REVIEW ARTICLE

MECHANISMS OF DISEASE

Alzheimer's Disease

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More than 35 million people worldwide — 5.5 million in the United States — have Alzheimer's disease, a deterioration of memory and other cognitive domains that leads to death within 3 to 9 years after diagnosis. Alzheimer's disease is the most common form of dementia, accounting for 50 to 56% of cases at autopsy and in clinical series. Alzheimer's disease combined with intracerebral vascular disease accounts for another 13 to 17% of cases.

The principal risk factor for Alzheimer's disease is age. The incidence of the disease doubles every 5 years after 65 years of age, with the diagnosis of 1275 new cases per year per 100,000 persons older than 65 years of age.[1] Data on centenarians show that Alzheimer's disease is not necessarily the outcome of aging[2]; nevertheless, the odds of receiving the diagnosis of Alzheimer's disease after 85 years of age exceed one in three. As the aging population increases, the prevalence will approach 13.2 to 16.0 million cases in the United States by mid-century.[3]

Many molecular lesions have been detected in Alzheimer's disease, but the overarching theme to emerge from the data is that an accumulation of misfolded proteins in the aging brain results in oxidative and inflammatory damage, which in turn leads to energy failure and synaptic dysfunction.

PROTEIN ABNORMALITIES IN ALZHEIMER'S DISEASE

β-AMYLOID

Cerebral plaques laden with β-amyloid peptide (Aβ) and dystrophic neurites in neocortical terminal fields as well as prominent neurofibrillary tangles in medial temporal-lobe structures are important pathological features of Alzheimer's disease. Loss of neurons and white matter, congophilic (amyloid) angiopathy, inflammation, and oxidative damage are also present.

Aβ peptides are natural products of metabolism consisting of 36 to 43 amino acids. Monomers of $A\beta_{40}$ are much more prevalent than the aggregation-prone and damaging $A\beta_{42}$ species. β-amyloid peptides originate from proteolysis of the amyloid precursor protein by the sequential enzymatic actions of beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), a β-secretase, and γ-secretase, a protein complex with presenilin 1 at its catalytic core[4] (Fig. 1). An imbalance between production and clearance, and aggregation of peptides, causes Aβ to accumulate, and this excess may be the initiating factor in Alzheimer's disease. This idea, called the "amyloid hypothesis," is based on studies of genetic forms of Alzheimer's disease, including Down's syndrome,[5] and evidence that $A\beta_{42}$ is toxic to cells.[6,7]

Aβ spontaneously self-aggregates into multiple coexisting physical forms. One form consists of oligomers (2 to 6 peptides), which coalesce into intermediate assemblies[8,9] (Fig. 1). β-amyloid can also grow into fibrils, which arrange themselves into β-pleated sheets to form the insoluble fibers of advanced amyloid plaques.

Soluble oligomers and intermediate amyloids are the most neurotoxic forms of

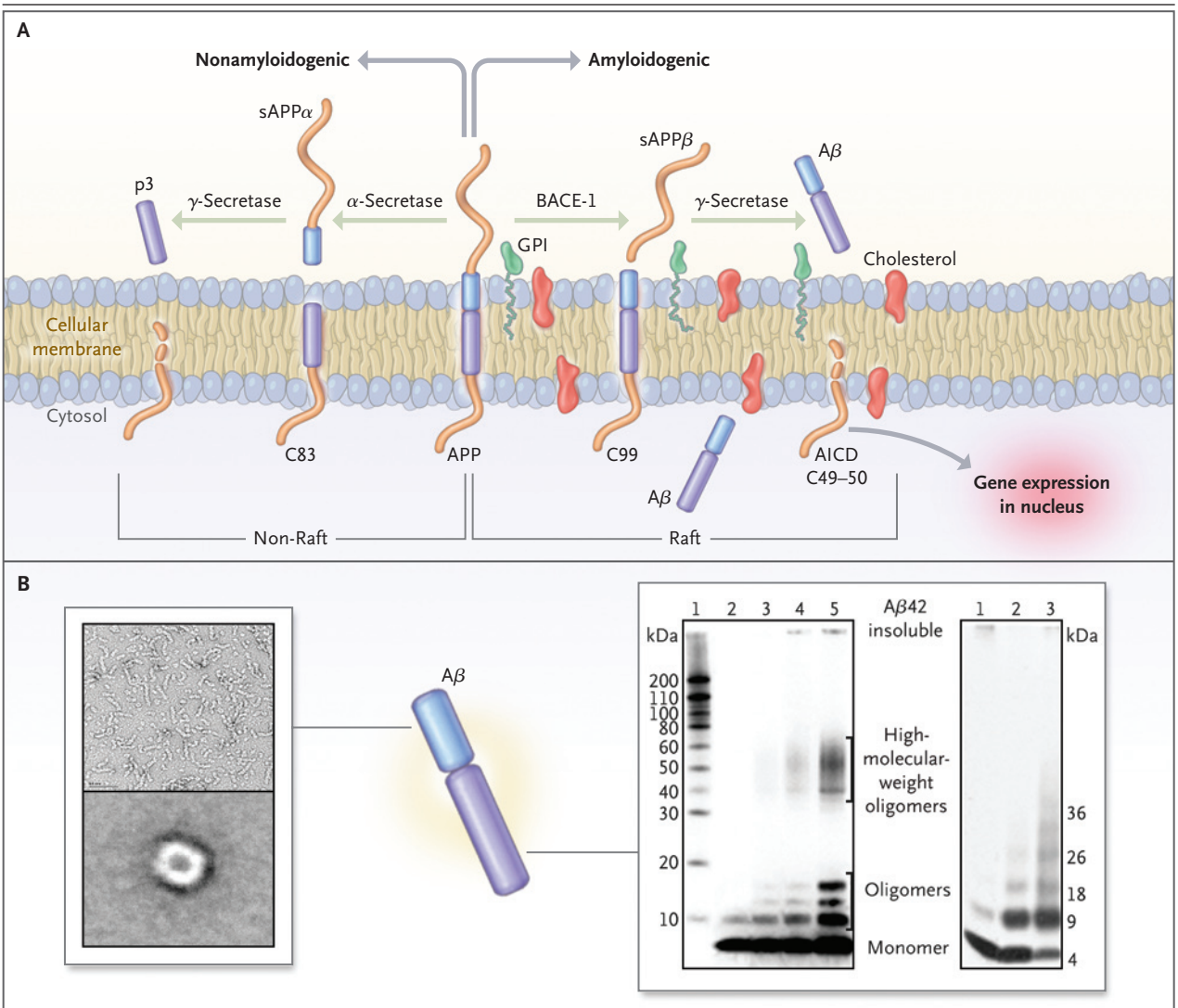

Figure 1. Processing of Amyloid Precursor Protein.

In Panel A, cleavage by α-secretase interior to the β-amyloid peptide (Aβ) sequence initiates nonamyloidogenic processing. A large amyloid precursor protein (sAPPα) ectodomain is released, leaving behind an 83-residue carboxy-terminal fragment. C83 is then digested by γ-secretase, liberating extracellular p3 and the amyloid intracellular domain (AICD). Amyloidogenic processing is initiated by β-secretase beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), releasing a shortened sAPPα. The retained C99 is also a γ-secretase substrate, generating Aβ and AICD. γ-Secretase cleavage occurs within the cell membrane in a unique process termed "regulated intramembranous proteolysis." sAPPα and sAPPβ are secreted APP fragments after α-secretase and β-secretase cleavages, respectively. AICD is a short tail (approximately 50 amino acids) that is released into the cytoplasm after progressive ε-to-γ cleavages by γ-secretase. AICD is targeted to the nucleus, signaling transcription activation. Lipid rafts are tightly packed membrane micro-environments enriched in sphingomylelin, cholesterol, and glycophosphatidylinositol (GPI)–anchored proteins. Soluble Aβ is prone to aggregation. In Panel B, left inset, protofibrils (upper) and annular or porelike profiles (lower) are intermediate aggregates. (Photomicrographs courtesy of Hilal Lashuel, Ph.D.) In the right inset, self-association of 2 to 14 Aβ monomers into oligomers is dependent on concentration (left immunoblot). In the right immunoblot, oligomerization is promoted by oxidizing conditions (lane 2) and divalent metal conditions (lane 3). (Immunoblots courtesy of Hongwei Zhou, Ph.D.)

