Neuropathologic Changes in Alzheimer's Disease

Gary L. Wenk, Ph.D.

Alzheimer's disease is characterized by degenerative changes in a variety of neurotransmitter systems. These include alterations in the function of the monoaminergic neural systems that release glutamate, norepinephrine, and serotonin as well as a few neuropeptide-containing systems. Alzheimer's disease is also characterized by degenerative changes in selected brain regions, including the temporal and parietal lobes and restricted regions within the frontal cortex and cingulate gyrus. The degeneration of these systems may underlie specific aspects of the dementia associated with Alzheimer's disease. A major problem in Alzheimer's disease research today is that none of the current hypothesized mechanisms are able to explain the cellular and regional distribution pattern that characterizes the neuropathology of Alzheimer's disease. This article summarizes the nature and extent of the changes associated with neural systems, possible treatment approaches, and a potential mechanism involving chronic neuroinflammation to explain the pattern of neuropathologic changes in Alzheimer's disease.
(J Clin Psychiatry 2003;64[suppl 9]:7–10)

The loss of forebrain cholinergic neurons commonly seen in Alzheimer's disease tends to be extensive and certainly underlies aspects of the dementia. Cell loss, senile plaques, and neurofibrillary tangles appear regularly in the neocortex, hippocampus (including the entorhinal cortex), amygdala, and basal nucleus of Meynert in Alzheimer's disease. To a lesser extent, these features appear in the medial nucleus of the thalamus, dorsal tegmentum, locus ceruleus, paramedian reticular area, and the lateral hypothalamic nuclei.[1] Understanding that specific regions in the brain are more vulnerable to these neuropathologic changes than others and that not all the neurotransmitter systems are involved helps researchers target what mechanisms may underlie these changes. Plaques forming in the cortex, for example, seem to involve and ultimately destroy specific neurotransmitter systems.

Because brain tissue from patients with Alzheimer's disease can be studied only after death, it has been difficult to establish directly the sequence of pathogenic events in the disorder.[2] What is known, however, is that the first component of the disease cascade is a dysfunctional gene that produces amyloid. Amyloid produces inflammation around the senile plaques, and the inflammation sets up a cascade of seemingly uncontrollable changes (more so in the aged brain than in the young brain). These changes lead to the up-regulation of the production of prostaglandins, which is where anti-inflammatory therapy may play a role, and to the increase in the extracellular concentration of glutamate. The increased level of glutamate contributes to the ultimate death of neurons.

DEGENERATIVE CHANGES

One of the most consistent changes in Alzheimer's disease is a reduction of the activity of choline acetyltransferase in the cerebral cortex and hippocampus (Table 1).[3] Selective loss of cholinergic neurons occurs in the cholinergic projection pathway from deep nuclei located in the septum near the diagonal band of Broca to the hippocampus, and from the nearby basal nucleus of Meynert, which provides the major cholinergic input to the neocortex and to the cerebral cortex.[1] The basal nucleus of Meynert undergoes profound neuron loss in Alzheimer's disease. The neocortex exhibits a loss of cholinergic fibers and receptors and a decrease of both choline acetyltransferase and acetylcholinesterase enzyme activity. Reductions also occur in the corticotropin-releasing factor and somatostatin, both of which have been identified within degenerating neurites of the neuritic plaque. Glutaminergic neurons are also involved, which account for many of the large neurons lost in the cerebral cortex and hippocampus in Alzheimer's disease.[1]

Since the symptoms of Alzheimer's disease are associated with an altered cholinergic function,[3] research has focused on the basal forebrain cholinergic system and some of the neurotransmitters that originate in the midbrain, such as dopamine, norepinephrine, and serotonin.[4] Why these neurotransmitters change and what mechanisms underlie the degeneration of these specific systems are

From the Division of Neural Systems, Memory & Aging, The University of Arizona, Tucson.
This article is derived from the teleconference "Noncholinergic Treatments for Alzheimer's Disease," which was held November 25, 2002, and supported by an unrestricted educational grant from Forest Laboratories.
Correspondence and reprints to: Gary L. Wenk, Ph.D., The University of Arizona, 350 Life Sciences N., Tucson, AZ 85724 (e-mail: gary@nsma.arizona.edu).

