Aging of the Brain and Alzheimer’s Disease

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Introduction
Over the past decade significant advances have been made in understanding the causes and mechanisms of dementia syndromes in humans, particularly Alzheimer’s disease (AD), the most common cause of dementia in older adults. Herein, we review the features of age-associated alterations in memory and cognition, the biology of AD, and therapies presently available for AD.

Cognitive and Memory Impairments in the Elderly
Although many older individuals remain intellectually intact, a significant number of the elderly show declines in memory and cognitive abilities. Alterations are often mild, occur relatively late, and involve speed of learning, complex problem solving, the ability to retain large amounts of new information, and visuospatial skills. Vocabulary, information storing, and comprehension skills remain relatively stable into old age. Some older individuals have mild cognitive impairments (MCI) in which memory loss exceeds that expected for age, but they do not meet criteria for AD. Many investigators regard this syndrome as a transitional state between the normal functional abilities of older persons and the syndrome of early AD. Thus MCI is a high-risk condition for the development of dementia. However, there may be considerable heterogeneity among subjects with MCI (i.e., interindividual variability in the rate and severity of progression). The variable alterations in memory with age makes it sometimes difficult to determine, after a single examination, whether an individual with mild age-associated memory impairments will remain relatively stable or will show progression to severe dementia. The most accurate approach to analyze the significance of age-related abnormalities is to measure cognitive abilities and memory performance repeatedly in the same patient over a period of time.

Neuropsychologic tests valuable in predicting AD are delayed recall (recently learned information) assembled by California Verbal Test and Wechsler Memory Scale and executive functions (ability to organize and plan) measured by the Trail-Making Test and Self-Ordering Test. Imaging studies, including magnetic resonance imaging (MRI) (with measurements of volumes of entorhinal cortex, hippocampus, banks of superior temporal sulcus, and caudal anterior cingulate) and positron emission tomography (with measures of glucose use or visualization of binding of labeled $\alpha\beta$ amyloid ligands) can help to predict which of these individuals are entering early stages of AD. Genetics studies of ApoE status (particularly of E4 allele) can predict 66% of individuals with memory problems who will develop AD (see following).

The brains of cognitively intact older individuals may show senile plaques and neurofibrillary tangles and loss of subset of neurons, but these lesions are usually much less frequent and more restricted than those that occur in cases of AD.

Alzheimer’s Disease: Clinical Features, Diagnostic Studies, and Neuropathology
AD is the most common cause of senile dementia, a term that refers to a syndrome occurring in older individuals that results in memory loss and cognitive impairments of sufficient severity to interfere with social, occupational, and personal functions. This type of dementia affects more than 4 million people in the United States. Because of increased life expectancy and the postwar baby boom, the older population is the fastest growing segment of our society. During the next 25 years, the number of people with AD in the United States will triple, as will the cost of treating them. Thus AD is one of society’s major public health problems.

Most individuals with sporadic AD exhibit the first clinical signs during their seventh decade. However, some cases develop in midlife; in these cases a family history of the disease is more likely. In both the sporadic and familial forms of AD, affected individuals show abnormalities of memory, problem solving, executive functions language, calculation, visuospatial perceptions, judgment, and behavior. Some patients develop psychotic symptoms, such as hallucinations and delusions. In these patients, mental functions and activities of daily living are increasingly impaired. In the late stages, these individuals are mute, incontinent, bedridden, and usually die of intercurrent medical illnesses. Other causes of dementia include: cerebrovascular disease, alone or in combination with AD; Lewy body dementia; Parkinson’s disease; alcoholism; drug
intoxications; infections, such as human immunodeficiency virus (HIV) infection (i.e., acquired immunodeficiency syndrome (AIDS)) and syphilis; brain tumors; vitamin deficiencies (e.g., B₁₂); thyroid disease; and a variety of other metabolic disorders.