Aβ.[10] In brain-slice preparations, dimers and trimers of Aβ are toxic to synapses.[11,12] The severity of the cognitive defect in Alzheimer's disease correlates with levels of oligomers in the brain, not the total Aβ burden.[13] Neuronal activation rapidly increases Aβ secretion at the synapse, a process tied to the normal release of vesicles containing neurotransmitters. Physiologic

levels of synaptic Aβ may dampen excitatory transmission and prevent neuronal hyperactivity.[14]

The proteases neprilysin and insulin-degrading enzyme regulate steady-state levels of Aβ. Neprilysin, a membrane-anchored zinc endopeptidase, degrades Aβ monomers and oligomers.[15] A reduction in neprilysin causes accumulation of cerebral Aβ.[16] Insulin-degrading enzyme, a thiol metalloendopeptidase, degrades small peptides such as insulin and monomeric Aβ.[17] In mice, deletion of insulin-degrading enzyme reduces Aβ degradation by more than 50%.[18] Conversely, overexpression of neprilysin or insulin-degrading enzyme prevents plaque formation.[19]

Clinical trials of a γ-secretase inhibitor (LY450139) (ClinicalTrials.gov number, NCT00765115),[20] aggregation blockers, vaccination with Aβ, and monoclonal antibodies against various Aβ epitopes are in progress. The antibodies bind Aβ, thereby triggering complement and Fc-receptor–mediated phagocytosis by microglia, or enhance clearance of Aβ, or both.[21] Vaccination in a phase 2a trial (NCT00021723)[22] resulted in encephalitis,[23] and follow-up of immunized patients showed no cognitive or survival benefit despite diminution of plaques.[24] A phase 2 trial of passive immunization resulted in vasogenic cerebral edema in some patients (NCT00112073). Phase 3 trials of two monoclonal antibodies against Aβ (NCT00574132 and NCT00904683) and of 10% intravenous immune globulin are under way (NCT00818662).

TAU

Neurofibrillary tangles, which are filamentous inclusions in pyramidal neurons, occur in Alzheimer's disease and other neurodegenerative disorders termed tauopathies.[25] The number of neurofibrillary tangles is a pathologic marker of the severity of Alzheimer's disease. The major component of the tangles is an abnormally hyperphosphorylated and aggregated form of tau. Normally an abundant soluble protein in axons, tau promotes assembly and stability of microtubules and vesicle transport. Hyperphosphorylated tau is insoluble, lacks affinity for microtubules, and self-associates into paired helical filament structures (Fig. 2). Enzymes that add and those that remove phosphate residues regulate the extent of tau phosphorylation.[26]

Like Aβ oligomers, intermediate aggregates of abnormal tau molecules are cytotoxic[27] and impair cognition.[28,29] Insoluble helical filaments may be inert, however, since decreases in axonal transport and neuron number are independent of the burden of neurofibrillary tangles.[30] These helical filaments sequester toxic intermediate tau species, a process that may be protective.[31]

More than 30 mutations of *Tau* on chromosome 17 have been detected in frontotemporal dementia with parkinsonism.[32] By contrast, *Tau* mutations do not occur in Alzheimer's disease, and the extent of neuron loss is out of proportion to the number of neurofibrillary tangles.[33] Nevertheless, increased levels of phosphorylated and total tau in the cerebrospinal fluid correlate with reductions in scores on cognitive examinations.[34] Elevated levels of phosphotau amino acids T181, T231, and total tau in the cerebrospinal fluid together constitute a biomarker test with good accuracy for predicting incipient Alzheimer's disease in patients with mild cognitive impairment.[35] Experimental evidence indicates that Aβ accumulation precedes and drives tau aggregation.[36-38] Moreover, Aβ-induced degeneration of cultured neurons and cognitive deficits in mice with an Alzheimer's disease–like illness require the presence of endogenous tau.[39,40]

Increased oxidative stress, the impaired protein-folding function of the endoplasmic reticulum, and deficient proteasome-mediated and autophagic-mediated clearance of damaged proteins — all of which are also associated with aging — accelerate the accumulation of amyloid and tau proteins in Alzheimer's disease.[41,42] Agents capable of counteracting these changes are not available, but trials of small-molecule inhibitors of β-amyloid (e.g., scylloinositol) (NCT00568776) and tau oxidation and aggregation (e.g., methylene blue) (NCT00568776) are under way.[43] Polyphenolic extracts from grape seeds (e.g., resveratrol), which stimulate aging-suppressor genes, also show promise as therapeutic agents.[44]

THE SYNAPSE IN ALZHEIMER'S DISEASE

SYNAPTIC FAILURE

Alzheimer's disease may be primarily a disorder of synaptic failure.[45] Hippocampal synapses begin to decline in patients with mild cognitive impairment (a limited cognitive deficit often preceding dementia) in whom remaining synaptic profiles show compensatory increases in size.[46] In mild Alzheimer's disease, there is a reduction