Table 1. Neuropathologic Factors of Alzheimer's Disease

Decreased choline acetyltransferase activity
Selective loss of cholinergic neurons
Decreased corticotropin-releasing factor and somatostatin within degenerating neurites and plaques
Increased accumulation of extracellular β-amyloid plaques
Increased accumulation of neurofibrillary tangles

still unknown. Why, for example, are concentrations of plaques and senile plaques seen in the amygdala, the hippocampus, and certain regions of the cortex, but not in basal ganglia and cerebellum?

Genetic Factors

Specific genes—mutant genes—may be one answer to the question of plaque specificity. Four genes that cause or predispose to Alzheimer's disease have been identified to date (amyloid precursor protein [APP], apolipoprotein [ApoE4], presenilin 1 [PS-1], and presenilin 2 [PS-2]).[5] Mutations or polymorphisms in these genes cause excessive cerebral accumulation of the β-amyloid protein and subsequent neuronal and glial pathology in brain regions important for memory and cognition (cerebral cortex and hippocampus).[5]

Numerous attempts to produce animal models of Alzheimer's disease have focused on the consequences of the destruction of cholinergic neurons within the nucleus basalis magnocellularis, which is the region of the rat brain that is analogous to the nucleus basalis of Meynert in humans.[6] Dynamic information about the disease cascade has been revealed by the study of mice transgenic for mutant human APP. Matsuoka et al.[7] found that mice carrying both mutant genes (PS/APP) develop Alzheimer's-like deposits composed of β-amyloid at an early age.

By examining cholinergic alterations in transgenic mice (APP23), Boncristiano et al.[4] found modest decreases in cortical cholinergic enzyme activity compared with activity in age-matched wild-type mice. They concluded, therefore, that the severe cholinergic deficit in Alzheimer's disease is caused both by the loss of cholinergic basal forebrain neurons and locally by cerebral amyloidosis in the neocortex. Still, mutant genes do not explain the selective neurotransmitter vulnerability, e.g., the loss of acetylcholine neurons within the basal forebrain or why the neuropathology occurs within the temporal cortex, hippocampus, and cingulate gyrus.

Neuroinflammation

Inflammation clearly plays a critical role in the pathogenesis of Alzheimer's disease.[8–14] Damaged neurons and neurites and highly insoluble β-amyloid peptide deposits and neurofibrillary tangles provide stimuli for inflammation.[8]

Chronic neuroinflammation may contribute to the initial stages of cellular dysfunction, increase cellular vulnerability, cause a decline in choline acetyltransferase activity, deplete acetylcholine, and determine the neuroanatomy of the pathology or the appearance of activated microglia. In an early report of activated microglia in dementia, Cagnin et al.[15] studied 15 healthy individuals (age range, 32–80 years), 8 patients diagnosed with probable Alzheimer's disease (DSM-IV criteria), and 1 patient with minimal cognitive impairment. Positron emission tomography and [^{11}C](R)-PK11195, a specific ligand for the peripheral benzodiazepine binding site, were used to provide quantitative in vivo measurements of glial activation. Regional binding did not substantially change with age in healthy individuals, except in the thalamus, where an age-dependent increase was found. Patients with Alzheimer's disease, on the other hand, showed significantly increased regional [^{11}C](R)-PK11195 binding in the entorhinal, temporoparietal, and cingulate cortex. In vivo detection of increased binding in Alzheimer's type dementia suggests that microglial activation is an early event in the pathogenesis of Alzheimer's disease that appears in brain regions that later show the greatest degree of atrophy.[15]

Neurotransmitter Systems

Excessive stimulation of glutamate receptors, in particular the *N*-methyl-D-aspartate (NMDA) receptor, seems intimately involved in the death of forebrain cholinergic neurons.[6] To the degree that abnormal glutamatergic function is causative in Alzheimer's disease, effective pharmacologic antagonism of the NMDA receptor, particularly by open channel antagonists, may be able to slow the progression of Alzheimer's disease.[6] If selective antagonists are used at the NMDA-receptor site, cholinergic neurons can be rescued from the consequences of chronic neuroinflammation of the brain.[6] There may be a connection, then, between the presence of amyloid and the presence of inflammation commonly seen in Alzheimer's disease.

