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Modeling Alzheimer's disease and other proteopathies in vivo: Is seeding the key?

Review Article

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Summary. Protein misfolding and aberrant polymerization are salient features of virtually all central neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease, triplet repeat disorders, tauopathies, and prion diseases. In many instances, a single amino acid change can predispose to disease by increasing the production and/or changing the biophysical properties of a specific protein. Possible pathogenic similarities among the cerebral proteopathies suggest that therapeutic agents interfering with the proteopathic cascade might be effective against a wide range of diseases. However, testing compounds preclinically will require disease-relevant animal models. Numerous transgenic mouse models of β-amyloidosis, tauopathy, and other aspects of AD have now been produced, but none of the existing models fully recapitulates the pathology of AD. In an attempt to more faithfully replicate the human disease, we infused dilute AD-brain extracts into Tg2576 mice at 3-months of age (i.e. 5–6 months prior to the usual onset of β-amyloid deposition). We found that intracerebral infusion of AD brain extracts results in: 1) Premature deposition of β-amyloid in eight month-old, β-amyloid precursor protein (βAPP)-transgenic mice (Kane et al., 2000); 2) augmented amyloid load in the injected hemisphere of 15 month-old transgenic mice; 3) evidence for the spread of pathology to other brain areas, possibly by neuronal transport mechanisms; and 4) tau hyperphosphorylation (but not neurofibrillary pathology) in axons passing through the injection site. The seeding of β-amyloid *in vivo* by AD brain extracts suggests pathogenic similarities between β-amyloidoses such as AD and other cerebral proteopathies such as the prionoses, and could provide a new model for studying the proteopathic cascade and its neuronal consequences in neurodegenerative diseases.

Keywords: Alzheimer's disease – Amyloid – Conformational disease – Huntington's disease – Parkinson's disease – Proteopathy – Senile plaque – Tau – Transgenic

Alzheimer's disease: Pathophysiology and relationship with other proteopathies

Research on Alzheimer's disease has burgeoned since the discovery in the 1970's and 1980's that basal forebrain neurons containing the neurotransmitter acetylcholine appear to be especially vulnerable to the disease process (Bowen et al., 1976; Davies and Maloney, 1976; Whitehouse et al., 1982; Geula and Mesulam, 1999). The "cholinergic hypothesis" spawned a wealth of basic research on all facets of AD, and led to the development of the first generation of approved therapies for AD in the United States (Giacobini and Becker, 1994). One outcome of this research was the reaffirmation that more than just the basal forebrain cholinergic system degenerates in AD, including neurons using various monoamines, peptides and amino acids as neurotransmitters (Hedera and Whitehouse, 1994; Sisodia et al., 1995; see also Martin (1999) for a critical review). The result of the degenerative process is widespread, but selective, neurochemical alterations and synaptic deafferentation, which contribute importantly to the dementia that characterizes AD (Terry et al., 1991; Hof and Morrison, 1999). Although therapeutic strategies for restoring transmitter function can be expected to improve cognitive decline to some degree when sufficient neuronal substrate remains, retarding the underlying disease process holds the best hope for long-term, effective treatment. Hence, many researchers in the field are returning to senile plaques and