To make a diagnosis of AD, clinicians rely on: histories from patients and informants; physical, neurologic, and psychiatric examinations; neuropsychologic testing; laboratory studies; and a variety of diagnostic tests, including neuroimaging studies. The clinical profile, in concert with a variety of laboratory assessments, allows the clinician to make a diagnosis of possible or probable AD. Alterations in levels of specific proteins in the serum or cerebrospinal fluid, such as the Aβ peptide and tau, may eventually prove useful in diagnosis. Levels of Aβ in cerebral spinal fluid (CSF) are usually low in full-blown AD, while levels of tau tend to be higher in cases of AD versus controls. However, values may vary among individuals, and single measures are not of great diagnostic value. The presence of the ApoE-4 allele confers risk in late-onset disease (see following), and ApoE genotyping is a useful research tool but is not helpful for routine diagnostic purposes. Computerized tomography (CT) or MRI, performed on the majority of patients with this syndrome, can identify other potentially treatable diseases and may detect abnormalities, particularly in the medial temporal lobe (atrophy of hippocampus and entorhinal cortex), that may have predictive values for establishing a diagnosis of AD. In AD, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) usually show decreased regional blood flow in the parietal and temporal lobes with involvement of other cortical areas at later stages. At present, except for brain biopsy, no tests definitively establish the diagnosis of AD in living subjects. It is extremely important for the physician to exclude other causes of dementia, because some other types of dementia respond to specific treatments. However, AD is a disorder for which no mechanism-based therapies yet exist. Only symptomatic treatments are available at present (see following).

AD is characterized by a series of abnormalities in the brain that selectively involve neurons in the neocortex, entorhinal area, hippocampus, amygdala, nucleus basalis, anterior thalamus, and several brain stem monoaminergic nuclei (in particular the locus coeruleus and raphe complex). Dysfunction and death of neurons in these regions and circuits are reflected by the presence of cytoskeletal abnormalities in these cells (neurofibrillary tangles), loss of neurons in these regions, the presence of neuritic plaques in brain regions receiving inputs from these nerve cells, and reductions in synaptic markers of these transmitter systems in target fields of these neurons.

Affected nerve cells often exhibit alterations in the cytoskeleton. Neurofibrillary tangles (filamentous inclusions in the cell bodies and proximal dendrites), contain paired helical filaments (PHF) and 15 nm straight filaments comprised of hyperphosphorylated isoforms of tau, a microtubule-binding protein. Other fibrillar tau-related abnormalities include neuropol threads (in dendrites) and neurites (predominantly in distal axons/terminals). It is likely that all of these fibrillar inclusions result from common mechanisms. Because the cytoskeleton is essential for maintaining cell geometry and for the intracellular trafficking and transport of proteins and organelles, it is likely that disturbances of the cytoskeleton are associated with impaired axonal transport and thereby they compromise the functions and viability of neurons. Eventually, affected nerve cells die (possibly by apoptosis), and intracellular neurofibrillary tangles are left behind as ‘tombstones’ of the nerve cells destroyed by disease. As these neurons dysfunction and die, their synapses degenerate in regions of the brain critical for the normal functions of cognition and memory.

The brain regions affected by AD contain neuritic, or senile, plaques comprised of neurites displayed around extracellular deposits of the Aβ-amyloid protein (Aβ40 and 42). Fibrillar, amyloid aggregates are formed of β-pleated sheet Aβ peptides that are birefringent when stained with Congo Red (or thioflavin) and viewed in polarized light (or fluorescence). Aβ, an ~4-kDa β-pleated sheet peptide, is derived from a larger precursor protein, termed the amyloid precursor protein (APP), encoded by a gene localized to the mid-portion of the long arm of human chromosome 21. APP, an integral membrane glycoprotein, has three principal isoforms of 695, 751, and 770 amino acids, all of which contain the Aβ sequence. In cell culture, a fraction of cell-surface APP is also internalized to generate Aβ peptides, which are then secreted. Aβ1-40 and low levels of Aβ1-42(43) appear in the conditioned medium of cultured cells and in normal human cerebrospinal fluid. Aβ1-42(43) appears to be the pathogenic peptide; these species are more fibrillogenic and toxic than Aβ1-40 and provide a substrate for amyloid aggregation and deposition. Enriched in neurons, APP, a single pass transmembrane protein, is rapidly transported anterograde, along with enzymes responsible for β- and γ-secretase activities (see following); it may serve as a kinesin cargo receptor in axons. APP is delivered to synaptic
terminals where BACE1 cleaves APP to form C-terminal derivatives; subsequently, the $\gamma$-secretase complex cleaves at positions 40, 42 and 43 to generate A$\beta$ peptides (see following). Normally released at terminals, A$\beta$42 may serve as a synaptic modulator. However, elevated concentrations of A$\beta$ at these synaptic sites, as occurs particularly in the genetic forms of disease occurring in both transgenic mice and humans, leads to the formation of A$\beta$ oligomers and multimers. These putatively toxic peptide multimers, situated in proximity to synapses, appear to interfere with synaptic functions, possibly by interacting with a class of glutamate receptors and eventually lead to neuritic degeneration of terminals. A$\beta$ species can assemble into protofibrils and then into the fibrils that are prominent components of the amyloid cores of neuritic plaques, which are complex structures surrounded by astrocytes and microglia.