INTERVENTIONS

Cholinesterase Inhibitors

As Alzheimer's disease progresses, acetylcholine decreases in areas of the brain associated with amyloid deposition.[3] To enhance cholinergic function, then, cholinesterase inhibitors are administered. The cholinesterase inhibitors tacrine, donepezil, rivastigmine, and galantamine are the only agents approved for the treatment of Alzheimer's disease worldwide.[3] These agents inhibit the enzyme acetylcholine in the brain by inhibiting the enzyme acetylcholinesterase.

Nonsteroidal Anti-Inflammatory Drugs

The study of transgenic mice expressing mutant β-amyloid APP found in familial Alzheimer's disease produced the first evidence that nonsteroidal anti-inflammatory drugs (NSAIDs), a group of pharma-

cologically related compounds with analgesic, antipyretic, and anti-inflammatory properties, can modify the generation of the amyloid peptide in brain.[16] Transgenic mice developed amyloid plaques with inflammatory activity that models Alzheimer's disease amyloid pathology.[16] Treating these mice with the NSAID ibuprofen reduced brain inflammatory activity and also reduced plaque deposition. This reduction in plaques occurred without change in APP. These results suggest that NSAID treatment may influence the processing of APP into amyloidogenic peptides.[14]

My colleagues and I recently studied the effects of nitric oxide flurbiprofen (NFP), a novel NSAID, in reducing brain inflammation in young rats.[17] NFP was administered daily, concurrently with galantamine, an acetylcholinesterase inhibitor that promotes cholinergic function. NFP therapy reduced microglial activation, and these effects were not attenuated by galantamine therapy. These results suggest that anti-inflammatory therapies might be effective in slowing the onset of the symptoms of Alzheimer's disease.

Studies comparing the effects of chronic neuroinflammation, produced by infusing the proinflammagen lipopolysaccharide (LPS) into the hippocampus of rats, on memory have supported the theory that the effects of NSAIDs on chronic neuroinflammation are age dependent.[11,12] When NFP was infused, the neuroinflammatory reaction was attenuated and the inflammation-induced memory deficit was reduced.[11] Interestingly, chronic LPS infusions impaired performance of young rats but not adult or old rats. Treatment with NFP improved the performance of LPS-infused young rats, but not LPS-infused adult and old rats. LPS infusions increased the number of activated microglia in young and adult rats but not old rats. These results suggest that NSAID therapies should be initiated in adults at high risk for Alzheimer's disease before age-associated inflammatory processes within the brain have a chance to develop.[11]

Results from another study[10] suggest that prostaglandins contribute to the degeneration of forebrain cholinergic neurons. Again, LPS was infused into the basal forebrain of young rats. Choline acetyltransferase activity decreased and the number of activated microglia increased within the basal forebrain region. Treatment with NSAIDs attenuated the toxicity of the inflammation on cholinergic cells, but did not provide neuroprotection for the cholinergic neurons.

NSAIDs inhibit cyclo-oxygenase (COX) enzymes and at high doses inhibit local inflammation by blocking the induction of interleukin pathways that rely on prostaglandin synthesis.[18] Two enzyme isoforms, COX-1 and COX-2, are encoded by distinct genes on different chromosomes,[19–23] but they share approximately 80% sequence homology and have similar catalytic activity.[18] COX-2, specifically, is induced at sites of local inflammation in the brain (at least in the periphery).[18]

In a review of the literature on the use of antioxidants, cholinergic agents, and NSAIDs in Alzheimer's disease, Prasad et al.[24] suggest that a combination of NSAIDs and multiple micronutrients, including antioxidants, may be more effective than the individual agents in prevention of Alzheimer's disease. Effectiveness is further enhanced when a cholinergic agent is added to this combination. Agents that prevent the formation of plaques or dissolve these plaques may further enhance the efficacy of the above combination treatment strategy.

