

The Aging Brain

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Key Words

Alzheimer's disease, amyloid, DNA damage, memory, microarray,
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Abstract

Aging is accompanied by cognitive decline in a major segment of the population and is the primary risk factor for Alzheimer's disease and other prevalent neurodegenerative disorders. Despite this central role in disease pathogenesis and morbidity, the aging of the brain has not been well understood at a molecular level. This review seeks to integrate what is known about age-related cognitive and neuroanatomical changes with recent advances in understanding basic molecular mechanisms that underlie aging. An important issue is how normal brain aging transitions to pathological aging, giving rise to neurodegenerative disorders. Toxic protein aggregates have been identified as potential contributory factors, including amyloid β -protein in Alzheimer's disease, tau in frontotemporal dementia, and α -synuclein in Parkinson's disease. However, current models of pathogenesis do not explain the origin of the common sporadic forms of these diseases or address the critical nexus between aging and disease. This review discusses potential approaches to unifying the systems biology of the aging brain with the pathogenesis of neurodegeneration.

AD: Alzheimer's disease

Cognitive decline: age-related cognitive decline may include deficits in short-term recall, spatial memory, and naming, whereas neurodegenerative disorders may involve more global and profound deficits in memory, language, reasoning, and behavior

INTRODUCTION

Neurodegenerative diseases share a common predisposing factor, the aging of the brain, which poses several basic questions. First, how can a human neuron survive for 100 years or more and remain functionally competent? Second, do human neurons possess unique mechanisms for the repair of DNA and protein damage and protection against toxic free radicals? And finally, how and when do these quality control and repair systems break down? The answers to these questions are likely to provide new insights into the aging process and may suggest directions for treating neurodegenerative diseases. This review discusses recent advances in understanding the aging brain by integrating multiple levels of analysis, from neuropsychology and pathology to molecular genetics.

COGNITIVE DECLINE IN THE AGING POPULATION

Memory Loss and Altered Activation of the Prefrontal Cortex and Hippocampus

Cross-sectional studies suggest that delayed recall of verbal information declines significantly in the normal aging human population (1). In addition, working memory and short-term recall, as well as the speed of processing information, gradually decline throughout the adult life span (2). A longitudinal study of the same individuals from 20 to 60 years of age showed that processing speed was the most affected modality (3), which may explain why normal aging individuals take longer to learn new information (4). Another feature of age-related memory loss that is highly conserved among mammalian species is reduced spatial memory, documented in aged humans (5), monkeys (6), dogs (7), and mice (8).

Long-term memory of life history and implicit memory, the unconscious response to previously encountered information, are well preserved through the normal aging process. Other age-stable measures of cognitive func-

tion include attention span, vocabulary, and verbal knowledge. Some cognitive processes may change or even improve with aging. For example, the emotional components of memories may receive greater emphasis in aged individuals than among young adults (9). Emotional stability, however, may improve with age, especially after age 65, possibly as a result of changing physiological responses of the medial prefrontal cortex (10).

Functional magnetic resonance imaging and positron emission tomography studies suggest that age-related memory changes may relate to altered functional activation of the prefrontal cortex and hippocampus. When presented with a task that involves executive function, regions of the prefrontal cortex activated in young adults typically exhibit reduced activation in aged adults (11, 12). In addition, aged adults often exhibit a broader area of activated prefrontal cortex and, in contrast to young adults, also activate the contralateral hemisphere—a phenomenon known as loss of hemispheric asymmetry. This may represent a normal compensatory response in the aging brain that is lost in mild cognitive impairment and Alzheimer's disease (AD) (13). Activation of the hippocampus is also reduced when healthy aged adults perform memory-related tasks. A cross-species study used functional magnetic resonance imaging to map hippocampal blood flow in aging rhesus monkeys, and *in situ* hybridization to map expression of Arc, an indicator of neuronal activity, in aging rats. This study suggested that the dentate gyrus was the hippocampal region most affected by aging in both species (14).

Normal age-related memory loss is distinguished from pathological memory loss by both the degree of impairment and the rate of cognitive decline. A structural correlate of pathological memory loss is volume loss in the medial temporal lobes, particularly the entorhinal cortex. This volume loss can appear at the earliest stages of mild cognitive impairment, progressing to severe atrophy in AD, but generally is not observed in normal aged individuals. In contrast, volume loss

in the prefrontal cortex can appear in normal aged individuals. There is increasing evidence, therefore, that altered brain activation on functional imaging and the appearance of early pathological changes in medial temporal lobe structures may distinguish incipient dementia from normal aging (15).

Loss of Neural Circuits and Synaptic Plasticity

Early studies suggested that substantial neuronal loss occurs in the aging neocortex and hippocampus. However, stereological methods of neuronal quantification developed in the early 1990s showed that neuronal loss was not significant in most regions of the aging neocortex and hippocampus (16). Similarly, early reports also suggested significant loss of dendritic branching in the aging hippocampus. More recent studies, however, suggest that these early reports were confounded by the inclusion of both normal and dementia cases in the analysis, and that dendritic branching could actually increase in some hippocampal regions in aged individuals (17). In contrast, the aging prefrontal cortex shows variable changes in dendritic branching patterns (16).

Aging also affects white matter density, with the greatest reductions occurring in the prefrontal cortex and anterior corpus callosum (15, 18). Reduction in white matter density, as measured by diffusion tensor imaging, correlates with changes in executive function, short-term recall, and processing speed (19). It has been suggested that white matter pathology in the aging frontal cortex might compromise circuits that integrate the prefrontal cortex, hippocampus, and striatum (15).

Loss of synaptic function is likely a contributing factor in age-related cognitive decline. Age-related changes in dendritic spine and synapse number vary among different regions of the aging neocortex and hippocampus. Decreased synapse density has been observed in the frontal cortex of aged humans

(20) and monkeys (21), and correlates with reduced activation of the prefrontal cortex when performing executive processing tasks. One of the most compelling examples of age-related synapse loss is in the hippocampal dentate gyrus in aged rats (22), a structural change that correlates with reduced excitatory postsynaptic potentials (23). Synapse loss in the dentate gyrus may also account for the spatial memory deficit in aged rats (24).

An important question is whether age-related changes in cognitive function correlate with changes in long-term potentiation (LTP) and long-term depression, electrophysiological correlates of learning. Impaired induction and maintenance of LTP have been observed in a number of studies of the aged rat hippocampus, but the nature of the defect varies among the different hippocampal subregions (23–25). Aged rats also show increased susceptibility to the induction of long-term depression (26).

Synaptic plasticity is critically dependent upon the regulation of neuronal calcium fluxes and calcium-mediated signaling pathways. It has been proposed that altered calcium homeostasis in the aged brain might contribute to altered synaptic plasticity. Voltage-activated calcium influx is increased in hippocampal CA1 neurons from aged rats and relates to increased L-type calcium channels (27). In addition to changes in calcium channels, impaired intraneuronal calcium buffering capacity may increase cytoplasmic free calcium levels. Reduced immunoreactivity for calbindin 1, a major neuronal calcium-buffering protein, has been demonstrated in basal forebrain cholinergic and cortical neurons in aging humans and nonhuman primates (28). Moreover, reduced mRNA expression of calbindin 1 and 2, calcium channel subunits, and critical calcium signaling proteins, such as calmodulin 1, have been demonstrated in the aging prefrontal cortex (29). Altered gene expression may therefore affect calcium homeostasis and synaptic plasticity in the aging brain. Moreover, the age-related decline in expression of calbindin and other calcium-binding proteins

LTP: long-term potentiation

Stress response: a general category of biological mechanisms used by cells to protect against the damaging effects of toxic agents such as ROS

may render neurons more vulnerable to a variety of toxic insults mediated by calcium, such as excitotoxicity, contributing to neuronal loss in AD and other neurodegenerative disorders (28, 30, 31).