These cellular abnormalities have profound clinical consequences. Abnormalities that damage the entorhinal cortex, hippocampus, and other circuits in the medial temporal cortex are presumed to be critical in memory impairments. Higher cognitive deficits, such as disturbances in executive functions language, calculation, problem solving, and judgment, are believed to be related to pathology in the neocortex. Alterations in the basal forebrain cholinergic system may also contribute to memory difficulties and attention deficits. The behavioral and emotional disturbances may reflect involvement of the limbic cortex, amygdala, thalamus, and monoaminergic systems.

**Recent Advances in Understanding the Role of $\beta$- and $\gamma$-Secretase in Processing of Amyloid Precursor Protein to Form A$\beta$ in Alzheimer's Disease**

BACE1 and BACE2, encoded by genes on chromosomes 11 and 21, respectively, have been shown to be transmembrane aspartyl proteases that are directly involved in the cleavage of APP. BACE1 mRNA is present in a variety of tissues, and BACE1 mRNA levels are high in many regions of brain. Intriguingly, BACE1 protein is only abundant in the brain, whereas it is undetectable in other nonneural tissues, such as the pancreas, where the mRNA is alternatively spliced to a smaller protein incapable of cleaving APP. BACE2 mRNA is very low in neural tissues, except for scattered nuclei in the hypothalamus and brain stem. The functions of BACE1 processed peptides generated from APP are unknown, but it has been suggested that A$\beta$ may influence synaptic activity. Interestingly, BACE1, along with APP and components of $\gamma$-secretase complex, is transported in axons and enriched at some synapses in several highly plastic structures of brain (i.e., the mossy fiber pathway originating from hippocampal granule cells and the glomeruli of olfactory bulb). These observations are consistent with the idea that A$\beta$ released in synaptic fields may influence synaptic plasticity.

BACE1 preferentially cleaves APP at the +1 and +11 sites of A$\beta$ in APP and is critical for the generation of A$\beta$. BACE1-deficient mice show no overt developmental phenotype. In cultures of BACE1$^{-/-}$ neurons, the secretion of A$\beta$1-40/42 and A$\beta$11-40/42 is abolished. Thus BACE1 is the principal neuronal $\beta$-secretase and makes proamyloidogenic cleavages. In contrast, BACE2 makes antiamyloidogenic cleavages at +19/+20 of A$\beta$. Thus BACE2 acts more like $\alpha$-secretase. Although BACE1 is critical for amyloidogenesis in brain, BACE2 does not appear to play a significant role in APP processing in neurons. In contrast to the ubiquitous expression of BACE1 mRNA in a variety of tissues, BACE1 protein is abundantly expressed in the brain but is undetectable in other nonneural tissues, such as the pancreas. Although BACE1 protein is expressed at comparable levels in most brain regions, BACE1-specific immunoreactivities are particularly localized in the hippocampus.