Other Interventions

Memantine, a low affinity NMDA receptor antagonist, has been used clinically in Europe for the treatment of patients with various forms and stages of dementia for many years.[6,25] A combination of therapeutic approaches utilizing both memantine and an acetylcholinesterase inhibitor may be beneficial at both slowing the progression of Alzheimer's disease, i.e., by providing neuroprotection from glutamate, as well as enhancing daily cognitive performance, i.e., by augmenting the function of forebrain cholinergic neurons.[6] Memantine, then, should be effective at all 3 stages of Alzheimer's disease—as monotherapy in the early stage, in concert with NSAID treatment and acetylcholinesterase inhibitors at the prodromal stage and also at the late symptomatic stage, possibly in combination with the next generation of vaccines.

Sigurdsson et al.[26] have suggested that vaccine-based therapy using compounds that target β-amyloid holds the most promise as therapy for patients with Alzheimer's disease. In vivo studies of vaccinations comprised of aggregated/fibrillar β-amyloid$_{1–42}$ in transgenic APP mice before the onset of Alzheimer's disease neuropathology have shown reductions in amyloid plaques and neuritic dystrophy. Concerns about the safety of this approach in humans (e.g., immunization with β-amyloid$_{1–42}$ crosses the blood-brain barrier, may seed fibril formation, and is fibrillogenic) led Sigurdsson et al. to develop a synthetic non-amyloidogenic peptide homologous to β-amyloid that confers a much lower risk of toxicity in humans. Immunization of this peptide in transgenic APP mice for 7 months reduced cortical and hippocampal brain amyloid burden by 89% and 81%, respectively.[27] Further, brain inflammation was reduced in these mice. Although more studies are needed, these promising findings suggest that immunization with a non-amyloidogenic/nontoxic β-amyloid derivative may be a safe approach to reducing amyloid burden in Alzheimer's disease.[26]

CONCLUSION

Alzheimer's disease is a complex disorder that affects a number of neurochemical systems in the brain, has a genetic component, and involves chronic neuroinflammation. Effectively treating such a complex disorder

with an agent that affects only 1 of the systems that show impairment is inadequate. When we understand the role various mechanisms play and what other systems are affected, we can begin to target these mechanisms with therapy. Despite unresolved questions, progress is being made in delineating the disease cascade, and several discrete targets for treatment have been identified.

To be effective, treatment with NSAIDs must begin well before the symptoms of Alzheimer's disease appear in order to slow the progression of the disease. If treatment with NSAIDs is delayed, the intervention is typically ineffective. Intervention at each stage can have a significant effect on the onset of symptoms and can essentially slow the progression and possibly delay significant onset of Alzheimer's disease to a later age. Understanding the inflammatory and immunoregulatory processes of Alzheimer's disease may enable researchers to develop anti-inflammatory approaches that may not cure Alzheimer's disease but may slow the progression or delay onset.[8,17,18,28] Therapies can then be rationally designed and possibly be more effective than those currently available.