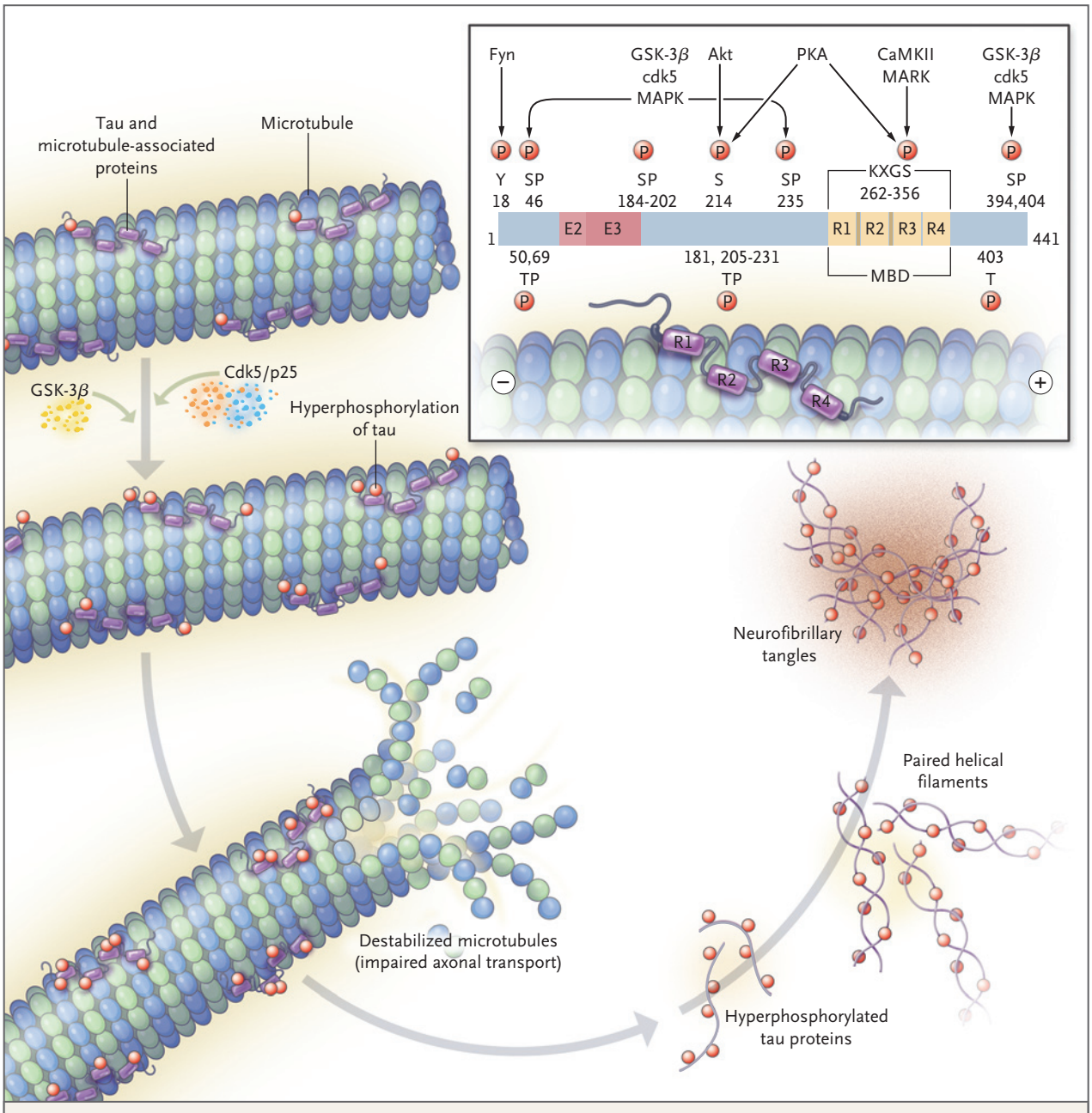

Figure 2. Tau Structure and Function.

Four repeat sequences (R1-R4) make up the microtubule-binding domain (MBD) of tau. Normal phosphorylation of tau occurs on serine (S; inset, above horizontal bar) and threonine (T; inset, below horizontal bar) residues, numbered according to their position in the full tau sequence. When followed by proline (P), these amino acids are phosphorylated by glycogen synthase kinase 3 (GSK-3β), cyclin-dependent kinase (cdk5) and its activator subunit p25, or mitogen-activated protein kinase (MAPK). Nonproline-directed kinases — Akt, Fyn, protein kinase A (PKA), calcium–calmodulin protein kinase 2 (CaMKII), and microtubule affinity-regulating kinase (MARK) — are also shown. KXGS (denoting lysine, an unknown or other amino acid, glycine, and serine) is a target motif. Hyperphosphorylated sites specific to paired helical filament tau in Alzheimer's disease tend to flank the MBD. Tau binding promotes microtubule assembly and stability. Excessive kinase, reduced phosphatase activities, or both cause hyperphosphorylated tau to detach and self-aggregate and microtubules to stabilize.

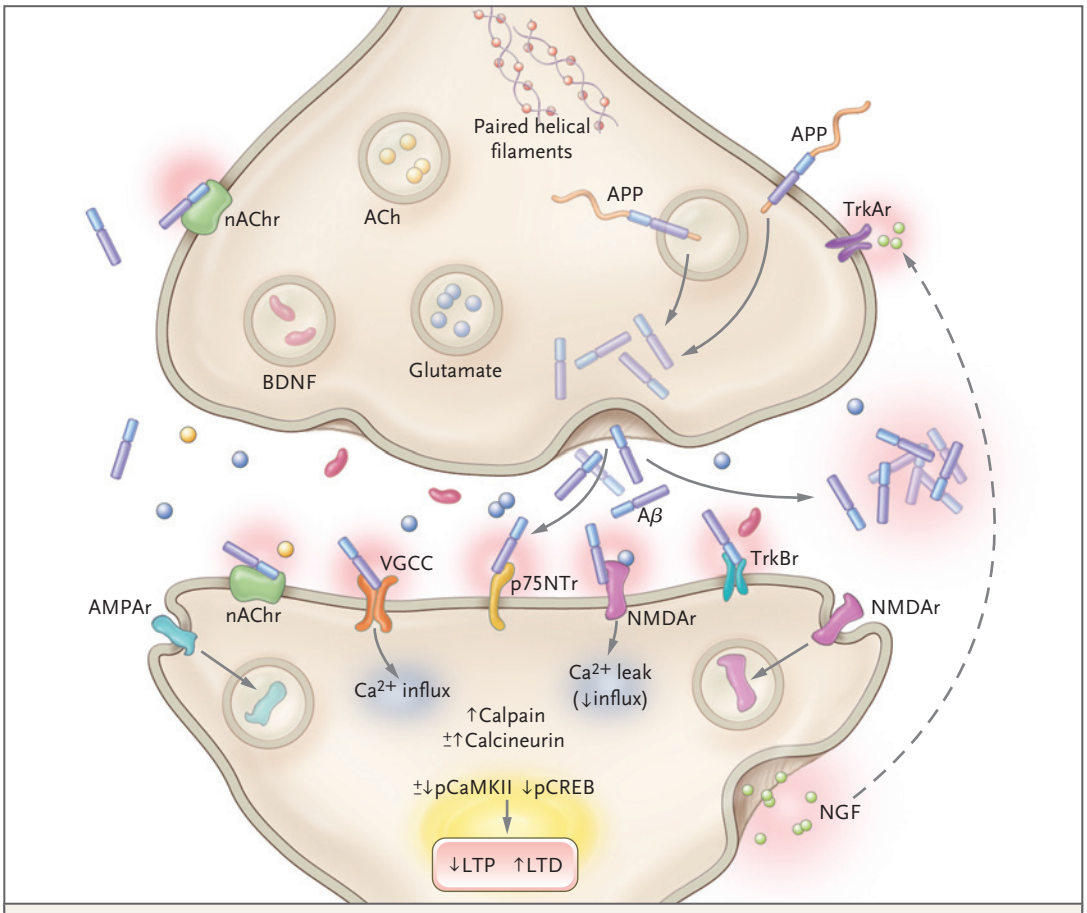

Figure 3. Synaptic Dysfunction in Alzheimer's Disease.

Synaptic loss correlates best with cognitive decline in Alzheimer's disease. A control synapse is shown at the top of the figure. At the bottom of the figure, an "Alzheimer's disease synapse" depicting the pleiotropic effects of the β-amyloid peptide (Aβ) is shown. Rings represent synaptic vesicles. Experimental application and expression of Aβ, especially oligomers, impair synaptic plasticity by altering the balance between long-term potentiation (LTP) and long-term depression (LTD) and reducing the numbers of dendritic spines. At high concentrations, oligomers may suppress basal synaptic transmission. Aβ facilitates endocytosis of receptors of *N*-methyl-D-aspartate (NMDAr) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAr). Aβ also binds to the receptors of p75 neurotrophin (p75NTr) and brain-derived neurotrophic factor (the BDNF receptor, also known as the tyrosine kinase B receptor [trkBr]), exacerbating a situation in which levels of BDNF and nerve growth factor (NGF) are already suppressed. Aβ impairs nicotinic acetylcholine (ACh) receptor (nAChr) signaling and ACh release from the presynaptic terminal. Numbers of hippocampal synapses decrease in mild cognitive impairment in which remaining synaptic profiles show compensatory increases in size. APP denotes amyloid precursor protein, pCaMKII phosphorylated calcium–calmodulin–dependent protein kinase 2, pCREB phosphorylated cyclic AMP response-element-binding protein, trkAr tyrosine kinase A receptor, and VGCC voltage-gated calcium channel.