GENE EXPRESSION AND THE SYSTEMS BIOLOGY OF BRAIN AGING

A growing number of microarray studies have been conducted to monitor genome-wide changes in gene expression associated with aging, particularly in the brain. Studies of *Caenorhabditis elegans* (32, 33) and *Drosophila* (34, 35) have examined the transcriptional effects of aging on the entire organism, whereas brain-specific studies have been conducted in mice (36, 37), rats (38), chimpanzees (39), and humans (29, 39, 40). Two primary themes arise from comparing the aging process in these six species (**Table 1**). First, age-related expression changes account for only a small fraction of the genes monitored in each of the six species. This observation lends support to the idea that specific biological pathways are being altered as a result of the aging process, as opposed to a genome-wide dysregulation of transcription. Second, although the underlying cause has not been identified, there is an age-associated induction of stress response genes that is common to all six species. Microarray studies in four out of the six species also detected a significant reduction in the expression of mitochondrial genes, suggesting that mitochondrial dysfunction may be a source of increased stress. Some of these studies were underpowered and therefore unable to detect all of the age-related expression changes. However, the fact that some biological changes, such as the increased stress response, are detected by all of the studies, despite differing experimental designs and analyses, suggests that these changes are robust (**Table 2**).

Microarray-based studies in *Drosophila* suggest that a large number of age-related gene expression changes can be reproduced

by exposing flies to oxidative stress (34). In addition, many of the single gene mutations found to increase the life span of various model organisms, including superoxide dismutase and *p66^{shc}* in *Drosophila* (41–44), are associated with an increased resistance to oxidative stress. Likewise, caloric restriction in mice extends life span together with increased oxidative stress resistance in the brain (45). Furthermore, a subset of age-related gene expression changes in the aging mouse brain can be reversed by caloric restriction (36). Oxidative stress may therefore contribute to many of the gene expression changes associated with aging.

Transcriptional profiling of the aging human frontal cortex in a group of 30 individuals ranging from 26 to 106 years of age showed that approximately 4% of the genes expressed in the brain are age regulated (29). Age-related changes in gene expression became apparent in middle age and most pronounced after 70 years of age. Genes involved in synaptic functions that mediate memory and learning were significantly age downregulated, including glutamate receptor subunits, synaptic vesicle proteins, and members of the major signal transduction systems that mediate LTP. Notably, the synaptic calcium signaling system appears to be particularly affected with reduced expression of calmodulin 1 and 3, CAM kinase II α and IV, calcineurin B α , and multiple protein kinase C isoforms. Other prominent categories of age-downregulated genes include genes involved in vesicle-mediated protein transport and mitochondrial function. Genes involved in stress responses constitute the largest category of age-upregulated genes, including antioxidant defense, DNA repair, and immune function. These findings were confirmed in another study that showed a similar expression profile in several different cortical areas of the aging human brain (39). However, extracortical regions, such as cerebellum and caudate, showed different patterns. For cerebellum, this difference was due to fewer age-related changes, particularly in age-downregulated genes, rather than to a

Table 1 Age-related biological pathways

<i>Caenorhabditis elegans</i>	<i>C. elegans</i> and <i>Drosophila*</i>	<i>D. melanogaster</i>	<i>Rattus norvegicus</i>	<i>Mus musculus</i>	<i>Homo sapiens</i>
Whole organism (32)	Whole organism (33)	Thorax and abdomen	Hippocampus (CA1) (38)	Neocortex and cerebellum (36)	Prefrontal cortex (29)
Stress response genes	DNA repair proteins	Stress response genes (34, 35)	Oxidative stress response	Stress response genes	Stress response genes
Insulin signaling pathway	Peptidase	Oxidative stress genes (34)	Protein processing	Oxidative stress response	DNA repair genes
Tc3 transposons	Hydrolase	Proteases (35)	Inflammatory response	Heat shock genes	Inflammatory response
Heat shock genes (up then down)	Carbon-carbon lyase	Mitochondrial genes (34, 35)	Glial/structure	Proteases	Metal ion homeostasis
	Mitochondrial membrane	Metabolism (34, 35)	Myelin-related proteins	Inflammatory response	Myelin-related proteins
	Molecular function: carriers	Reproduction (34)	Metal ion homeostasis	Cathepsins	Synaptic function
	Primary active transporters		Growth/maintenance	Neural plasticity	Vesicular transport
	Ion transporters		Signal transduction (Ca ²⁺ related)	CNS development	Neuronal survival
			Negative transcriptional regulation	Hypothalamus (37)	Mitochondrial function
			Mitochondrial and metabolism		Amino acid modification
			Synaptic/neurite plasticity		Ca ²⁺ homeostasis
			Biosynthesis	Proteases	
			Signaling (extracellularly regulated)	Mitochondrial genes	Prefrontal cortex (40)
			Extracellular matrix/structure	Stress response genes	
			Protein trafficking	Neural plasticity	Glial enriched
				Synaptic transmission	Immune response/cellular defense
				ATPases	Growth factors
					Microtubule structure & function
				Cortex (37)	Neuronal enriched
					Synaptic transmission
				Proteases	Ca ²⁺ homeostasis
				Mitochondrial genes	Voltage-gated ion channels
				Stress response genes	G protein-coupled receptors
				Neural plasticity	Microtubule structure and function
				Synaptic transmission	Kinase-phosphatase
				ATPases	

Induced

Repressed

Age-upregulated (red) and age-downregulated (blue) gene categories are shown for microarray studies of aging in species from *Caenorhabditis elegans* to man. The insert shows the phylogenetic relationship and estimated time of the last common ancestor between species in millions of years (green), as previously described (163).

Table 2 Experimental designs of microarray studies of aging

Species—Tissue	Platform	Sample size	Primary analysis	Reference
<i>C. elegans</i> —whole body	cDNA arrays	6 time points (3, 4, 6–7, 9–11, 12–14, 16–19 days)	One-way ANOVA	(32)
<i>C. elegans</i> —whole body	Spotted arrays	2 time points w/4 repeats each (0, 6 day adults)	Interspecies correlations of young-old	(33)
<i>Drosophila</i> —whole body	Affymetrix arrays	2 time points w/4 repeats each (3, 23 days)	Expression differences	(33)
<i>Drosophila</i> —thorax and abdomen	cDNA arrays	7 time points w/2 repeats each (3, 10, 15, 25, 30, 40, 50 days)	Fold change cutoff	(34)
<i>Drosophila</i> —whole body	Affymetrix arrays	6 time points w/5 repeats each (7, 18, 23, 28, 42, 47 days)	ANOVA and weighted regression	(35)
Rat—hippocampus (CA1)	Affymetrix arrays	3 time points w/10 repeats each (4, 14, 24 months)	One-way ANOVA and correlation analysis	(38)
Mouse—neocortex and cerebellum	Affymetrix arrays	2 time points w/3 repeats each (5, 30 months)	Fold change cutoff	(36)
Mouse—hypothalamus and cortex	Affymetrix arrays	2 time points w/2 repeats each (2, 22 months)	Fold change cutoff	(37)
Human—prefrontal cortex	Affymetrix arrays	30 samples (26–106 years)	Significance analysis of microarrays	(29)
Human—prefrontal cortex (BA9 and BA47)	Affymetrix arrays	39 samples (13–79 years)	Correlation and multifactorial analysis	(40)

qualitatively different pattern. A similar age-related reduction in genes involved in synaptic function was reported for the aging rat hippocampus and was associated with cognitive impairment (38). These studies suggest that systems involved in higher-order cognitive functions may be compromised in the aging mammalian brain.