$\gamma$-Secretase activity is essential for the regulated intramembrane proteolysis of a variety of transmembrane proteins dependent upon a multiprotein catalytic complex, including PS and several other transmembrane proteins. It is not clear whether PS1 itself acts as an aspartyl protease, functions as a cofactor critical for the activity of $\gamma$-secretase, or exerts its influence by playing a role in trafficking of APP or other essential proteins critical for enzyme activity to the proper compartment for $\gamma$-secretase cleavage. The concept that PS1 may act as an aspartyl protease or may be a critical cofactor essential for the activity of $\gamma$-secretase is suggested by several observations: PS1 is isolated with $\gamma$-secretase under specific detergent-soluble conditions; PS1 is selectively cross-linked or photoaffinity labeled by transition state inhibitors; substitutions of aspartate residues at D257 in TM6 (although controversial) and at D385 in TM7 have been reported to reduce secretion of A$\beta$ and ultimately cleavage of Notch1 in vitro; and cells in which PS1 has been targeted show decreased levels of secretion of A$\beta$. Recent work is focused on roles of different proteins in the multiprotein catalytic complex, including (Nct), Aph-1, and Pen-2 domain. Studies of NCT null (NCT$^{-/-}$) mice and NCT$^{-/-}$ fibroblasts
have shown that NCT is an integral member of the
γ-secretase complex. Partial decreases in the level of
NCT significantly reduce the secretion of Aβ, and NCT
may be a valuable therapeutic target for AD. Aph-1 and Pen-2 are novel transmembrane proteins:
Aph1 has seven predicted transmembrane domains;
whereas Pen-2 has two predicted transmembrane
regions. These proteins interact with sel-12/PS and
aph-1/nicastrin, and their inactivation with RNAi
methods in Drosophila cells decreases γ-secretase
cleavages of APP and Notch and reduces levels of
processed PS. For these reasons, Aph-1 and Pen-2
are now believed to be critical components of
γ-secretase complex.

Genetics of Alzheimer’s Disease

Five principal risk factors exist for AD: (1) age, (2)
mutations in the presenilin 1 (PS1) gene on
chromosome 14, (3) mutations in the presenilin 2
(PS2) gene on chromosome 1, (4) mutations in the
APP gene on chromosome 21, and (5) ApoE alleles
positioned on the proximal long arm of chromo-
some 19. The presence of any of the mutations in
genes encoding APP, PS1, or PS2 causes the
disorder to occur earlier in the third through sixth
decades. Specific ApoE alleles appear to predispose
to later onset AD and some cases of late-onset
familial AD. Approximately 5–10% of cases of AD
exhibit clinical syndromes in mid-life (early onset)
and are inherited in an autosomal dominant manner.

In a small fraction of early-onset families, mis-
sense mutations have been identified in the APP
gene on chromosome 21. In all cases mutations invariably
occur within or immediately proximal to the Aβ
region. In several families the normally occurring
valine residue at position 717 (of APP-770) is
replaced with either Ile, Gly, or Phe. Cells that
express APP with mutations at position 717 secrete
increased levels of Aβ1-42,43. These longer Aβ
forms have a propensity to nucleate rapidly into
amyloid fibrils. In two large, related, early-onset AD
families from Sweden, a double mutation at codons
670 and 671 results in a substitution of the normal
Lys-Met dipeptide to Asn-Leu. Cells that express
this mutant polypeptide and secrete approximately
six- to eightfold higher levels of Aβ. In a hereditary
disease associated with Aβ deposition around blood
vessels and cerebral hemorrhage, an APP mutation
at position 693 leads to a Glu-Gln substitution
(corresponding to amino acid 22 of Aβ). This
mutation is associated with the Aβ peptide species
that are more prone to aggregate into fibrils. Thus
some of the mutations linked to AD can change the
processing of APP and influence the biology of Aβ
by increasing the production of Aβ peptides or the
amounts of the longer, more toxic Aβ42 or by
promoting fibril formation. In those pedigrees in
which missense mutations in either APP or PS genes
promote the formation of the more toxic form of
Aβ, it is highly likely that Aβ is central to the
pathogenesis of disease.

Nearly 50% of cases of early-onset familial AD
are linked to the PS1 gene (chromosome 14), which
encodes a 467-amino-acid polypeptide containing
between seven and nine transmembrane domains.
Two mutations in the PS2 gene, which encodes a
protein homologous to PS1, cause autosomal domi-
nant AD in two familial AD pedigrees. Approxi-
manly 50% of PS1 mutations occur within or
immediately adjacent to predicted transmembrane
domains. Mutant PS1 and PS2 influence APP
processing in a fashion that results in the elevated
production of Aβ1-42/43. In cultured cells and
brains (human, monkey, and mouse), PS1 accumu-
lates as an N-terminal ~28-kDa fragment and a
C-terminal ~18-kDa fragment, providing strong
support for the idea that PS1 is subject to endoprotein-
lytic processing in vivo. In view of the paucity of
accumulated full-length PS, it has been suggested
that PS fragments may be functional units. As
indicated previously, it is believed that PS are critical
components of the γ-secretase complex. PS are
highly homologous to sel-12, a gene product that
plays a role in the determination of cell fates during
development, suggesting roles for PS in these
processes. Recent work indicates that γ-secretase
cleaves APP and Notch-1, generating intracellular
domains that traffic to the nucleus where they are
involved in transcriptional activation. The results of
studies of PS1 and Nct are consistent with the
concept that they are components of γ-secretase
and the phenotype of knockout mouse embryos are the
result of failed Notch1 signaling. Mutant PS1 and
PS2 influence APP processing in a fashion that
results in the elevated production of Aβ1-42/43.