of about 25% in the presynaptic vesicle protein synaptophysin.[47] With advancing disease, synapses are disproportionately lost relative to neurons, and this loss is the best correlate with dementia.[48-50] Aging itself causes synaptic loss,[51] which particularly affects the dentate region of the hippocampus.[52]

Basal transmission of single impulses and "long-term potentiation," an experimental indicator of memory formation at synapses, are impaired in plaque-bearing mice with Alzheimer's disease and after Aβ peptide has been applied to brain slices.[11,53] Subsequent to this impairment, signaling molecules important to memory are in-

hibited. Disruptions of the release of presynaptic neurotransmitters and postsynaptic glutamate-receptor ion currents[54,55] occur partially as a result of endocytosis of *N*-methyl-D-aspartate (NMDA) surface receptors[56] and endocytosis of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid surface receptors[57] (Fig. 3). The latter further weakens synaptic activity by inducing a lasting reduction in currents after a high-frequency stimulus train. A similar shift in the balance between potentiation and depression in synapses occurs with normal aging. Intraneuronal Aβ can trigger these synaptic deficits even earlier.[58]

DEPLETION OF NEUROTROPHIN AND NEUROTRANSMITTERS

Neurotrophins promote proliferation, differentiation, and survival of neurons and glia, and they mediate learning, memory, and behavior. The normally high levels of neurotrophin receptors in cholinergic neurons in the basal forebrain are severely reduced in late-stage Alzheimer's disease (Fig. 3). Injection of nerve growth factor can rescue basal neurons in animal models,[59] and a phase 1 trial of treatment with the *NGF* gene in Alzheimer's disease showed improvement in cognition and brain metabolism.[60] In Alzheimer's disease and mild cognitive impairment, levels of brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, are depressed,[61] a finding reproduced experimentally with $A\beta_{42}$ oligomers.[62] BDNF treatment in rodents and nonhuman primates supports neuronal survival, synaptic function, and memory,[63] suggesting that BDNF replacement is another option for the treatment of Alzheimer's disease.[64]

The deficiency of cholinergic projections in Alzheimer's disease has been linked to the buildup of Aβ and tau. Presynaptic α-7 nicotinic acetylcholine receptors are essential for cognitive processing, and their levels increase in early Alzheimer's disease,[65] before decreasing later.[66] Experimental studies show that Aβ binds to α-7 nicotinic acetylcholine receptors, impairing the release of acetylcholine and maintenance of long-term potentiation.[67] The level of muscarinic acetylcholine receptors, or receptor coupling, is reduced in the brains of patients with Alzheimer's disease. Pharmacologic stimulation of the postsynaptic muscarinic type 1 (M1) acetylcholine receptors activates protein kinase C, favoring processing of amyloid precursor protein that does not yield amyloid.[68] Furthermore, activation of nicotinic acetylcholine receptors or M1 receptors limits tau phosphorylation.[69,70] Although cholinesterase inhibitors improve neurotransmission and provide mild palliative relief in Alzheimer's disease, they lose efficacy over time. The use of agonists and modulators of α-7 nicotinic acetylcholine receptors is under investigation. Clinical trials of selective M1 agonists have shown improvements in cognition[71] and reduced Aβ levels in the cerebrospinal fluid,[72] but these agents are toxic.

MITOCHONDRIAL DYSFUNCTION

Aβ is a potent mitochondrial poison, especially affecting the synaptic pool.[73] In Alzheimer's disease, exposure to Aβ inhibits key mitochondrial enzymes in the brain and in isolated mitochondria.[74,75] Cytochrome *c* oxidase is specifically attacked.[76] Consequently, electron transport, ATP production, oxygen consumption, and mitochondrial membrane potential all become impaired. The increase in mitochondrial superoxide radical formation and conversion into hydrogen peroxide cause oxidative stress, release of cytochrome *c*, and apoptosis (Fig. 4).

The accumulation of Aβ within structurally damaged mitochondria isolated from the brains of patients with Alzheimer's disease[77] and transgenic brains[76] is consistent with other evidence of intraneuronal Aβ in Alzheimer's disease.[78] Alcohol dehydrogenase is one such mitochondrial-binding target of Aβ.[79] Similar changes occur in normal cells that have been repopulated with mitochondrial DNA (mtDNA) from patients with sporadic Alzheimer's disease.[80] Both in Alzheimer's disease and in the normal aging process, mtDNA sustains high levels of oxidative damage.[77] This instability and the irreparability of the brain's mitochondrial genome allow the gradual accumulation of mtDNA mutations.[81] Fragmentation (or fission) of mitochondria from the oxidation of a dynamin-like transporter protein may cause synapse loss in Alzheimer's disease.[82] The antihistamine dimebolin hydrochloride, a putative mitochondrial stimulant, has been reported to improve cognition and behavior in patients with mild-to-moderate Alzheimer's disease.[83]

OXIDATIVE STRESS

Dysfunctional mitochondria release oxidizing free radicals, and in Alzheimer's disease and the nor-