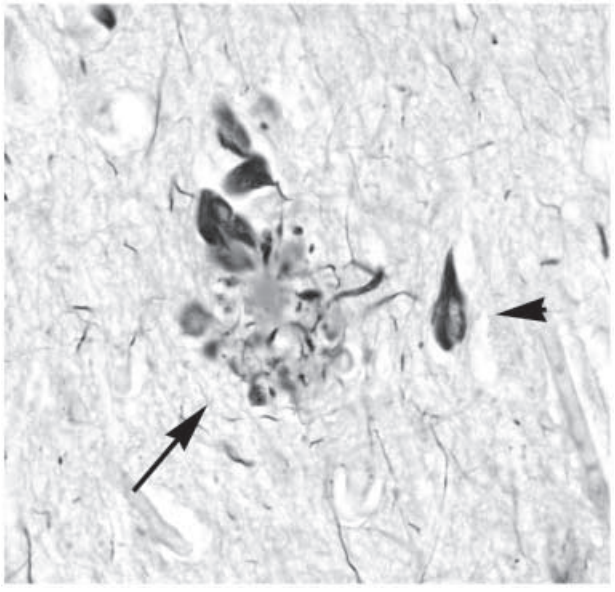

Fig. 1. Senile plaque (arrow) and neurofibrillary tangle (arrowhead) in the hippocampal formation of a patient who had died of AD. The cores of senile plaques are formed primarily of aggregated, fibrillar Aβ, whereas neurofibrillary tangles are bundles of paired helical filaments that are composed of abnormally polymerized tau protein. Note the numerous dark, enlarged, abnormal neurites that surround the light-gray plaque core. Naoumenko-Feigen silver stain, periodic acid-Schiff (PAS) counterstain

neurofibrillary tangles (the canonical neuropathological hallmarks of AD; Fig. 1) as the main source of insight into the origins of AD and into potential disease-modifying therapies.

The most salient feature of senile plaques and neurofibrillary tangles is the abnormal assembly and accumulation of particular proteins. The peptide *Aβ* aggregates into senile plaques in the brain parenchyma, and also collects to a variable extent in the walls of cerebral blood vessels. Hyperphosphorylated forms of the microtubule-associated protein *tau* polymerize within neurons to form paired helical filaments (identified with the light microscope as neurofibrillary tangles). Exactly how Aβ and tau contribute to disease pathogenesis is still disputed. With regard to Aβ, a growing school of thought holds that a non-fibrillar intermediate, such as an oligomeric form of the peptide, is responsible for cytopathology, and that plaques are just an obvious byproduct of this more insidious process (Klein et al., 2001; Walker & LeVine III, 2000b).

In the context of aging, specific mutations in the gene encoding βAPP (the protein that spawns Aβ) result in autosomal dominant AD (Selkoe, 1999), as do mutations in the presenilins (St. George-Hyslop, 1999) (proteins that are involved in the carboxy-terminal gamma-site cleavage of Aβ from βAPP). Familial AD and the more common "sporadic" forms of AD are characterized by the same types of lesions, although such factors as age of onset and rate of progression, as well as various other known and unknown modifiers, can influence the degree and distribution of pathology. The involvement of Aβ is constant, despite the phenotypic variability of AD. Indeed, all known risk factors for AD result in an increase in the production and/or deposition of Aβ (Selkoe, 1999).

The participation of tau in the pathogenesis of AD also is indisputable, but which lesion initiates the Alzheimer's disease process, the plaque or the tangle? The familial tauopathies (Mandelkow and Mandelkow, 1998; Spillantini and Goedert, 1998; Hardy et al., 1998; Lee and Trojanowski, 1999; Tolnay and Probst, 1999) suggest a tentative answer to this question. Certain mutations in tau result in dementing disorders characterized histologically by numerous neurofibrillary tangles, but β-amyloid deposits are usually absent (Buée et al., 2000). Thus, mutations in tau result in dementing disorders characterized pathologically only by the presence of tangles, but mutations in βAPP engender *both* senile plaques and neurofibrillary tangles in Alzheimer's disease. Interestingly, in AD, tau pathology tends to correlate better with dementia than does plaque load (Berg et al., 1993; Arriagada et al., 1998). Hence, it appears that tauopathy is sufficient to cause dementia, but the road to tau pathology in Alzheimer's disease first passes through Aβ. In any event, both tau and Aβ are legitimate therapeutic targets for altering the course of AD.

In fact, the misfolding and aberrant polymerization of specific proteins are common characteristics of an astonishing variety of diseases of the central nervous system and beyond (Walker and LeVine III, 2000a; Walker and LeVine III, 2000b). In many instances, a single amino acid change is sufficient to render a protein pathogenic (various posttranslational modifications as well as interactions with other proteins also can play a part). Understanding these proteopathic mechanisms is the next major frontier for biomedical research; to reach it, valid animal models will be needed. In the 1980's and early 1990's, the only available animal models of cerebral β-amyloidosis were aged dogs and nonhuman primates, which naturally produce β-amyloid (Walker et al., 1994; Cummings et al., 1996; Walker, 1997a,b; Walker and Cork, 1999; Walker, 2000). More recently, genetically modified

mice have been playing a growing part in establishing the significance of protein aggregation in neurodegenerative processes, in dissecting the pathogenic mechanisms involved, and in testing novel therapies.

