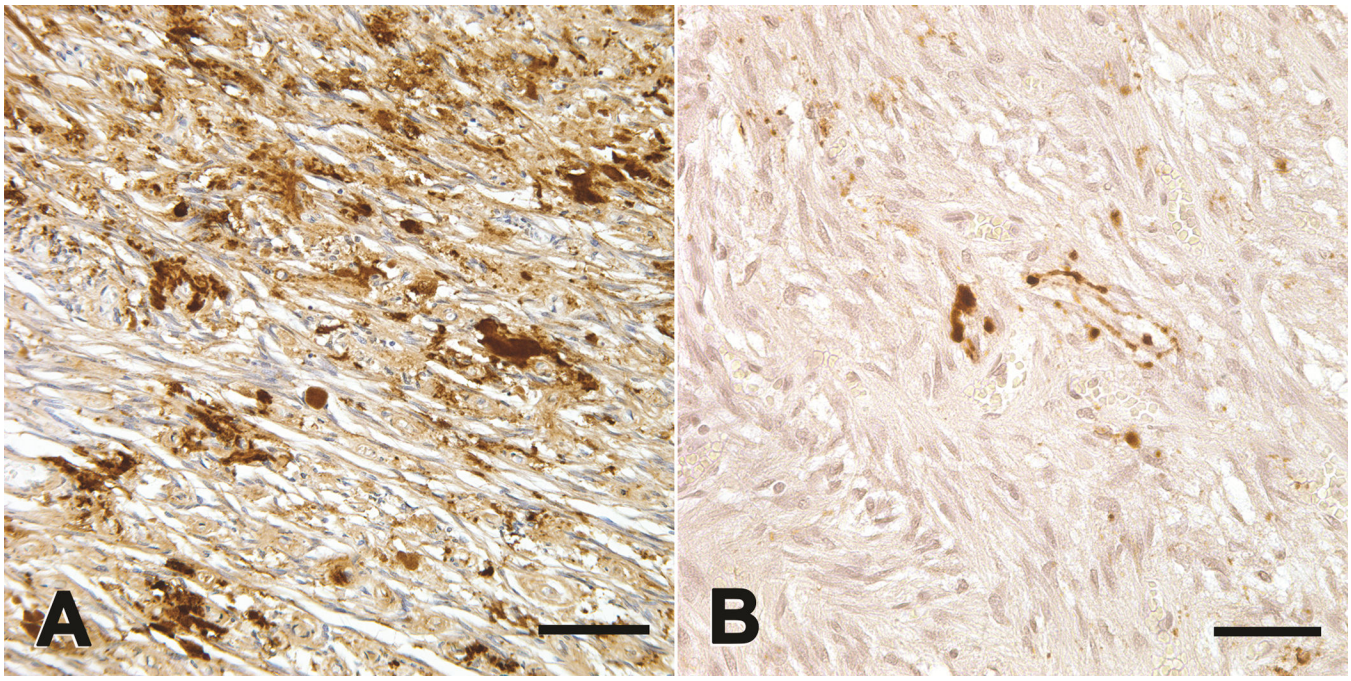

Figure 4.

Immunoreactive deposits (brown) of aggregated Aβ (**A**) and hyperphosphorylated tau (**B**) in the posterior lobe of the pituitary gland from a patient who had died with AD. Aβ was detected with antibody 82E1 to the N-terminal segment of Aβ, and tau was detected with antibody CP13 to an epitope around phosphoserine 202. The accumulation of Aβ and tau is generally mild in the pituitary. Hematoxylin counterstain (blue). Bars = 100μm in A and 50μm in B.