An important question is whether gene expression changes play a role in the susceptibility of the aging brain to neurodegenerative disorders such as AD. A microarray study of AD demonstrated a substantial number of expression changes that correlated with pathological markers and cognitive test scores; these included upregulation of signaling and tumor suppressor genes and downregulation of protein folding, metabolism, and energy-related genes (46). Profiling of several affected brain regions suggested that expression of the retromer trafficking gene *VPS35* correlated closely with the spatiotemporal pattern of AD (47). Cell culture studies using small inter-

fering RNAs to *VPS35* suggested that *VPS35* might regulate levels of the A β peptide.

Gene expression profiling can also be used to monitor the effects of therapeutic interventions in animal models. Microarray analysis of a transgenic mouse model expressing AD-linked amyloid precursor protein (APP) and presenilin-1 variants identified specific changes associated with placing the mice in an enriched environment, including upregulation of genes involved in synaptic plasticity, neurogenesis, neuronal survival, and A β degradation (48). These expression changes correlated with reduced cortical A β levels and amyloid deposits. Another study showed that pharmacologic inhibitors of histone deacetylases, which activate silenced genes, restore memory function and induce synapse formation in the p25/cdk5 mouse model of neurodegeneration (49). There is increasing evidence, therefore, that neurodegeneration and cognitive decline may be associated with specific changes in gene expression.

APP: amyloid precursor protein

DNA DAMAGE

DNA Repair and Accelerated Aging Syndromes

The association of human syndromes of accelerated aging with inherited mutations in DNA repair genes strongly implicates DNA damage in the human aging process. These disorders, known as segmental progeroid syndromes, are characterized by accelerated onset of a subset of human aging phenotypes that frequently include neurodegeneration (50). Mutations in genes involved in single- or double-strand DNA break repair result in cerebellar degenerative syndromes known as ataxias, which are manifested by movement disorders. The continued proliferation of cerebellar granule cells during postnatal development may underlie the vulnerability of the cerebellum to inherited deficits in genome stability. In contrast, inherited mutations in DNA helicases, such as Werner and Rothmund-Thomson syndromes, give rise to features of accelerated aging that often do not include nervous system dysfunction. This may reflect the role of RecQ-like helicases in recombinant events in replicating cells. Inherited mutations in enzymes involved in nucleotide and base excision repair, including xeroderma pigmentosum and Cockayne syndrome, are characterized by accelerated aging phenotypes that include neurodegeneration, mental retardation, and delayed psychomotor development (50). A new human progeroid syndrome that is caused by a loss of function mutation in the XPF-ERCC1 endonuclease that repairs helix-distorting DNA lesions was recently described. Mice deficient in ERCC1 recapitulate the progeroid features and exhibit a gene expression profile in the liver that overlaps with that of normal aging mice (correlation coefficient 0.32), suggesting that this type of DNA damage may contribute to the aging process (51). Segmental progerias typically have a short life span of less than 20 years, which may account for the absence of Alzheimer-type neuropathological

changes. However, individuals with Werner syndrome, a longer-lived progeroid syndrome, can have variable neuropathology, with one 57-year-old case reportedly showing unusually high levels of amyloid β -protein deposition in the brain (52).

Consequences of Unrepaired DNA Damage

The role of DNA double-strand breaks (DSBs) in the aging of the brain is just beginning to be explored. DSBs are repaired by two major pathways: homologous recombination, which occurs during DNA replication, and nonhomologous end joining (NHEJ), the predominant pathway in postmitotic cells such as neurons. NHEJ is mediated by a number of core factors, four of which are highly conserved from yeast to mammals, including Ku80, Ku70, Ligase IV, and XRCC4 (53). Targeted knockouts of the NHEJ factors in mice result in embryonic lethality, genomic instability, and apoptosis of neurons in the brain soon after postmitotic differentiation. Apoptosis was prevented by reducing p53 expression, suggesting that it is a manifestation of the DNA damage response (54). A broader role for p53 in neuronal aging was suggested by selectively reducing p53 activity in *Drosophila* neurons, which increased life span and resistance to oxidative stress (55).

The predominant class of oxidative DNA lesions in the aging brain are single base modifications, such as 8-oxoguanine, which increase with aging in rodent models and humans (29, 56–58). In addition, oxidative base damage to DNA and RNA is increased further in AD (59, 60). A dynamic role of DNA damage in the transcriptional regulation of genes in the aging brain was suggested by a recent study showing that oxidative DNA damage accumulates in the promoters of a subset of age-downregulated genes (29). Reduced transcription of genes involved in synaptic function, protein transport, and mitochondrial function occurred together with DNA

Double-strand break (DSB): a severe form of DNA damage involving scission of both DNA strands, usually induced by ionizing radiation or ROS

NHEJ: nonhomologous end joining

damage to these genes starting in middle age. The vulnerability of particular genes to DNA damage was recapitulated in cultures of primary neurons and neuroblastoma cells subjected to a mild oxidative stress (29). Another study also provided evidence that particular regions of the genome may be selectively vulnerable to oxidative DNA damage by showing that *in situ* staining of 8-oxoguanine is concentrated in chromosomal regions corresponding to recombination hot spots (61). Previous studies using chromatographic methods had normalized 8-oxoguanine levels to the total content of genomic DNA, concluding that median values of 0.5–4.0 oxoguanines per megabase of DNA appeared in cells (62). The implicit assumption in these measurements was that oxidative damage is randomly distributed

throughout the genome. It will be important to confirm, therefore, whether oxidative DNA damage is nonrandom, resulting in regions of the genome with concentrated damage.

Transcriptional repression may be a mechanism whereby aging neurons can silence damaged regions of the genome, enabling them to survive in the presence of unrepaired DNA damage (Figure 1). In dividing cells, unrepaired DNA damage predisposes to neoplastic transformation. Hence, mammalian cells have evolved to remove persistently damaged cells, particularly those with unrepaired DSBs, through p53-mediated apoptosis. Post-mitotic cells, however, do not undergo neoplastic transformation. Hence, it may be advantageous for the aging brain to prevent the apoptosis of irreplaceable neurons, even in the

