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Review

Alzheimer disease and the prion disorders amyloid β-protein and prion protein amyloidoses

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ABSTRACT **Alzheimer disease and the prion disorders/spongiform encephalopathies share many common features. These chronic, progressive, sometimes familial diseases of the central nervous system are characterized by the presence of different types of amyloid deposits in the brain. This review provides a perspective on these two types of neurodegenerative disorders.**

Alzheimer Disease (AD)

AD, the most common type of senile dementia (1), manifests as a gradual loss of memory, followed by progressive deterioration of higher cognitive functions and behavior (Table 1) (2). These signs are the result of abnormalities of neurons in a variety of brain regions/neural circuits that lead to the loss of synaptic inputs to targets in the amygdala, hippocampus, and neocortex (3–8). Affected neurons develop neurofibrillary tangles [i.e., accumulations of insoluble paired helical filaments (PHFs) in cell bodies and proximal dendrites] and neurites (i.e., enlarged neuronal processes filled with PHFs and, frequently, abnormal membranous organelles) (9–11). PHFs are composed principally of abnormally phosphorylated isoforms of tau (11–13), a low molecular weight microtubule-associated protein. Goedert *et al.* (14) demonstrate that tau is phosphorylated during development, that fetal brain tau is hyperphosphorylated relative to levels of phosphorylation in the six adult tau isoforms, and that the six normally expressed tau isoforms are phosphorylated abnormally in the brains of AD patients. Specifically, serine-202, normally phosphorylated in fetal tau, is phosphorylated in the brains of individuals with AD, suggesting that the disease-related phosphorylation recapitulates a pattern that occurs during development. The aberrant phosphorylation of tau is likely to alter microtubule-related functions and, thus, compromise intracellular transport, cellular geometry, and neuronal viability.

A characteristic lesion of AD is the presence of β-pleated amyloid deposits, particularly in hippocampus and neocortex (4, 15). Amyloid appears as preamyloid accumulations in the neuropil, as cores of senile plaques, and as accumulations around blood vessels (9, 15–18). Amyloid fibrils (≈8 nm) are composed of a 4-kDa peptide (amyloid β-protein; Aβ or β/A4) (16–18) derived from larger amyloid precursor proteins (APPs) coded for by a gene on chromosome 21 (19). APPs are integral membrane glycoproteins that mature, in cultured cells, through a constitutive secretory pathway (20). APPs appear at the cell surface and can be endoproteolytically cleaved by APP α-secretase at position 16 within Aβ (21–24) to release the APP ectodomain; alternatively, some APPs are endocytosed and degraded via endosomal–lysosomal pathways (25–27). Furthermore, soluble Aβ (4 kDa) is secreted normally from cultured cells and is present in cerebrospinal fluid (28–31). *In vitro* studies with synthetic Aβ have demonstrated that the β-peptide forms fibrils and that disease-linked mutations enhance fibrillogenic potential (32–35).

APP transcripts and proteins are expressed in most neurons (36); APPs are present in cell bodies, proximal dendrites, and axons (37) and are delivered to axons and terminals via the fast anterograde axonal transport system (38, 39).

The biological functions of APPs in neurons are presently uncertain but APPs may be involved in synaptic interactions (40) or serve as a receptor coupled to trimeric G_o proteins (41). In cultured cells, activators of protein kinase C activity increase the release of soluble APP derivatives (42). Furthermore, cholinergic agonist-activated stimulation of muscarinic receptor subtypes M1 and M3 enhances the release of soluble APP derivatives (43). Nitsch *et al.* (44) document that electrical depolarization of superfused rat hippocampal slices increases the release of neurotransmitters and soluble APP derivatives; these processes are inhibited by tetrodotoxin, a poison that blocks sodium channels necessary for the generation of action potentials. These results suggest that neuronal activity can influence the processing of APPs.