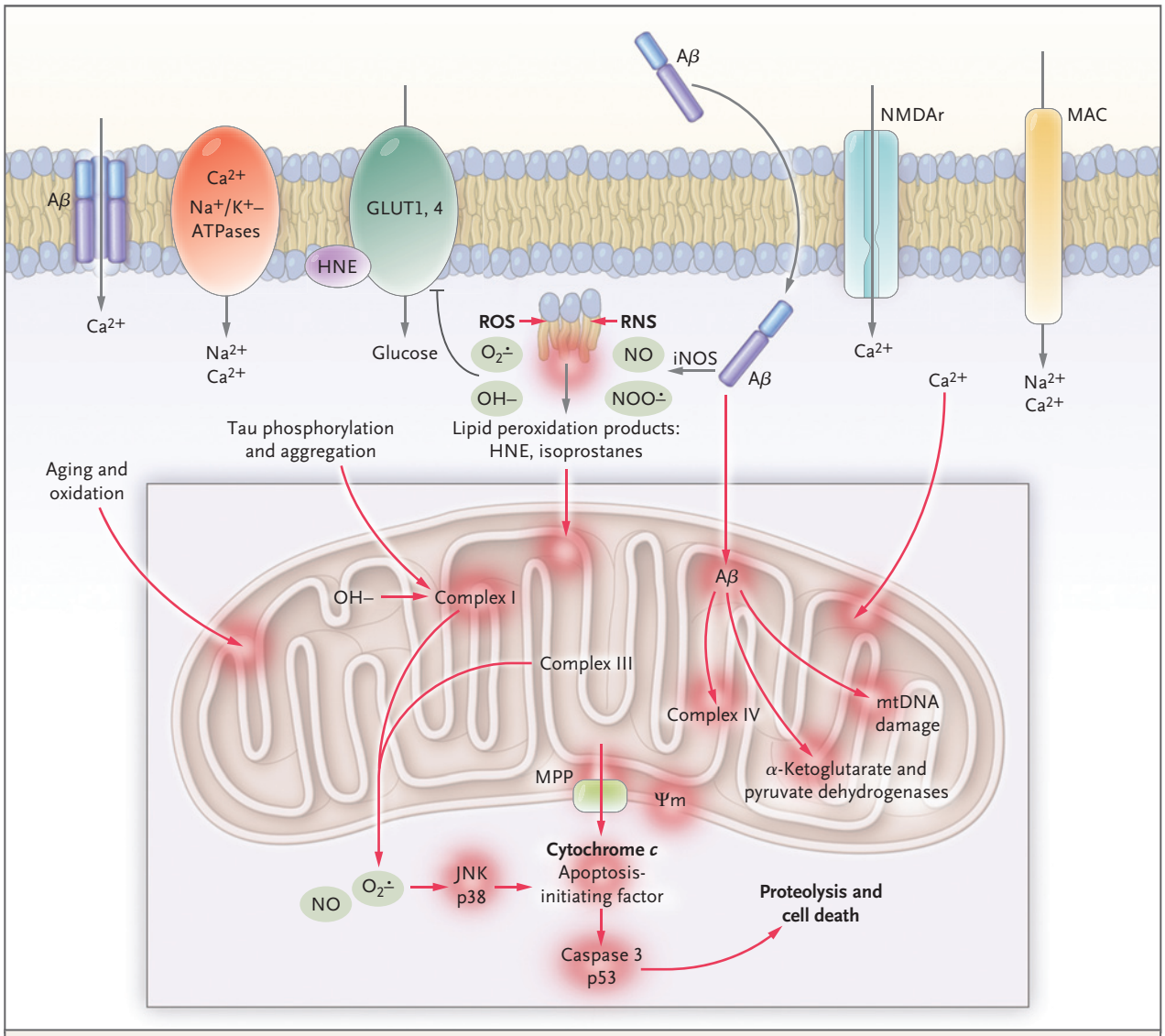

Figure 4. Oxidative Stress and Mitochondrial Failure.

A β-amyloid peptide (Aβ)–centric scheme depicts production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Their peroxidative attack on cell and organelle membrane lipids yields the mitochondrial toxins hydroxynonenal (HNE) and malondialdehyde. Oxidative damage to membrane-bound, ion-specific ATPases and stimulation of calcium (Ca^{2+}) entry mechanisms — for example, glutamate (*N*-methyl-D-aspartate [NMDA]) receptors (NMDAr), membrane-attack complex (MAC) of complement, and ion-selective amyloid pore formation — cause cytosolic and mitochondrial Ca^{2+} overload. Cellular Aβ directly attacks electron transport complex IV (cytochrome *c* oxidase) and key Krebs-cycle enzymes (α-ketoglutarate and pyruvate dehydrogenase) and damages mitochondrial DNA (mtDNA), leading to fragmentation. Lipid peroxidation products also promote tau phosphorylation and aggregation, which in turn inhibit complex I. Exaggerated amounts of ROS and RNS are generated at complexes I and III. As the mitochondrial membrane potential (MPP) collapses and permeability-transition pores (ψm) open, caspases are activated. Aβ also induces the stress-activated protein kinases p38 and c-jun N-terminal kinase (JNK), as well as p53, which are further linked with apoptosis. Substrate deficiencies, notably NADH and glucose, combine with electron transport uncoupling to further diminish ATP production. Alcohol dehydrogenase was recently identified as the mitochondrial-binding target for Aβ. Endoplasmic reticulum contributions are shown. GLUT1, 4 denotes glucose transporter 1, 4.

mal aging brain, they cause considerable oxidative stress.[84,85] Experimental models show that markers of oxidative damage precede pathological changes.[86] Aβ, a potent generator of reactive oxygen species[87] and reactive nitrogen species,[88] is a prime initiator of this damage. The receptor for advanced glycation end products mediates Aβ's pro-oxidant effects on neural, microglial, and cerebrovascular cells.[89] Mitochondrial hydrogen peroxide readily diffuses into the cytosol to

participate in metal ion–catalyzed hydroxyl radical formation. Stimulated microglia are a major source of the highly diffusible nitric oxide radical. These reactive oxygen species and reactive nitrogen species damage several molecular targets. Peroxidation of membrane lipids yields toxic aldehydes,[90] which impair critical mitochondrial enzymes.[77,91] Other essential proteins are directly oxidized, yielding carbonyl and nitrated derivatives.[92] Subsequently, increases in membrane permeability to calcium, other ionic imbalances, and impaired glucose transport[93] aggravate the energy imbalance.

Elevated levels of free divalent transition metal ions (iron, copper, and zinc) and aluminum are linked with reactive oxygen species–mediated damage and neurodegeneration in several ways.[94-100] These metal ions also promote aggregation of tau and changes in its conformation or phosphorylation.[95] Zinc, typically thought to be a toxin in Alzheimer's disease, might at lower concentrations actually protect cells by blocking Aβ channels[96] or compete with copper for Aβ binding.[97]

Although animal models and most cross-sectional studies in aging populations show an association between antioxidant intake and cognitive performance, randomized trials of antioxidants have generally failed.[98] Therapeutic chelation of divalent metals is potentially harmful because essential enzymes rely on coordination with them. In a pilot phase 2 trial (NCT00471211), PBT2, a safe compound derived from clioquinol that attenuates metal proteins,[99] showed some efficacy.

INSULIN-SIGNALING PATHWAY

Another metabolic disturbance of emerging importance in Alzheimer's disease and tied into synaptic and energy homeostasis involves insulin signaling in the brain. Subgroups of patients with advanced Alzheimer's disease have high fasting insulin levels and low rates of glucose disposal (peripheral resistance).[100] Glucose intolerance and type 2 diabetes are considered to be risk factors for dementia.[101] Levels of insulin receptors, glucose-transport proteins, and other insulin-pathway components in the brain are reduced in some studies of Alzheimer's disease[102] (central resistance). Insulin (mostly bloodborne) and brain-derived insulin-like growth factor I initiate signals in the brain by activating the phosphatidylinositol-3-kinase–Akt (also known as protein kinase B) pathway and the mitogen-activated protein kinase–extracellular signal-regulated kinase pathway,[103] but it is unclear whether signaling is up-regulated (compensatory) or down-regulated (pathologic) in Alzheimer's disease. Aging and life span are also influenced by insulin.[104] Resistance to insulin signaling renders neurons energy-deficient and vulnerable to oxidizing or other metabolic insults and impairs synaptic plasticity. Moreover, the higher serum glucose levels that are common in normal aging directly damage hippocampal structures,[105] up-regulate the tau kinase, glycogen synthase kinase 3β,[106] and reduce levels of insulin-degrading enzyme in the brain in Alzheimer's disease.[107] Treatment with thiazolidine drugs (peroxisome-proliferator-activated receptor [PPAR] agonists, which activate insulin-responsive gene transcription) prevented Alzheimer's disease–associated changes and cognitive decline in transgenic mice[103,108] and had significant effects in subpopulations of patients with Alzheimer's disease.[109]

VASCULAR EFFECTS

In Alzheimer's disease, vascular injury and parenchymal inflammation perpetuate the cycle of protein aggregation and oxidation in the brain; damage from strokes and white-matter lesions contribute greatly to cognitive decline. Ischemic disease affects 60 to 90% of patients with Alzheimer's disease, with major infarctions representing one third of vascular lesions in autopsy cases. Conversely, one third of putative cases of vascular dementia have coincidental pathological features of Alzheimer's disease. Although clinically and radiographically "pure" cases of vascular dementia are recognized,[110,111] most cases of dementia are in fact mixed. Pervasive pathological changes include cerebral amyloid angiopathy,[112] affecting more than 90% of patients with Alzheimer's disease, capillary abnormalities, disruption of the blood–brain barrier, and large-vessel atheroma.[113] None of these changes alone explain the symmetric reductions of cerebral blood flow in patients with Alzheimer's disease, which are more likely to reflect regional energy underutilization.[114,115]

Another hypothesis holds that clearance of Aβ along diseased perivascular channels and through the blood–brain barrier is impeded in Alzheimer's disease. The source of vascular Aβ (mostly 40 amino acid form) is heterogeneous, comprising neurons, degenerating myocytes, and the circulation. Amyloid deposition in the arteriolar

wall enhances vasoconstriction in ex vivo studies.[116] Aβ is also cytotoxic to endothelial[117] and smooth-muscle[118] cells, conferring a predisposition to lobar hemorrhage in advanced age. The "neurovascular uncoupling" hypothesis proposes that deregulation of Aβ transport across the capillary blood–brain barrier is caused by the imbalanced expression of low-density lipoprotein receptor–related proteins and receptors for advanced glycation end products, which mediate Aβ efflux and influx, respectively[119] (Fig. 5).