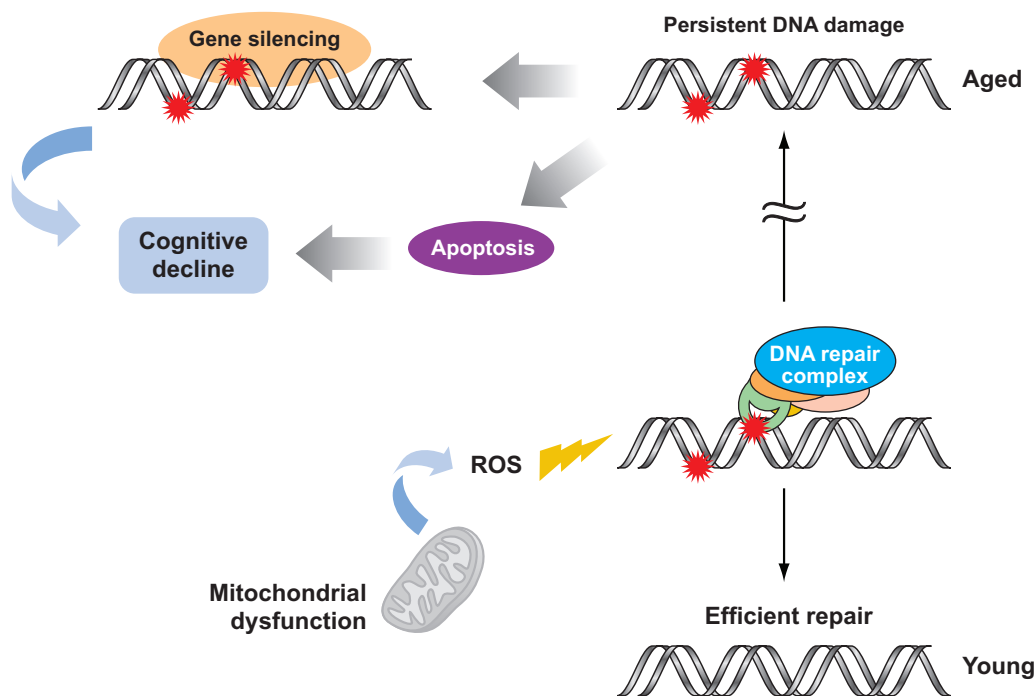


Figure 1

DNA damage and brain aging. Oxidative damage of DNA may be mediated by reactive oxygen species (ROS) derived from aging mitochondria. DNA damage is repaired efficiently in the young adult brain, but persists in the aged brain. During normal aging, this may result in the silencing of genes involved in synaptic plasticity, mitochondrial function, and protein trafficking, potentially contributing to cognitive decline. In neurodegenerative diseases, DNA damage may additionally compromise neuronal survival.

presence of unrepaired DNA damage. It will be important, therefore, to achieve a greater understanding of the regulation of the DNA damage response in the brain.

MITOCHONDRIAL DYSFUNCTION

A substantial body of evidence suggests that progressive degeneration and dysfunction of mitochondria contribute to the aging process and in particular the aging of postmitotic tissues such as brain and muscle (**Figure 2**). The projection neurons of the cerebral cortex, which degenerate in Alzheimer's dis-

ease, are highly dependent upon mitochondrial oxidative phosphorylation to support energy-intensive ion fluxes and axonal transport across long distances in the brain. Hence, this neuronal population is also quite vulnerable to mitochondrial dysfunction. Two major sites of mitochondrial damage during aging are the respiratory chain enzymes and mitochondrial DNA (63).

Generation of Reactive Oxygen Species

Inefficient electron transport through the mitochondrial respiratory complexes can lead

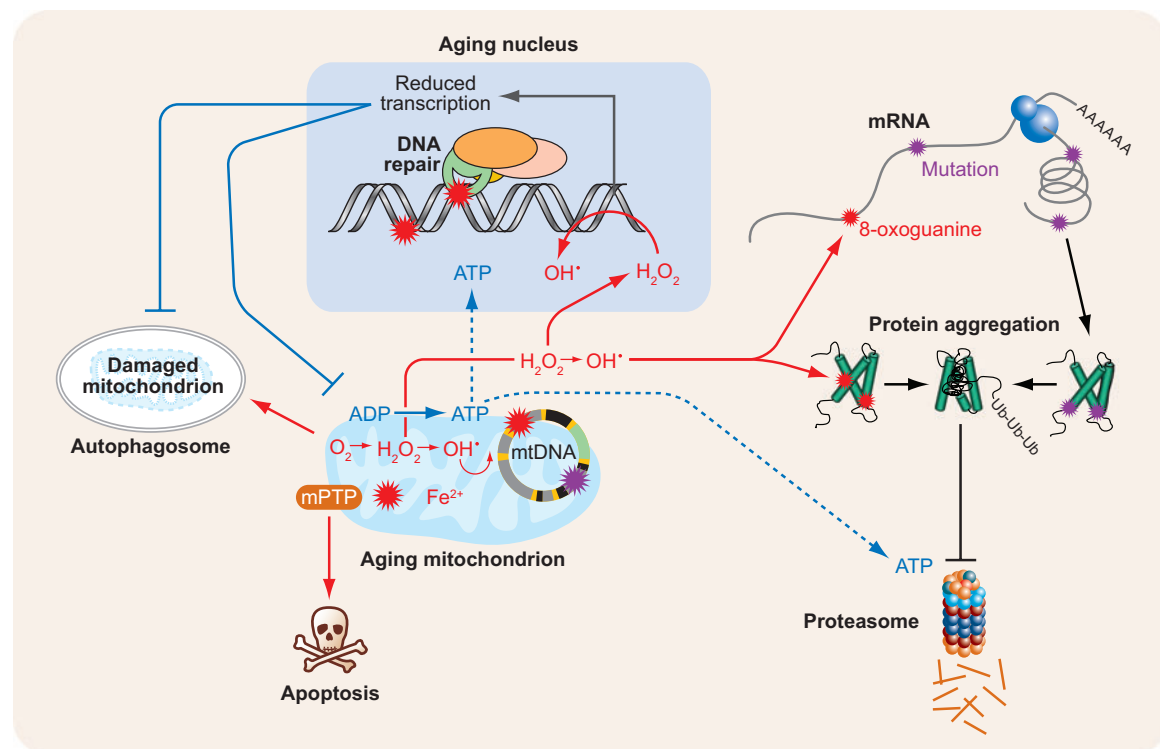


Figure 2

Global impact of mitochondrial aging. In the aging brain, reduced autophagic clearance of degenerating mitochondria and increased mitochondrial DNA (mtDNA) damage may reduce ATP levels and elevate the level of reactive oxygen species. Reactive oxygen species can further damage nuclear and mitochondrial DNA, resulting in reduced transcription, and damage RNA and protein, giving rise to protein misfolding and aggregation. Aggregated proteins may accumulate in the aging brain as a result of inefficient clearance through the autophagic and ubiquitin-proteasome pathways. Toxic protein aggregates may also lower the mitochondrial permeability transition pore (mPTP) threshold for inducing apoptosis.

Reactive oxygen species (ROS): free radicals derived from oxygen that damage macromolecules by introducing unpaired electrons

to reduced ATP synthesis and the generation of superoxide radical as a byproduct. Mitochondria are protected against endogenously generated reactive oxygen species (ROS) by a number of antioxidant defenses, including manganese superoxide dismutase, periredoxins, and redox reactions mediated by cytochrome C and cytochrome oxidase. However, there is considerable evidence that these defenses are overcome during aging, resulting in local oxidative damage to mitochondrial proteins and DNA. In addition, hydrogen peroxide, generated by the action of superoxide dismutase on superoxide radicals in mitochondria, is a stable molecule that can diffuse to other parts of the cell. Upon interaction with transition metals, hydrogen peroxide is converted by the Fenton reaction to the highly reactive and damaging hydroxyl radical. The destructive potential of this oxidative pathway is controlled through enzymatic deactivation of hydrogen peroxide by cytoplasmic glutathione peroxidase or peroxisomal catalase.