Transgenic mouse models of Alzheimer pathology

After some early setbacks (Marx, 1992), the AD field has enjoyed a profusion of transgenic and/or knockout mice for a variety of AD-related proteins, such as βAPP, tau, presenilins, and apolipoprotein E (for reviews see Walker, 1997a; Price et al., 1998; Sommer, 1998; Masliah, 1999). The outcome is a wealth of *in vivo* models of aspects of AD, but, to date, no mouse acquires the complete pathology of AD. βAPP-transgenic mice, including some with plentiful, age-associated Aβ-deposition, have been particularly well-characterized (Walker, 1997a; Price et al., 1998; Sommer, 1998; Masliah, 1999; Callahan et al., 2001). The components of senile plaques in βAPP-transgenic mice resemble in many ways those seen in humans (Games et al., 1995; Hsiao et al., 1996; Irizarry et al., 1997; Sturchler-Pierrat et al., 1997; Frautschy et al., 1998; Masliah, 1999; Stalder et al., 1999), except that neurofibrillary tangles have never been seen, either in the abnormal neurites that surround plaques or in neuronal somata.

Many groups have now developed mouse models of tauopathy that express different tau protein constructs (Götz et al., 1995; Brion et al., 1999; Ishihara et al., 1999; Spittaels et al., 1999; Duff et al., 2000; Lewis et al., 2000; Probst et al., 2000; Götz et al., 2001). Because hyperphosphorylation of tau is thought to contribute to its pathogenic state (Buée et al., 2000), mice expressing sundry transgenes that promote phosphorylation also have been generated (James et al., 1996; Brownlees et al., 1997; Ahlijanian et al., 2000; Tesseur et al., 2000; Tesseur et al., 2000; Bian et al., 2002). Possibly the closest approximation to human tauopathy is a transgenic mouse model that expresses mutant (P301L) tau protein (Lewis et al., 2000; Götz et al., 2001), but there remain important differences between the murine and human lesions. In short, there is still no completely faithful transgenic mouse model of human-like tangles, but, as with βAPP transgenics, the field is still young. As a possible means of stimulating more human-like pathology in mice, we have been investigating the intracerebral infusion of AD brain extract in βAPP-transgenic mice. Our findings are briefly reviewed below.

The Tg2576 (Hsiao) mouse model of β-amyloidosis

Tg2576 mice overexpress the human βAPP transgene (695 amino acid isoform) with the "Swedish" double mutation (K670N-M671L) driven by a hamster prion promoter (Hsiao et al., 1996). Protein expression with this construct is directed primarily to neurons and astrocytes, and in brain is approximately five times the expression of endogenous, mouse βAPP. Although the expression of the transgene remains stable as the mice age, the presence of cerebral Aβ begins to increase dramatically around the age of nine months, in conjunction with the appearance of small, scattered senile plaques in certain brain regions (Hsiao et al., 1996; Callahan et al., 2001). By 24 months of age, amyloid burden can be pronounced (Fig. 2), although interindividual variability is high. Surprisingly, female Tg2576 mice deposit significantly more β-amyloid than do male mice (Callahan et al., 2001). Both plaque load measured histologically and the levels of the 40- and 42-amino acid versions of Aβ (Aβ40 and Aβ42) measured by ELISA are increased in the females. The effect of sex is most evident at around 15–19 months of age, when nearly three times as much cortical/hippocampal area is occupied by plaques in females than in males.

Seeding Aβ proteopathy in Tg2576 mice

If, as we suspect, the abnormal assembly of Aβ into multimeric species impels the neurodegenerative process, then it is imperative to understand how Aβ polymerization is initiated and sustained. Taking our cue from early studies of the prionoses (Prusiner et al., 1990; Prusiner et al., 1999), as well as primate studies of intracerebral AD homogenate injections (Baker et al., 1994), we hypothesized that Aβ aggregation might be induced, or "seeded", in βAPP-transgenic mice by material from diseased brains (Kane et al., 2000). To test this hypothesis, we infused dilute extracts of AD- and control brain homogenates into young (3-month-old), male Tg2576 mice. Autopsy-derived samples of human neocortex were homogenized, centrifuged to remove plaque cores, blood vessels and other debris, and the clear supernatant diluted to 1% final concentration (w/v). The resulting extracts from four AD cases, one young control, and one aged control case were then infused unilaterally into the dorsal hippocampus and overlying neocortex of Tg2576 and non-transgenic littermate control mice. In the month