Short of prophylaxis against stroke, there are few specific therapies for the vascular changes in Alzheimer's disease. Centrally acting angiotensin-converting–enzyme inhibitors were associated with reductions in yearly cognitive decline in one observational study.[120] Patients with hypertension who are receiving medication have fewer neuropathologic features of Alzheimer's disease.[121] Folic acid reduces homocysteine levels and may lower the risk of Alzheimer's disease, but it does not improve cognition in established Alzheimer's disease.[122,123] A phase 2 study of inhibitors of receptors for advanced glycation end products in mild-to-moderate Alzheimer's disease (NCT00566397) is under way. Concern has been expressed about the safety of Aβ immunotherapy because of the possibilities of increased vascular amyloid, microhemorrhages, and vasogenic edema as the efflux of Aβ into vascular compartments is stimulated.[124]

INFLAMMATION

Activated microglia and reactive astrocytes localize to fibrillar plaques, and their biochemical markers are elevated in the brains of patients with Alzheimer's disease.[125] Initially, the phagocytic microglia engulf and degrade Aβ. However, chronically activated microglia release chemokines and a cascade of damaging cytokines — notably, interleukin-1, interleukin-6, and tumor necrosis factor α (TNF-α)[126] (Fig. 5). In common with vascular cells, microglia express receptors for advanced glycation end products, which bind Aβ, thereby amplifying the generation of cytokines, glutamate, and nitric oxide.[89,127] In experimental studies, chemokines promote the migration of monocytes from the peripheral blood into plaque-bearing brain.[128]

Fibrillar Aβ and glial activation also stimulate the classic complement pathway.[129] Tangles and plaques contain complement cleavage products, C1q and C5b-9, indicating that opsonization and autolytic attack are under way.[126] Stimulated astroglia also release acute-phase reactants, $alpha_1$-antichymotrypsin, $alpha_2$-macroglobulin, and C-reactive protein, which can both aggravate and ameliorate Alzheimer's disease. Although inflammatory (and oxidative) events are implicated in a breakdown of the vascular blood–brain barrier in Alzheimer's disease, it is not certain that this leads to monocyte or amyloid influx from the circulation in humans.[130,131]

The contradictory roles of microglia — eliminating Aβ and releasing proinflammatory molecules — complicate treatment.[132] Nonsteroidal antiinflammatory agents have been reported to lower the risk of Alzheimer's disease and slow progression of the disease, but only in prospective observational studies.[133,134] Their mechanisms of action include selective reduction of $A\beta_{42}$,[135,136] inhibition of cyclooxygenase-2 or the prostaglandin E_2 receptor, stimulation of phagocytosis by microglia, and activation of PPAR-γ. Recent randomized trials of nonsteroidal antiinflammatory agents[137] and a trial of a derivative, tarenflurbil (Flurizan) (NCT00105547), did not show evidence of reducing the risk of Alzheimer's disease or slowing cognitive decline. In addition to the Aβ-immunization efforts, various TNF-α and complement factor blockers and agents that promote phagocytosis are being investigated.[138]

CALCIUM

Loss of calcium regulation is common to several neurodegenerative disorders. In Alzheimer's disease, elevated concentrations of cytosolic calcium stimulate Aβ aggregation and amyloidogenesis.[139,140] The presenilins modulate calcium balance. Presenilin mutations cause about one half of the few cases of Alzheimer's disease (<1%) that are of the early-onset, familial type. These mutations might disrupt calcium homeostasis in endoplasmic reticulum.[141,142] However, the main effect of the mutations is to increase $A\beta_{42}$ levels, which in turn increases calcium stores in the endoplasmic reticulum and the release of calcium into the cytoplasm.[143] The relevance of these mechanisms to sporadic Alzheimer's disease is unclear.

A chronic state of excitatory amino acid (glutaminergic) receptor activation is thought to aggravate neuronal damage in late-stage Alzheimer's disease.[144] Glutamate increases cytosolic calcium, which in turn stimulates calcium-release channels in the endoplasmic reticulum. How-

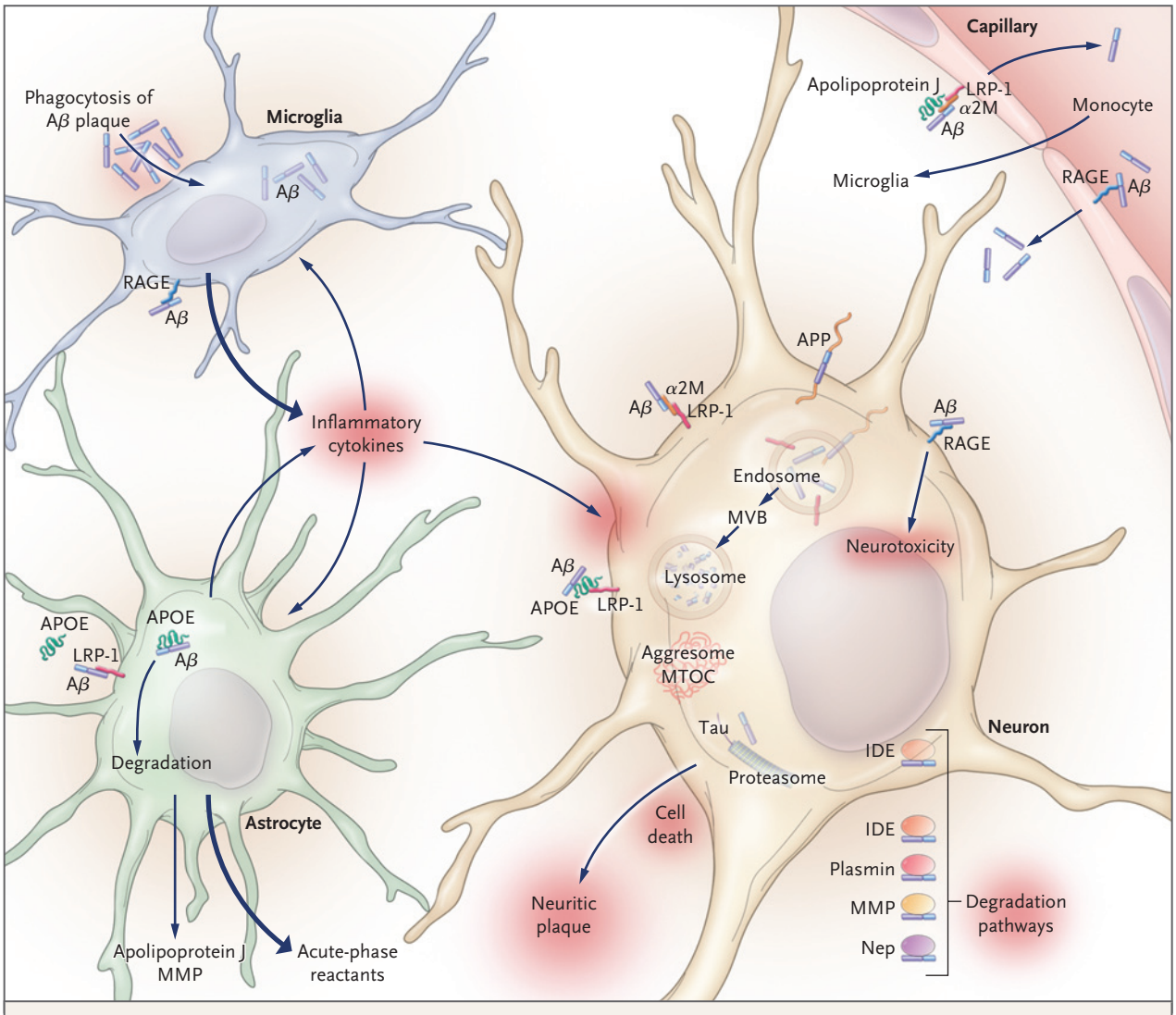

Figure 5. Inflammation and Mechanisms of Aβ Clearance.