In addition to the generation of superoxide and hydrogen peroxide, the availability of redox-active iron is a major determinant of ROS-mediated cellular damage. Elevated levels of redox-active iron accumulate in the normal aging brain and in several neurodegenerative diseases (64), and may be derived in part from degenerating mitochondria. Iron is highly concentrated in mitochondria, where it is sequestered in heme and in iron sulfur clusters that serve as cofactors for respiratory enzymes. Recent studies suggest that damaged mitochondria are removed and degraded by the autophagic pathway (65). Autophagic function may be compromised in the aging human brain by reduced expression of beclin-1, a key regulator of autophagy (66), and other autophagy-related genes (T. Lu & B.A. Yankner, unpublished results). This may, in turn, lead to the accumulation of dysfunctional or degenerating mitochondria, resulting in increased ROS generation and the release of redox-active iron.

Mitochondrial DNA Mutations

A potentially important mechanism of age-related mitochondrial damage is mutation of the mitochondrial DNA. Inherited mitochondrial DNA mutations give rise to multisystem disorders that predominantly affect brain and muscle (67, 68). Furthermore, somatic mitochondrial mutations appear in the normal aging brain and in AD, together with increased oxidative DNA damage, and may be related to the proximity of mitochondrial DNA to ROS-generating respiratory enzymes and the absence of protective histones (29, 56, 59, 69–71). Decreased mitochondrial base excision repair in the aging brain may also be contributory (72). Mitochondrial DNA mutations are not randomly distributed, but rather accumulate in control regions where they impair the transcription and replication of mitochondrial DNA (71) and reduce the activity of respiratory chain enzymes (70).

To obtain greater insight into the role of mitochondrial DNA mutations in aging, two groups recently created knock-in mice expressing a mutated version of mitochondrial DNA polymerase γ (POLG) that was deficient in DNA proofreading but retained DNA polymerase activity. Mice with proofreading-deficient POLG accumulated high levels of mitochondrial DNA mutations and showed reduced respiratory chain activity (73, 74). These mutator mice were initially normal, but by 6–9 months of age showed signs of accelerated aging, including weight loss, alopecia, kyphosis, osteoporosis, anemia, cardiomegaly, and shortened life span. This was accompanied by markers of apoptosis in a variety of tissues, including activated caspase-3 and DNA fragmentation (74). However, there was a distinct absence of markers of oxidative stress or damage, suggesting that the accelerated aging phenotype might be related to increased apoptotic cell death but not to oxidative stress. This surprising result is at odds with the widely held view that mitochondrial mutations result in respiratory chain dysfunction, which causes cellular

damage through elevated ROS generation. Support for this view was provided by another study in which transgenic mouse lines were created that selectively targeted human catalase to mitochondria, peroxisomes, or the nucleus (75). Catalase targeted to mitochondria extended mouse life span by ~20% and also reduced age-related cardiac pathology and cataract development. Targeting catalase to the nucleus had no effect, although it was unclear whether this manipulation effectively reduced oxidative DNA damage. The mutator mouse and catalase targeting studies did not report any adverse effects on the nervous system, although it was unclear whether detailed neuropathological or behavioral studies were performed.

The expression of multiple nuclear-encoded mitochondrial genes declines in the aging brain, suggesting a potential nuclear contribution to age-related mitochondrial dysfunction (29, 38, 39). Reducing the expression of one of these genes, the α subunit of the F1-ATP synthase, by using small interfering RNA in neuroblastoma SH-SY5Y cells, reduced mitochondrial ATP synthesis and led to nuclear DNA damage (29). DNA damage was partially reversed by vitamin E, suggesting a role for ROS generation. These observations suggest that impaired mitochondrial function can lead to nuclear DNA damage that may, in turn, reduce the expression of nuclear-encoded mitochondrial genes, setting up a deleterious feedback loop in the aging brain.

PATHOGENESIS OF NEURODEGENERATION

The Pathology of Alzheimer's Disease

Since the identification of neurofibrillary tangles (NFTs) and amyloid plaques as pathological hallmarks of Alzheimer's disease, the role of these lesions in the pathogenesis of dementia has been debated. Early studies suggested that amyloid plaques correlated with

cognitive decline (76). Subsequent studies, however, suggested that plaques were not the closest correlate and that NFT number and synapse loss correlated more closely with cognitive test scores in individuals with dementia (77). With the advent of stereological methods for neuronal quantification, it has become apparent that neuronal loss, particularly in the CA1 field of the hippocampus and layer 2 of entorhinal cortex, distinguishes normal aging from the earliest stages of cognitive decline and Alzheimer's disease (**Figure 3**) (78–80). Although synapse loss also parallels cognitive decline (81), this may in part be secondary to neuronal loss. In particular, synapse loss in the dentate gyrus of the hippocampus, an

NFT:
neurofibrillary tangle

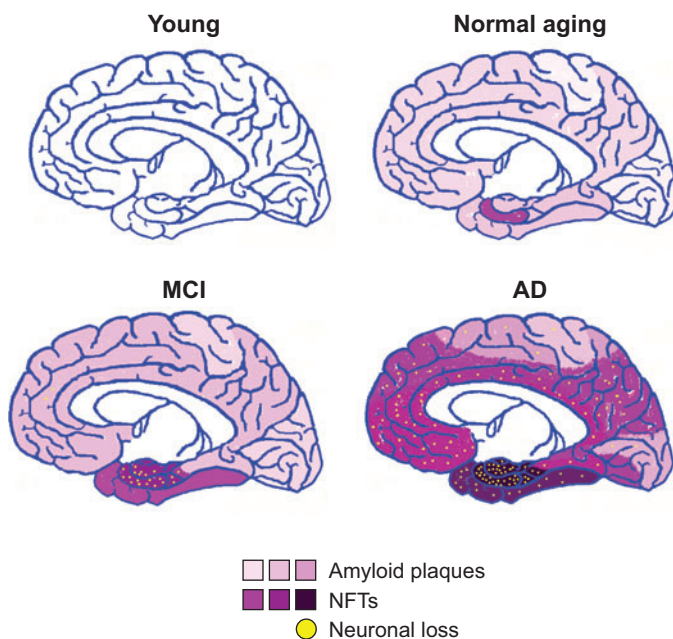


Figure 3

Progression of neuropathology in aging and Alzheimer's disease. Shown is the neuroanatomical distribution of amyloid plaques, neurofibrillary tangles (NFTs), and neuronal loss during normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD). In cognitively intact aging individuals, amyloid plaques can appear in the neocortex and hippocampus, whereas NFTs are localized predominantly to the entorhinal cortex. MCI is marked by the appearance of neuronal loss in layer 2 of the entorhinal cortex and the CA1 region of the hippocampus, and is often accompanied by an increase in the number and distribution of plaques and NFTs. Plaques and NFTs are generally more widespread in AD, although this is variable. However, the extent of neuronal and synaptic loss correlates with dementia.

early site of pathology, may be secondary to loss of afferent projection neurons in layer 2 of the entorhinal cortex (82). Taken together, these studies suggest that amyloid deposits and NFTs may not be sufficient to cause dementia, but may need to be accompanied by an as yet unidentified process that leads to neuronal cell death and the loss of synaptic connections.