Drug names: donepezil (Aricept), galantamine (Reminyl), ibuprofen (Motrin and others), rivastigmine (Exelon), tacrine (Cognex).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Katzman R. The dementias: Alzheimer disease. In: Rowland LL, ed. Merritt's Textbook of Neurology. 8th ed. Philadelphia, Pa: Lea & Febiger; 1989:637–644
2. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 2001;81:741–766
3. Mullan M. Genetic contributions to causes of Alzheimer's disease: current perspectives and future directions. pp 307–309. In: New Insights Into Genetics and Pathophysiology of Alzheimer's Disease: What Are the Clinical and Therapeutic Implications? [ACADEMIC HIGHLIGHTS] J Clin Psychiatry 2000;61:307–315
4. Boncristiano S, Calhoun ME, Kelly PH, et al. Cholinergic changes in the APP23 transgenic mouse model of cerebral amyloidosis. J Neurosci 2002;22:3234–3243
5. Selkoe DJ, Podlisny MB. Deciphering the genetic basis of Alzheimer's disease. Annu Rev Genomics Hum Genet 2002;3:67–99
6. Wenk GL, Quack G, Moebius HJ, et al. No interaction of memantine with acetylcholinesterase inhibitors approved for clinical use. Life Sci 2000;66:1979–1983
7. Matsuoka Y, Picciano M, Malester B, et al. Inflammatory responses to amyloidosis in a transgenic mouse model of Alzheimer's disease. Am J Pathol 2001;158:1345–1354
8. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21:383–421
9. Rogers J. Inflammation as a pathogenic mechanism in Alzheimer's disease. Arzneimittelforschung 1995;45:439–442
10. Wenk GL, McGann K, Mencarelli A, et al. Mechanisms to prevent the toxicity of chronic neuroinflammation on forebrain cholinergic neurons. Eur J Pharmacol 2000;402:77–85
11. Hauss-Wegrzyniak B, Vraniak P, Wenk GL. The effects of a novel NSAID on chronic neuroinflammation are age dependent. Neurobiol Aging 1999;20:305–313
12. Willard LB, Hauss-Wegrzyniak B, Wenk GL. Pathological and biochemical consequences of acute and chronic neuroinflammation within the basal forebrain cholinergic system of rats. Neuroscience 1999;88: 193–200
13. Hauss-Wegrzyniak B, Lynch MA, Vraniak PD, et al. Chronic brain inflammation results in cell loss in the entorhinal cortex and impaired LTP in perforant path-granule cell synapses. Exp Neurol 2002;176:336–341
14. Weggen S, Eriksen JL, Das P, et al. A subset of NSAIDs lower amyloidogenic Ab42 independently of cyclooxygenase activity. Nature 2001;414:212–216
15. Cagnin A, Brooks DJ, Kennedy AM, et al. In-vivo measurement of activated microglia in dementia. Lancet 2001;358:461–467
16. Lim GP, Yang F, Chu T, et al. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. J Neurosci 2000;20:5709–5714
17. Wenk GL, Rosi S, McGann K, et al. A nitric oxide-donating flurbiprofen derivative reduces neuroinflammation without interacting with galantamine in the rat. Eur J Pharmacol 2002;453:319–324
18. Zanadi PP, Breitner JCS. Do NSAIDs prevent Alzheimer's disease? and, if so, why? the epidemiological evidence. Neurobiol Aging 2001;22: 811–817
19. Fletcher BS, Kujubu DA, Perrin DM, et al. Structure of the mitogen-inducible TIS10 gene and demonstration that the TIS10-encoded protein is a functional prostaglandin G/H synthase. J Biol Chem 1992;267: 4338–4344
20. Kujubu DA, Fletcher BS, Varnum BC, et al. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. J Biol Chem 1991;266:12866–12872
21. O'Banion MK. Cyclooxygenase-2: molecular biology, pharmacology, and neurobiology. Crit Rev Neurobiol 1999;13:45–82
22. O'Banion MK, Winn VD, Young DA. cDNA cloning and functional activity of a glucocorticoid-regulated inflammatory cyclooxygenase. Proc Natl Acad Sci U S A 1992;89:4888–4892
23. O'Banion MK, Sadowski HB, Winn V, et al. A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase-related protein. J Biol Chem 1991;266:23261–23267
24. Prasad KN, Cole WC, Prasad KC. Risk factors for Alzheimer's disease: role of multiple antioxidants, non-steroidal anti-inflammatory and cholinergic agents alone or in combination in prevention and treatment. J Am Coll Nutr 2002;21:506–522
25. Kilpatrick GJ, Tilbrok GS. Memantine. Curr Opin Investig Drugs 2002;3:798–806
26. Sigurdsson EM, Wisniewski T, Frangione B. A safer vaccine for Alzheimer's disease? Neurobiol Aging 2002;23:1001–1008
27. Sigurdsson EM, Scholtzova H, Mehta PD, et al. Immunization with a nontoxic/nonfibrillar amyloid-beta homologous peptide reduces Alzheimer's disease-associated pathology in transgenic mice. Am J Pathol 2001;159:439–447
28. Aisen PS. Anti-inflammatory agents in Alzheimer's disease. Curr Neurol Neurosci Rep 2002;2:405–409