β-amyloid peptide (Aβ) is formed within intracellular compartments (the endoplasmic reticulum, Golgi apparatus, and endosomes) or it can enter multiple cell types through the low-density lipoprotein receptor–related protein. The ubiquitous apolipoprotein E (APOE) and α2-macroglobulins (α2M) are chaperones in this process and in the genesis of extracellular plaques. Microglia directly engulf Aβ through phagocytosis. Astrocytes also participate in Aβ clearance through receptor-mediated internalization and facilitation of its transfer out of the central nervous system and into the circulation. Microglia and astrocytes are recruited and stimulated in Alzheimer's disease to release proinflammatory cytokines and acute-phase reactants. Receptors for advanced glycation end products (RAGE) molecules transduce extracellular Aβ toxic and inflammatory effects and mediate influx of vascular Aβ. The inflammatory milieu provokes neuritic changes and breakdown of the vascular blood–brain barrier. In addition to cell-mediated reactions, Aβ clearance occurs through enzymatic proteolysis, mainly through neprilysin (Nep) and insulin-degrading enzyme (IDE). Aβ oligomers block proteasome function, facilitating the buildup of intracellular tau and accumulation of Aβ into "aggresomes." APP denotes amyloid precursor protein, MMP matrix metalloproteinase, MOTC microtubule-organizing center, and MVB multivesicular body.

ever, the evidence of excessive excitatory amino acid mechanisms in Alzheimer's disease is modest. Aβ forms voltage-independent, cation channels in lipid membranes,[145] resulting in calcium uptake and degeneration of neuritis.[146] Indirectly, glutamate activates voltage-gated calcium channels. The L-type voltage-gated calcium-channel blocker, MEM 1003, is in a phase 3 trial, and memantine, an NMDA-receptor blocker, is approved by the Food and Drug Administration.

AXONAL-TRANSPORT DEFICITS

Another internal derangement that is probably an effect rather than a cause of Alzheimer's dis-

ease is a reduction in the transport of critical protein cargoes to the synapse. Molecular motors of the kinesin family drive vesicles and mitochondria destined for the synaptic terminal along axonal microtubules. The kinesin superfamily heavy-chain protein 5 and its associated kinesin light chain 1 facilitate "fast" anterograde transport. Tau forms the cross-bridges that maintain the critical spacing between microtubules.

The riddle of Alzheimer's disease is entwined with the elusive goal of finding the biologic function of amyloid precursor protein. It was exciting when amyloid precursor protein, BACE-1, and presenilin 1 were reported to undergo fast anterograde transport[147] into terminal fields where Aβ and other proteolytic derivatives are released.[148] Impairment of transport causes amyloid precursor protein, vesicle, and kinesin accumulations in axonal swelling, local Aβ deposition, and neurodegeneration.[149,150] However, whether amyloid precursor protein functions as the critical cargo vesicle receptor for the motor protein complex remains unclear.[151] Furthermore, an essential role is not evident from studies of amyloid precursor protein–deficient mice, which are viable, with only subtle synaptic and learning defects.[152,153]

The anatomical distribution of pathological features in Alzheimer's disease nonetheless suggests that microtubules are dysfunctional, since tau is primarily deranged in the source of cortical projections.[154] In addition, defects in the white-matter tract are observed in patients at all stages of Alzheimer's disease[155] and in animal models.[156] Pharmacologic disruption of microtubules and inhibition of tau phosphatases cause similar axonal swelling and synaptic failure.[157] Since paclitaxel reverses these defects in mouse models,[158] inhibitors of tau polymerization, phospho tau peptide vaccines,[159] and other microtubule stabilizers[160] are being investigated.

ABERRANT CELL-CYCLE REENTRY

In league with secondary deregulations of calcium and transport, a failure in the normal suppression of the cell cycle in Alzheimer's disease has been hypothesized.[161] Markers of aberrant cell-cycle reentry are detected in all stages of Alzheimer's disease and in mild cognitive impairment,[162] but they are most prominent at the G_1–S-phase boundary.[163] This may progress to completion of DNA replication, resulting in tetraploid neurons and activation of mitotic cyclins, but mitoses are absent.[164] Cyclin-dependent kinase–inhibitor proteins, which maintain cell-cycle exit, are also deranged in Alzheimer's disease.[165] Oxidative stress and DNA-damaging agents, including Aβ and the carboxyl-terminal 99 amino acid BACE-1 product C99, all initiate DNA replication and death in cultured neurons.[166] The event inciting cell-cycle reentry in Alzheimer's disease is unknown. Furthermore, whether it is pathogenic or just reflects a survival response to repair damaged DNA[167] is unclear.

CHOLESTEROL METABOLISM

A defect in cholesterol metabolism is an appealing hypothesis because it ties together the apolipoprotein E (*APOE*) genetic risk, amyloid production and aggregation, and vasculopathy of Alzheimer's disease. However, proof is also lacking for this hypothesis. Cholesterol is an essential component of neuronal membranes and is concentrated in sphingolipid islands termed "lipid rafts." Rafts are ordered platforms for the assembly of β-secretases and γ-secretases and processing of amyloid precursor protein into Aβ[168] (Fig. 1 and 2). Aβ generation and aggregation are promoted and clearance from the brain is reduced when an overabundance of esterified cholesterol decreases membrane lipid turnover. Glial-derived APOE is the primary cholesterol transporter in the brain. A major determinant of the risk of late-onset Alzheimer's disease is the APOE isoform inheritance pattern (APOE2, APOE3, or APOE4)[169]; a single E4 allele increases the risk by a factor of 4, and two E4 alleles increase the risk by a factor of 19.[170] APOE4 is not only a pathological chaperone, promoting Aβ deposition[171] and tau phosphorylation,[172] but it is also the least effective of the three in promoting healthy membrane lipid turnover and the uptake of lipoprotein particles.

High serum cholesterol levels in midlife increase the risk of Alzheimer's disease.[173] In observational studies, use of statins was shown to be associated with a reduced risk. Statins appear to reduce the membrane pool of free cholesterol.[174] Other actions of statins that are not dependent on cholesterol include reductions in inflammation[175] and isoprenoids and up-regulation of both α-secretase[176] and vascular function. One prospective trial of statins showed cognitive improvements in patients with mild Alzheimer's disease,[177] but a recent multicenter trial did not.[178] Thus, the benefit of statins remains controversial. An alternative pharmacologic approach is to

limit the esterification of cholesterol.[179] Improvement of membrane biophysics and function through ingestion of n–3 fatty acid supplements has also been studied (NCT00440050).[180]