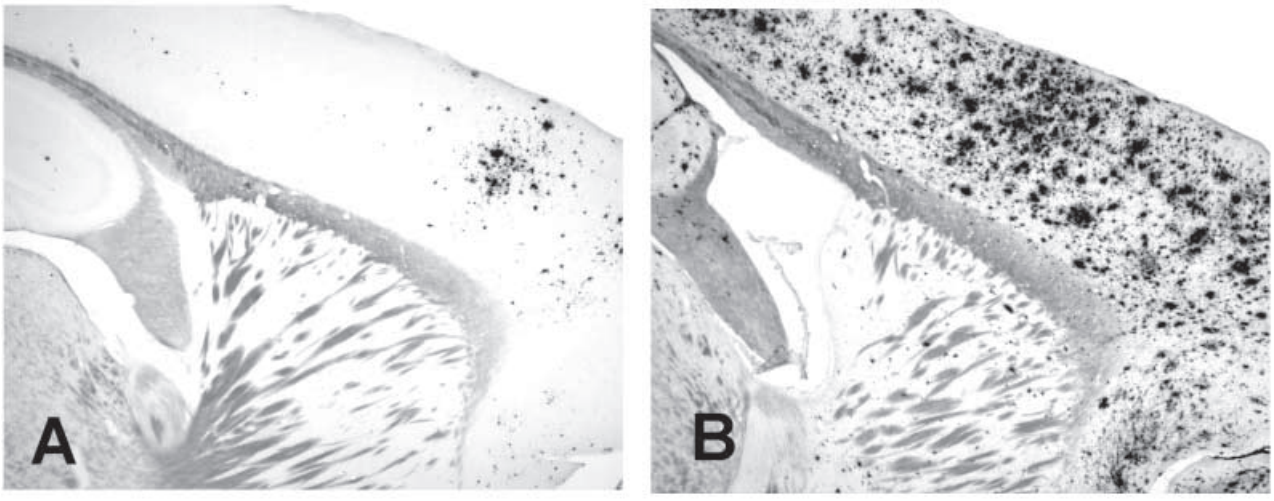

Fig. 2. β-Amyloid accumulation in 15-month-old (**A**) and in 24-month-old (**B**) Tg2576 mice. The amyloid deposits are mostly diffuse in nature, and are stained black. White matter pathways appear light gray in these black and white images. Note the massive accumulation of amyloid in the neocortex (top and right of the tissue section) at age 24 months. Aβ-deposits also become increasingly numerous in subcortical structures of severely affected animals. Sagittal section through the anterior forebrain, rostral is to the right. Campbell-Gallyas silver stain