Genetics of Alzheimer's Disease

Major advances in our understanding of AD and other age-related neurodegenerative disorders have come from the identification of inherited disease-causing mutations. The first genetic clue to the etiology of AD came from the observation that individuals with Down syndrome (trisomy 21) have a very high incidence of AD with early onset (83). Hence, it was suspected that a pathogenic gene was present on chromosome 21. The localization of the APP gene to chromosome 21 (84) suggested that APP might be a site of disease-causing mutations. The first disease-causing mutation in APP was identified within the amyloid β -protein domain of APP in patients with a disorder known as hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D) (85, 86). In contrast to AD, this disorder is characterized by the deposition of amyloid β -protein predominantly in blood vessel walls, resulting in mortality from multiple cerebral hemorrhages. In 1992, the first APP mutation associated with familial AD was identified (87). This mutation and others were located proximate to the C-terminal end of the A β peptide and altered its proteolytic generation such that the relative amount of a slightly longer form of A β (A β 42) was increased (88). This longer form of the A β peptide has a greater propensity to aggregate, potentially accounting for the pathogenicity of these APP mutations (89). Another APP mutation was identified proximate to the N terminus of A β that increased A β generation by augmenting the β -secretase cleavage (90, 91).

The second disease-causing gene identified in families with autosomal dominant inheritance of AD was presenilin-1 on chromosome 14 (92). Disease-causing mutations span the presenilin-1 gene and are the most common known cause of early-onset autosomal dominant AD. Mutations in a homologous gene, presenilin-2, account for a much smaller number of cases (93–96). Presenilin-1 and -2 are part of the γ -secretase complex that mediates the intramembrane proteolysis of APP that liberates the C terminus of the A β peptide (97–99). γ -Secretase is a novel complex comprising four core components: presenilin, nicastrin, Aph-1, and Pen-2. Each of these is required for enzymatic activity (100). Disease-causing mutations in presenilin-1 or -2 increase the level of the longer A β 42 peptide relative to the shorter A β 40 peptide (101). When these pathogenic variants of APP and presenilin-1 are overexpressed in transgenic mice, they result in age-dependent formation of amyloid deposits, providing support for the idea that altered APP metabolism can give rise to an early-onset form of AD (102, 103).

The only gene that has been unequivocally linked to the prevalent late-onset form of AD is apolipoprotein E (apoE) (104). The E4 allele of apoE is a significant risk factor for the development of AD, increasing the risk by as much as 10–12-fold when present in the homozygous state (105). In contrast, another variant, the E-2 allele, protects against the development of AD. The presence of an apoE4 allele correlates with increased A β deposition in the human brain, and apoE4 induces A β fibrillization in APP transgenic mice (106). In addition, apoE may have neurotrophic and antioxidant activity and may facilitate recovery after a variety of neuronal insults (107). However, the mechanism by which apoE4 increases the risk of AD remains an active area of investigation.

The Amyloid Hypothesis

The initial studies of A β in cell culture showed that aggregated forms of the peptide

are neurotoxic, suggesting that A β could be a proximate cause of neurodegeneration in AD (108–110). In contrast, early analysis of transgenic mouse models that over-expressed mutant forms of APP that cause familial AD and develop A β deposits did not show widespread cytoskeletal pathology or neuronal loss (102, 111). A subsequent study, however, using confocal microscopy with a sophisticated cross-correlation mapping of neuronal density showed that significant neuronal loss occurred in direct contiguity to fibrillar thioflavin S-positive A β deposits (112). Nonetheless, these mouse models did not demonstrate the widespread neuronal loss that typically occurs in AD. A potential explanation came from studies of fibrillar A β injection into the brains of aging nonhuman primates. When a plaque-equivalent concentration of fibrillar A β was injected into the brains of aged but not young rhesus monkeys, it resulted in substantial neuronal degeneration, tau pathology, and microgliosis (113). However, injection of A β into the aging rat brain had no detectable pathological effects at a plaque-equivalent concentration. These results suggest that aging renders the brain vulnerable to A β toxicity and that a species barrier may reduce A β toxicity in the aging rodent brain.

More recent studies have focused on the toxic effects of lower molecular weight oligomeric forms of A β that may be more toxic than larger fibrillar aggregates (114). The initial observation of oligomer toxicity was made by Klein and associates, who showed that small diffusible A β oligomers referred to as ADDLs killed mature neurons in organotypic cultures at nanomolar concentrations. In addition, these oligomeric A β peptides inhibited hippocampal LTP, raising the possibility that they could impair synaptic plasticity and memory (115). Subsequent studies showed that smaller dimeric and trimeric forms of A β synthesized by cells in culture could also impair LTP and learned behavior following intracerebral injection in the rat (116, 117). However, in contrast to the larger

ADDL-type oligomers, there is no evidence that the smaller A β dimers or trimers can induce synaptic or neuronal loss. A recent study correlated the appearance of a larger 56-kDa A β oligomer with cognitive deficits in the Tg2576 transgenic mouse model of AD (118). Isolation of this oligomeric A β species from the transgenic mouse brain and infusion into the brains of rats resulted in a transient deficit in memory retention. These studies raise the possibility that particular oligomeric species may impair synaptic plasticity and learning. It will be important to determine whether these A β species are present at functionally significant levels in the brains of AD patients, as A β oligomers are unstable and rapidly aggregate to higher molecular weight forms.

The toxic effects of A β have been associated with a variety of cellular mechanisms, including activation of caspases and calpain, stimulation of microglial inflammatory pathways, and compromise of the vascular endothelium (**Figure 4**) (110, 119–121). Recent studies suggest that A β can also alter glutamatergic neurotransmission by promoting the endocytosis of NMDA and AMPA receptors (122, 123). The clinical efficacy of the drug memantine, an NMDA receptor antagonist, suggests a role for altered glutamatergic neurotransmission in AD (124). Another potentially important mechanism of A β toxicity is the activation of cell cycle reentry in post-mitotic neurons. Aberrant cell cycle activation and DNA synthesis have been detected in neurons in the brains of patients with mild cognitive impairment and AD (125). Moreover, cell cycle reentry occurs when neurons are exposed to toxic doses of A β in culture (126).

The role of A β as the sole or dominant cause of cognitive decline in AD has recently been questioned by a study in which a mutation in the cytoplasmic domain of APP (Asp-664) was knocked into APP transgenic mice. This mutation did not alter total A β levels or plaque formation, but prevented the degenerative features of the transgenic model, including synaptic loss, astrogliosis, and cognitive