An allele of ApoE, a glycoprotein that carries
cholesterol and other lipids in the blood, has been
implicated as a risk factor for the disease in AD. At
the single ApoE locus, three alleles are expressed:
ApoE2, ApoE3, and ApoE4. The ApoE3 allele is
most common in the general population (frequency
of 0.78), whereas the allelic frequency of ApoE4 is
0.14. However, in clinic-based studies, patients with
late-onset disease (>65 years of age) have an ApoE4
allelic frequency of 0.50; thus the risk for AD is
increased by the presence of apoE4. The mechan-
isms whereby the ApoE allele type elevates the risk
for late-onset disease are not known but may reflect
differences in the abilities of ApoE isoforms to bind
Aβ and possibly influence aggregation, deposition, and/or clearance.

Animal Models of Aging and Alzheimer’s Disease

Both spontaneously occurring and genetically produced diseases in animals have now been used to model features of AD. Rhesus monkeys, *Macaca mulatta*, with an estimated life span of more than 35 years, show cognitive and memory deficits that appear at the end of the second and the beginning of the third decades of life. These animals develop virtually all of the brain abnormalities (amyloid deposits, scattered tangles, and mild reductions in synaptic/transmitter markers) observed in older humans and, to a lesser degree, patients with AD.

The ability to introduce wild-type or mutant transgenes into mice provides an opportunity to determine whether the overexpression of wild-type or mutant APP or PS transgenes causes behavioral abnormalities, Aβ deposition, and reductions in synaptic/transmitter markers. These studies are reviewed in Animal Models of Aβ amyloidogenes.

Therapies for Alzheimer’s Disease

At present no cure exists for this devastating illness. Available treatments for AD are symptomatic in nature, many present-day therapies focus on treating associated conditions, such as depression, agitation, sleep disorders, hallucinations, and delusions. One of the principal therapeutic targets has been the functions of basal forebrain cholinergic system, which is severely damaged in AD. Several strategies have been developed to influence this neurotransmitter system. Unfortunately, precursor loading (i.e., choline, lecithin) and muscarinic agonist approaches to improve cholinergic functions have not proved to be very effective. Recently, several acetylcholinesterase inhibitors, including rivastigmine, have been approved in the United States for the treatment of AD. These drugs are sometimes associated with side effects and they have, at best, a very modest effect on cognitive functions and the ability to perform activities of daily living. Clinical trials have begun to test the efficacies of anti-inflammatory compounds, estrogens, plant extracts, and antioxidants without great benefit. In an anti-glutaminergic approach in one small trial, Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been suggested to reduce the rate of clinical deterioration of patients with moderate to severe AD.

When mice harboring mutant genes linked to familial AD were injected with β42 peptide and Freund’s adjuvant, the levels of αβ and the plaque burden were reduced. Subsequently a phase 1 human clinical trial was completed with no evidence of adverse events. However, in a phase 2 trial with a significantly larger number of patients, there were at least 15 individuals who suffered adverse events, consistent with meningoencephalitis. The trial was stopped. Autopsy findings of one of these patients were interpreted to indicate that there were reductions in the numbers of αβ plaques in the cortex, but there was persistent pathologic neurofibrillarity and αβ angioopathy, as well as T-lymphocyte meningoencephalitis.

At this writing many pharmaceutical companies are using high throughput screening and molecular modeling to identify inhibitors for β- and γ-secretase activities. It is anticipated that these mechanism-based therapies may be available at the time of the next revision of this article.

See also: Alzheimer’s Disease; Alzheimer’s Disease, Molecular Genetics of; Aging of the Brain; Cognition in Aging and Age-Related Disease; Learning and Memory; Dementia; Acetylcholine [Classic Paper].

Relevant Website

http://www.alzforum.org

Further Reading


Aging of the Brain and Alzheimer’s Disease