The major risk factors for AD are age and genetic loci on chromosomes 21 and 14 linked to the presence of early-onset disease (45–52). At least 10 pedigrees of early-onset, autosomal dominant familial AD exhibit linkage to missense mutations in APPs at codons 717 (of APP-770) and 693 (45, 47–49, 53–55). In these families with early-onset autosomal dominant AD, the valine residue at position 717 is replaced by isoleucine, phenylalanine, or glycine; these mutations occur within the transmembrane domain of APP, two amino acids downstream from the C terminus of Aβ. More recently, a double mutation at codons 670 and 671, resulting in a substitution of the normal Lys-Met dipeptide by Asn-Leu, has been demonstrated in two large, related, early-onset AD families from Sweden (52). The pathology in one autopsied individual is very severe, with abundant plaques and tangles (B. Winblad, personal communication). Significantly, cells transfected with cDNA encoding APP, which harbor this double amino acid substitution, secrete elevated levels of Aβ-related peptides (56, 57). Moreover, recent studies have also identified a major early-onset locus on the distal part of chromosome 14 (14q24.3) (50, 51) and a susceptibility on chromosome 19 associated with late-onset illness (58). The latter is thought to code for apolipoprotein E, the principal transporter of cholesterol (58, 59). In these late-onset kindreds, a significant association exists between the apolipoprotein E type ε4 allele (the brain-enriched isoform) and the presence of AD (58).

Mechanisms that lead to the deposition of Aβ *in vivo* are not yet well defined (60–62). Studies in aged monkeys, the best currently available model that reproduces some of the features of AD (61, 63), have shown APP-immunoreactive neurites, often decorated or capped by Aβ deposits (37, 64). These degenerating neurites are thought to be one source of parenchymal Aβ that presumably accumulates amyloidogenic fragments (37, 64, 65). An experimental study (66) suggests that the degeneration of neurons can alter

Abbreviations: AD, Alzheimer disease; Aβ, amyloid β-protein; APP, amyloid precursor protein; CJD, Creutzfeldt–Jakob disease; GSS, Gerstmann–Sträussler–Scheinker syndrome; PrP^{sc}, scrapie prion protein.

Table 1. Comparison of AD and prion disorders

	AD	Prion disorders
Onset	Mid-to-late life (usually late)	Any age (usually later in life)
Progression	8–12 years	6 months to 8 years
Signs	Dementia	Dementia, ataxia, myoclonus
Sporadic	Majority	Majority
Transmissible	Not documented	Well documented
Familial	5–10%	Well documented
Chromosomal loci	21, 14, 19	20
Gene with mutation	APP	PrP
Vulnerable cells	Cortical, hippocampal, cholinergic basal forebrain neurons	Many regions of brain
Cytoskeletal pathology	Neurofibrillary tangles, neurites, neuropil threads	Rare
Amyloid	Aβ	PrP^{sc}
Cell death	Severe	Variable
Models	Aged nonhuman primates; transgenic mice (?)	Scrapie; transgenic mice with PrP mutations

APP processing. In quinolinic acid-induced lesions of rat striatum, levels of potential amyloidogenic fragments were increased in projection areas and terminal fields. In cases of AD, it is highly likely that other cells, including astroglia, microglia, and vascular cells, may play important roles in the production of amyloidogenic fragments and, potentially, deposits of Aβ.

Several *in vitro* systems have been used to explore the influences, toxic or trophic, of Aβ on neurons (67). Koo *et al.* (68) used *in vitro* systems to determine whether Aβ can influence neurite outgrowth from cultured rat peripheral sensory neurons. In combination with low doses of laminin or fibronectin, Aβ enhanced outgrowth from the explants, suggesting that these extracellular matrix proteins, in concert, provide an environment conducive for sprouting, a phenomenon believed to occur in the neuropil of AD patients (69).

In vivo studies have focused on aged nonhuman primates as an animal model of Aβ amyloidogenesis (61, 63) and on transgenic mice that harbor cDNA encoding full-length APP or APP fragments (70–73). Unfortunately, several of these studies have been confounded by incomplete documentation of levels of the transgene product and/or misinterpretations of the microscopic pathology; at present, none of the reported transgenic mice fully reproduces the features of AD-type pathology (62). However, recent studies that utilize yeast artificial chromosome and embryonic stem cell technologies have successfully introduced and expressed an ≈400-kb human genomic sequence of APP into embryonic stem cells and into the germ line of transgenic mice (99). These animals express the human gene, and steady-state levels of mRNA and protein are equivalent to those of the endogenous APP gene. This approach, coupled with the introduction of APP mutations, should be a valuable strategy for future efforts to produce transgenic mice that exhibit some of the brain abnormalities, including Aβ deposits, that occur in cases of AD and Down syndrome (74).