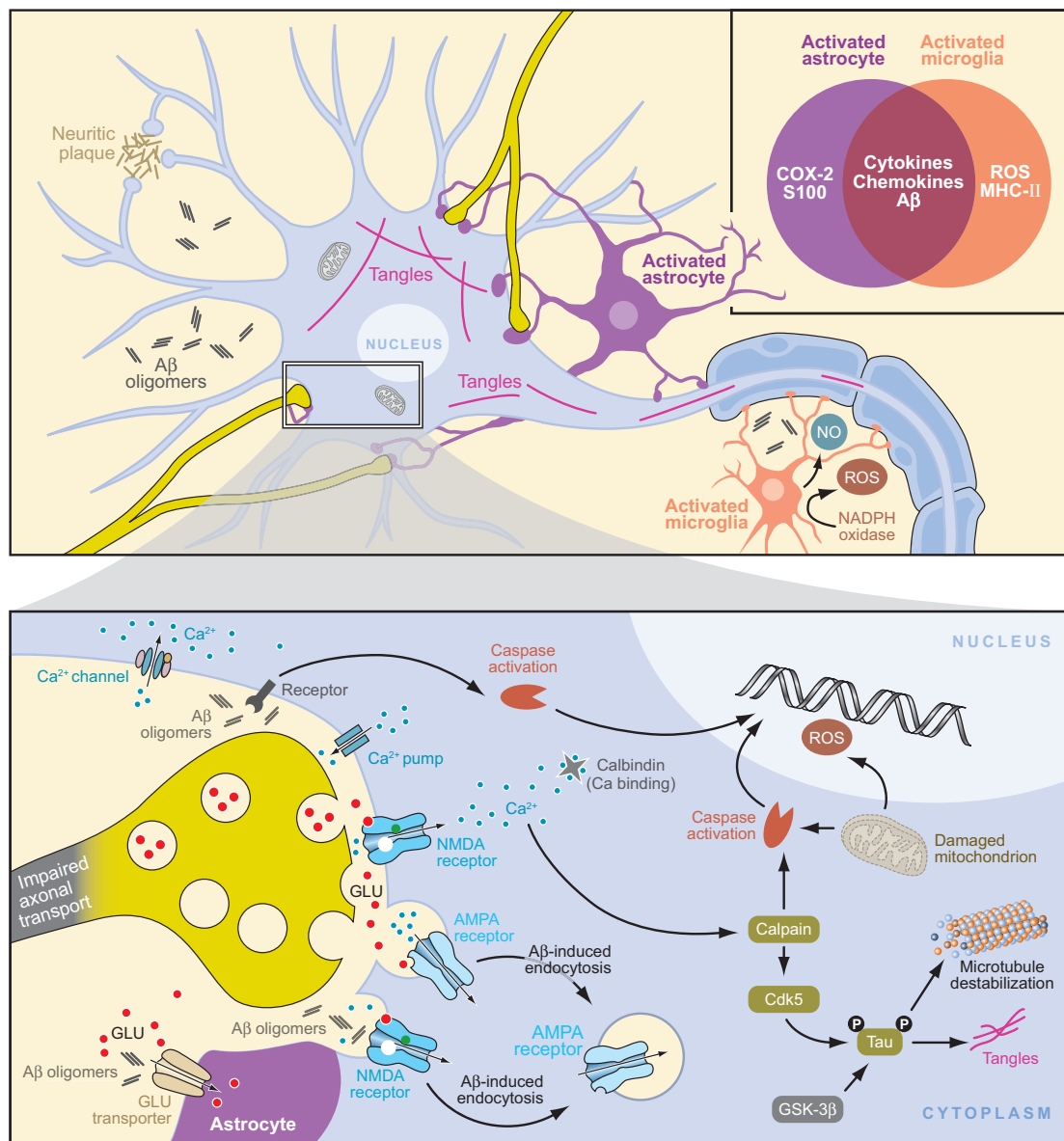


Figure 4

Neurodegenerative mechanisms in Alzheimer's disease. (*Upper panel*) Abnormal accumulation of Aβ and tau as oligomers, neuritic plaques, and neurofibrillary tangles may impair neuronal function. In addition, Aβ aggregates can induce the proliferation and activation of astrocytes and microglia, leading to the elaboration of neurotoxic cytokines and reactive oxygen species (ROS). (*Lower panel*) The inset in the upper panel is expanded in the lower panel to show mechanisms of synaptic dysfunction, including Aβ-induced endocytosis of AMPA and NMDA receptors, increased calcium influx through L-type calcium channels, and impaired glutamate (GLU) reuptake by astrocytes. In addition, Aβ aggregates can activate caspases through several pathways, including cell death receptors (FAS and the p75 NGFR), calpain activation and mitochondrial damage, leading to neuronal apoptosis. Hyperphosphorylation and aggregation of tau can destabilize microtubules and impair axonal transport, compromising synaptic function and giving rise to neurofibrillary tangles.

deficits (127). One potential model is that the mutation prevents the proteolytic release of a toxic APP C-terminal fragment (128–131). Another possibility is that altered regulation of the biological functions of the APP holoprotein may contribute to the neurodegenerative process.

Tau Mutations and Neurodegeneration

Neurofibrillary tangles (NFTs) are a characteristic feature of the normal aging human brain that can become widespread in hippocampal, neocortical, and limbic neurons in AD. NFTs are composed predominantly of posttranslationally modified forms of tau, a microtubule-associated protein. Phosphorylation of tau at multiple sites is associated with its dissociation from microtubules and aggregation into oligomeric and fibrillar forms. This may destabilize microtubules and impair antegrade axonal transport of essential macromolecules and organelles to synaptic endings. Although tau-related pathology is characteristic of AD, the role of tau in neurodegeneration was firmly established in another disorder, frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Frontotemporal dementias constitute a spectrum of clinical disorders characterized by the onset of a dementing illness in which language and behavioral deficits are the presenting symptoms rather than deficits in episodic memory characteristic of AD. At the histological level, these disorders are characterized by widespread neuronal cell death in the frontal and temporal lobes and the appearance of a variety of aggregated forms of tau, ranging from oligomeric forms to NFTs (132). Mutations in two genes, tau and progranulin, have been identified as causes of familial FTDP-17 (133–135). Tau mutations may act through three pathologic mechanisms: to alter splicing leading to abnormal gene expression, to alter the ability of tau to stabilize microtubules, or to increase tau protein aggregation. The expression of the P301L tau mutation in

transgenic mice recapitulates major features of human FTDP-17, including the age-dependent appearance of NFTs, neuronal loss, and behavioral deficits (136, 137).

Overexpression of AD-causing APP or presenilin mutations in transgenic mice does not give rise to the formation of NFTs or the extensive tau pathology characteristic of AD (102, 103). However, creation of a triple transgenic mouse that overexpressed pathogenic variants of APP, presenilin-1, and tau gave rise to progressive formation of amyloid plaques and NFTs, as well as synaptic dysfunction (138). Synaptic dysfunction appeared at four months of age and correlated with hippocampal accumulation of intraneuronal A β , but preceded the appearance of plaques and tangles. Treatment of these animals with an A β antibody improved cognitive function only under circumstances in which both soluble A β and tau were reduced, suggesting the importance of an A β -tau interaction (139). This idea was supported by crossing another APP transgenic mouse model with tau-deficient mice, which substantially improved A β -related deficits in spatial memory (140). Cognitive improvement was not related to changes in tau phosphorylation or neuritic dystrophy, but correlated with protection against excitotoxicity. It was suggested that tau might contribute to neuronal dysfunction and toxicity by modulating sensitivity to excitatory neurotransmission.

PREVENTION OF COGNITIVE DECLINE AND NEURODEGENERATION

The prevalent comorbid medical conditions of aging, including hypertension, hyperlipidemia, and diabetes, are major contributing factors for stroke and white matter ischemic changes during aging, and may also predispose to AD. Hence, management of these conditions through medical and lifestyle interventions is likely to benefit cognitive function (141). A substantial body of literature suggests that physical exercise not only

FTDP-17:
frontotemporal
dementia with
Parkinsonism linked
to chromosome 17

Sirtuins: a family of proteins related to the histone deacetylase SIR2 that regulates longevity in yeast

reduces vascular disease, but may also directly benefit cognitive function through a number of mechanisms, including increased production of brain-derived neurotrophic factor and increased neurogenesis (142, 143). Aerobic exercise increased cerebral blood volume in the dentate gyrus of the human hippocampus in a study of 11 subjects ranging in age from 21–45 years (144). This was accompanied by improvement in immediate recall on cognitive testing. Another study showed that long-term physical activity was associated with improved cognitive function in a large population of women ranging in age from 70–81 years (145). An important question, however, is whether exercise can prevent or slow the onset of neurodegenerative diseases. In a transgenic mouse model of AD, increased exercise on a running wheel was associated with reduced amyloid deposition and improved cognitive function (48). Other studies suggest that placing mice in an enriched, stimulating environment may have a greater effect on spatial memory than exercise alone (146).