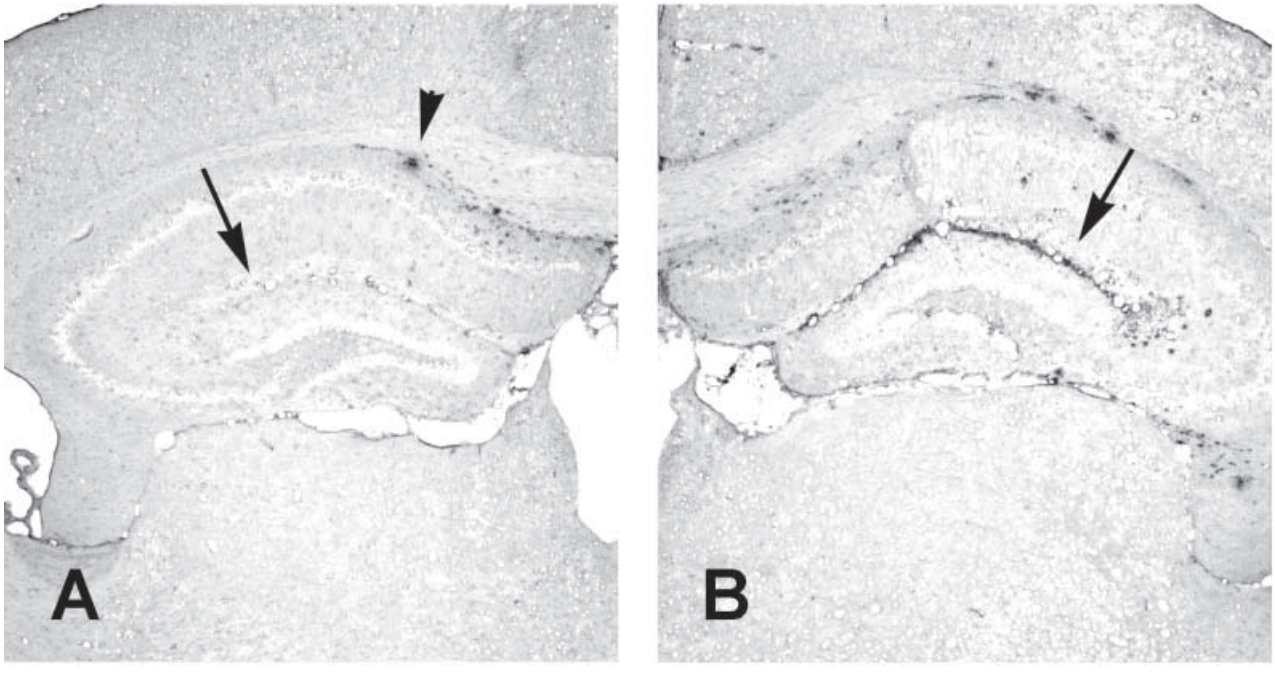

Fig. 3. Seeded, Aβ-immunoreactive amyloid deposits in the AD extract-injected hemisphere (**B**) and in the non-injected hemisphere (**A**) of an 8-month-old Tg2576 mouse injected at three months of age. Note the heavy accumulation of Aβ along the hippocampal fissure on the injected side (the fissure is indicated in each hemisphere by an arrow). Note also small patches of Aβ-immunoreactivity extending along the ventral corpus callosum into the non-injected hemisphere (arrowhead denotes one deposit). The amyloid burden was approximately ten times greater in the injected hemisphere than in the non-injected hemisphere (see Kane et al., 2000). Coronal section, antibody 4G8 immunostain for Aβ

immediately following injection, there was no evidence of Aβ immunoreactivity. Five months later (i.e., at eight months of age) the transgenic mice that had been injected with AD brain homogenate had pronounced deposition of diffuse and compact Aβ deposits primarily in the injected hemisphere (Fig. 3). The non-transgenic control mice were negative, as were transgenic mice injected with the brain homogenate from a young, control human. Interestingly, homogenate from a non-demented aged human with mild β-amyloidosis stimulated a small amount of Aβ deposition in Tg2576 mice (Kane et al., 2000).

To assess the long-term effects of seeding, we recently studied mice one year post-infusion, at the age of 15 months. These mice had abundant β-amyloid deposition bilaterally (as expected in Tg2576 mice of this age) that was concentrated most heavily in the injected hemisphere. There was also evidence of hyperphosphorylated tau (antibody AT8)-immunoreactive axons in the surgery-damaged corpus callosum, particularly where this white matter pathway was beset by amyloid deposits (Walker et al., submitted). In the five-month seeded mice, we had observed, in the ipsilateral entorhinal cortex of some AD extract-injected mice, a small patch of Aβ-immunoreactive microglial cells that intermingled with neurons projecting to the extract-injection site (Walker et al., submitted). At one year post-injection, the ipsilateral entorhinal cortex contained a much greater plaque load than did the contralateral entorhinal cortex, suggesting that axonal transport mechanisms contribute to the spread of the seeded pathology.

Our data thus show that β-amyloid deposition can be actuated by exogenous material. Studies are currently in progress to identify the necessary factors in the brain extract for seeding Aβ *in vivo*. This seeding paradigm can provide insights into the early pathogenesis of β-amyloidosis and related pathologies, and may also reveal important commonalities in the mechanisms whereby diverse proteopathies are instigated and propagated in the brain.

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