Prion Disorders

The human prion disorders/spongiform encephalopathies, including kuru (occurring in Fore tribesman of New Guinea), Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker syndrome (GSS), and familial fatal insomnia, can occur at any age (Table 1). Depending on a variety of factors, prion diseases display a remarkable spectrum of clinical abnormalities that include cognitive impairments, myoclonus, motor dysfunction, and ataxia; these symptoms reflect spongiform changes, neuronal loss, and gliosis, particularly the hippocampus, neocortex, subcortical nuclei, cerebellum, and brainstem (75). Similar diseases occur in animals—i.e., scrapie in sheep and goats, transmissible mink encephalopathy, and bovine spongiform encephalopathy, a disease that has caused great concern in the dairy/meat industries in the United Kingdom.

Pioneering studies by Gibbs, Gajdusek, and colleagues (76, 77) showed that spongiform encephalopathies could be transmitted by the inoculation of brain tissues from affected individuals. Although these diseases have historically been classified as unconventional slow viral diseases, a large body of work by Prusiner (78) and other investigative groups argues convincingly that these illnesses are transmitted by an abnormal cellular protein, designated the scrapie prion protein (PrP^{sc}). The single copy PrP^{c} gene is located on chromosome 20, and specific mutations in this gene cause specific clinical syndromes, termed familial CJD, GSS, and familial fatal insomnia (78). For example, in some CJD families, affected members have point mutations at codons 178 (Asp → Asn) or 200 (Glu → Lys) (79–82), whereas cases of familial fatal insomnia are associated with a mutation at codon 178 (83). Affected individuals in GSS families have mutations at codon 102, 117, 198, or 217 (84–87); moreover, in one GSS kindred, the brain shows PrP^{sc} deposits as well as senile plaques and neurofibrillary tangles (87, 88). Transgenic mice with the 102 mutation develop disease (89), whereas Prp null mice do not exhibit a phenotype (90).

An invariant feature of prion diseases is the synthesis and accumulation of protease-resistant PrP^{sc}, the principal component of the PrP amyloid plaques that occur *in vivo* (91). Partial proteolysis of PrP^{sc} (33–35 kDa) generates PrP-27–30, which forms amyloid rods *in vitro* (92). Available evidence suggests that PrP^{sc} is derived from PrP^{c} via a posttranslation conformational modification (93–96) that occurs in the endosomal compartment (97). It has been suggested that disease-linked mutations in PrP cause conformational changes in PrP that promote its spontaneous conversion into amyloid (85, 89). In the report by Goldfarb *et al.* (98), polypeptides were synthesized corresponding to sequences encoded by normal PrP and by PrP with mutations in codons 178 and 200, which have been linked to familial CJD. Synthetic peptides that correspond to these mutant sequences are more fibrillogenic than their normal counterparts; moreover, the morphology of codon 178 fibrils differs from that of the codon 200 fibrils, and the mutant peptides accelerate the amyloidogenesis of normal peptides. These findings are consistent with the idea that specific amino acid substitutions resulting from point mutations may alter the *in vivo* folding behavior of the normal host protein to favor the formation of insoluble PrP^{sc} amyloid fibrils. Thus, in both familial AD and the prion disorders, disease-linked mutations in either APP or PrP enhance the fibrillogenic nature of the peptides (32, 98), observations consistent with the concept that conformational changes in these polypeptides are pivotal in the production of amyloid fibrils.

Conclusions

In conclusion, AD and the prion disorders show many parallels. Ongoing genetic, neuropathologic, and cellular/molecular biological investigations of AD and the prion diseases will enormously enhance our knowledge of the mechanisms of these two types of neurodegenerative disorders.

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