A potentially important therapeutic approach to aging is the prevention of oxidative damage to DNA and other macromolecules. However, there is surprisingly little evidence yet for the efficacy of this approach in the human population. This may relate to the fact that free radical scavengers act stoichiometrically on their targets, requiring high doses to significantly impact oxidative stress in the brain. Epidemiological studies suggest that dietary intake of vitamin E might reduce the incidence of AD (147). In addition, treatment of AD patients with high doses of vitamin E or selegiline, a selective monoamine oxidase inhibitor, had a modest effect on functional indices of cognitive decline (148). The evidence for this approach is more compelling in aged rats that show mitochondrial degeneration and oxidative damage to DNA and RNA in the brain. Feeding aged rats the mitochondrial metabolite acetyl-L-carnitine and the antioxidant lipoic acid improved spatial memory and prevented structural decay of

mitochondria in the hippocampus (58). Similarly, administration of coenzyme Q₁₀, a co-factor of the mitochondrial electron transport chain and an antioxidant, showed neuroprotective effects in rats (149). Initial studies in patients with Parkinson's disease also suggest that coenzyme Q₁₀ may reduce the rate of functional decline (150).

Increased inflammation is a feature of brain aging that is conserved from mouse to man (Table 1). Epidemiologic studies suggested that individuals treated with non-steroidal anti-inflammatory agents for arthritis may have a lower incidence of AD (151). This observation led to clinical trials of cyclooxygenase-2 inhibitors in patients with AD that did not demonstrate efficacy (152). Supplementation with dietary omega-3 fatty acids has received considerable attention because of their positive vascular and anti-inflammatory effects. Epidemiologic studies show that individuals with a high dietary intake of fish and, in particular, the omega-3 fatty acid docosahexaenoic acid, have a reduced incidence of AD (153). Moreover, treatment of transgenic mouse models of AD with omega-3 fatty acids can improve cognitive function and reduce A β levels and deposition (154, 155).

Caloric restriction has been shown to significantly increase life span and promote resistance to a broad range of age-related pathology in worms, flies, and mice. Some of the effects of caloric restriction may be mediated through the sirtuin family of genes, as exemplified by *SIR2*, which prolongs life span in yeast (156). It was found that resveratrol, a naturally occurring compound in grapes and red wine, can activate sirtuins and increase longevity in yeast, worms, and flies (157, 158). Moreover, treatment with high doses of resveratrol can significantly increase the survival of mice on a high-fat diet and increase insulin sensitivity (159, 160). The role of sirtuins in the brain is still relatively unexplored. It has been reported that *SIRT1*, the mammalian ortholog of the yeast *SIR2* gene, is involved in a biosynthetic pathway for NAD that

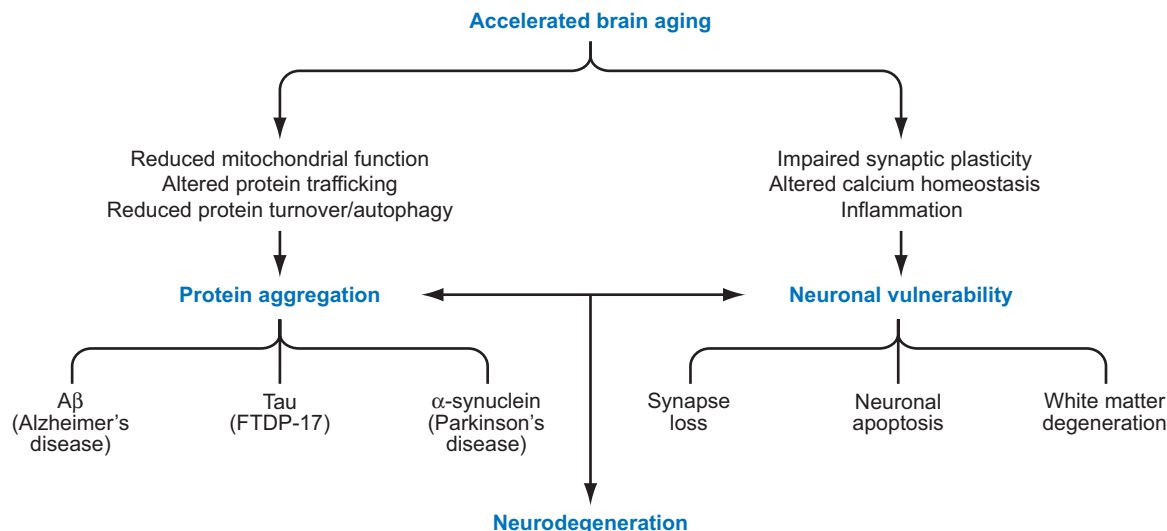


Figure 5

Neurodegeneration and accelerated brain aging. Genetic or environmental factors that accelerate underlying mechanisms of brain aging may affect biological systems that regulate protein aggregation and neuronal survival. Pathological protein aggregation and age-dependent neuronal vulnerability may act together to induce neurodegeneration.

protects axons from degeneration in a mouse model known as Wallerian degeneration slow (161). It remains to be determined whether activation of sirtuins can protect against cognitive decline and neurodegeneration, possibly by activating global anti-apoptotic and stress resistance pathways.

CONCLUSION

The question of how the brain ages at a molecular level is complex and has recently been addressed by a systems biology approach. Genome-scale transcriptional profiling studies in multiple species suggest that a conserved set of biological systems involved in synaptic function, mitochondrial energy metabolism, and stress resistance change in the aging brain (Table 1). A subset of age-related transcriptional changes may be caused by DNA damage and genomic instability, an established etiologic factor in cancer and accelerated aging syndromes (Figure 1). There is also increasing evidence for a role of mitochondrial dysfunction as a source of oxidative

stress and neuronal dysfunction in the aging brain. Moreover, feeding rats mitochondrial metabolites can partially reverse age-related cognitive decline (58). Hence, nuclear and mitochondrial dysfunction may coordinately alter the systems biology of the brain, leading to a spectrum of age-related cognitive changes (Figure 1 and Figure 2).

A central issue is the relationship of normal to pathological aging and the mechanisms that underlie this transition. The risk of AD increases 14-fold from age 65–85, afflicting as much as 47% of individuals over age 85 (162). The onset of AD is therefore closely associated with the aging process. Moreover, normal age-related changes appear to be increased in AD at several levels, including the spread of plaque and tangle pathology (Figure 3), changes in gene expression, and exaggerated age-related changes in autophagy, mitochondrial function, and protein trafficking (Figure 5). What appears to distinguish AD, frontotemporal dementia, and Parkinson's disease from normal aging is the extreme degree of neuronal

loss, which is minimal in most brain regions during normal aging. This distinguishing feature is not phenocopied in mouse transgenic models of AD and Parkinson's disease, suggesting that key features of human brain

aging may be missing. Thus, a greater understanding of the normal aging brain may be necessary before we can fully understand the causes of pathological aging and cognitive decline.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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