CONCLUSIONS

An effective treatment for sporadic Alzheimer's disease rests on the translation of the disease pathways we have discussed, as well as additional molecular mechanisms or new risk genes (e.g., apolipoprotein J) defined by gene-expression profiling and whole-genome association studies,[181,182] into specific pharmacologic targets. Examples of recently discovered proteins encoded by these risk genes and mechanisms include apolipoprotein J (clusterin), another Aβ chaperone,[183] TOMM40, a transporter of proteins across the mitochondrial membrane, and Sortillin-related receptor, which functions to partition amyloid precursor protein away from β-secretase and γ-secretase; this is consistent with observations that levels are reduced in the brains of patients with Alzheimer's disease and mild cognitive impairment.[184,185] Another potential risk factor for sporadic Alzheimer's disease, general anesthesia, promotes tau insolubility and Aβ oligomerization,[186,187] deficiency of estrogen in the brains of postmenopausal women,[188] and chronic activation of the glucocorticoid axis.[189] However, their underlying mechanisms are diverse, and whether any of these factors lead to amyloid deposition and tauopathy in humans is unknown. Prospective studies also show that cognitive leisure activity and training can lower the risk of dementia[190]; findings from these studies provide support for the concept of building a "cognitive reserve." The figure in the Supplementary Appendix (available with the full text of this article at NEJM.org) summarizes the heterogeneity of pathways that could initiate and drive Alzheimer's disease. There is no single linear chain of events. Complicating matters, some changes are not pathologic but reactionary or protective. Thus, the development of a multitargeted approach to prevent or symptomatically treat Alzheimer's disease, as used in current practice for other multigenic disorders, is needed.[191] Recent studies point to brain atrophy and other pathologic conditions, not severe amyloid or tangle load, in accounting for dementia in the oldest old (persons 80 years of age or older).[192] It remains possible that many of these mechanisms, including the amyloid hypothesis, are minor or wrong and that some critical aging-related process is the disease trigger.

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REFERENCES

1. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology 2007;68:326-37.
2. den Dunnen WF, Brouwer WH, Bijlard E, et al. No disease in the brain of a 115-year-old woman. Neurobiol Aging 2008;29:1127-32.
3. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119-22.
4. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat Rev Mol Cell Biol 2007;8:101-12.
5. Busciglio J, Pelsman A, Wong C, et al. Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome. Neuron 2002;33:677-88.
6. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 2001;81:741-66.
7. Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell 2005;120:545-55.
8. Kayed R, Head E, Thompson JL, et al. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 2003;300:486-9.
9. Klein WL, Krafft GA, Finch CE. Targeting small Abeta oligomers: the solution to an Alzheimer's disease conundrum? Trends Neurosci 2001;24:219-24.
10. Walsh DM, Selkoe DJ. A beta oligomers — a decade of discovery. J Neurochem 2007;101:1172-84.
11. Walsh DM, Townsend M, Podlisny MB, et al. Certain inhibitors of synthetic amyloid beta-peptide (Abeta) fibrillogenesis block oligomerization of natural Abeta and thereby rescue long-term potentiation. J Neurosci 2005;25:2455-62.
12. Klyubin I, Betts V, Welzel AT, et al. Amyloid beta protein dimer-containing human CSF disrupts synaptic plasticity: prevention by systemic passive immunization. J Neurosci 2008;28:4231-7.
13. Lue LF, Kuo YM, Roher AE, et al. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. Am J Pathol 1999;155:853-62.
14. Kamenetz F, Tomita T, Hsieh H, et al. APP processing and synaptic function. Neuron 2003;37:925-37.
15. Kanemitsu H, Tomiyama T, Mori H. Human neprilysin is capable of degrading amyloid beta peptide not only in the monomeric form but also the pathological oligomeric form. Neurosci Lett 2003;350:113-6.
16. Iwata N, Tsubuki S, Takaki Y, et al. Metabolic regulation of brain Abeta by neprilysin. Science 2001;292:1550-2.
17. Qiu WQ, Walsh DM, Ye Z, et al. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. J Biol Chem 1998;273:32730-8.

18. Farris W, Mansourian S, Chang Y, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. Proc Natl Acad Sci U S A 2003;100:4162-7.
19. Leissring MA, Farris W, Chang AY, et al. Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. Neuron 2003;40:1087-93.
20. Siemers ER, Quinn JF, Kaye J, et al. Effects of a gamma-secretase inhibitor in a randomized study of patients with Alzheimer disease. Neurology 2006;66:602-4.
21. McGeer PL, McGeer E. Is there a future for vaccination as a treatment for Alzheimer's disease? Neurobiol Aging 2003; 24:391-5.
22. Hock C, Konietzko U, Streffer JR, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. Neuron 2003;38:547-54.
23. Gilman S, Koller M, Black RS, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology 2005;64:1553-62.
24. Holmes C, Boche D, Wilkinson D, et al. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. Lancet 2008;372:216-23.
25. Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci 2001;24:1121-59.
26. Iqbal K, Alonso Adel C, Chen S, et al. Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys Acta 2005;1739:198-210.
27. Khlistunova I, Biernat J, Wang Y, et al. Inducible expression of Tau repeat domain in cell models of tauopathy: aggregation is toxic to cells but can be reversed by inhibitor drugs. J Biol Chem 2006;281:1205-14.
28. Santacruz K, Lewis J, Spires T, et al. Tau suppression in a neurodegenerative mouse model improves memory function. Science 2005;309:476-81.
29. Oddo S, Vasilevko V, Caccamo A, Kitazawa M, Cribbs DH, LaFerla FM. Reduction of soluble Abeta and tau, but not soluble Abeta alone, ameliorates cognitive decline in transgenic mice with plaques and tangles. J Biol Chem 2006;281:39413-23.
30. Andorfer C, Kress Y, Espinoza M, et al. Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. J Neurochem 2003;86:582-90.
31. Lee HG, Perry G, Moreira PI, et al. Tau phosphorylation in Alzheimer's disease: pathogen or protector? Trends Mol Med 2005;11:164-9.
32. Goedert M, Jakes R. Mutations causing neurodegenerative tauopathies. Biochim Biophys Acta 2005;1739:240-50.
33. Gómez-Isla T, Hollister R, West H, et al. Neuronal loss correlates with but exceeds neurofibrillary tangles in Alzheimer's disease. Ann Neurol 1997;41:17-24.
34. Wallin AK, Blennow K, Andreasen N, Minthon L. CSF biomarkers for Alzheimer's disease: levels of beta-amyloid, tau, phosphorylated tau relate to clinical symptoms and survival. Dement Geriatr Cogn Disord 2006;21:131-8.
35. Mattsson N, Zetterberg H, Hansson O, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009;302: 385-93.
36. Oddo S, Caccamo A, Shepherd JD, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 2003;39:409-21.
37. Gotz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. Science 2001;293:1491-5.
38. Lewis J, Dickson DW, Lin WL, et al. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 2001;293:1487-91.
39. Roberson ED, Scearce-Levie K, Palop JJ, et al. Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 2007;316:750-4.
40. Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A. Tau is essential to beta-amyloid-induced neurotoxicity. Proc Natl Acad Sci U S A 2002;99:6364-9.
41. López Salon M, Morelli L, Castaño EM, Soto EF, Pasquini JM. Defective ubiquitination of cerebral proteins in Alzheimer's disease. J Neurosci Res 2000;62: 302-10.
42. Hoozemans JJ, Veerhuis R, Van Haastert ES, et al. The unfolded protein response is activated in Alzheimer's disease. Acta Neuropathol 2005;110:165-72.
43. McLaurin J, Kierstead ME, Brown ME, et al. Cyclohexanehexol inhibitors of Abeta aggregation prevent and reverse Alzheimer phenotype in a mouse model. Nat Med 2006;12:801-8.
44. Ono K, Condron MM, Ho L, et al. Effects of grape seed-derived polyphenols on amyloid beta-protein self-assembly and cytotoxicity. J Biol Chem 2008;283:32176-87.
45. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science 2002;298:789-91.
46. Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. Neurology 2007;68:1501-8.
47. Masliah E, Mallory M, Alford M, et al. Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. Neurology 2001;56:127-9.
48. DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Ann Neurol 1990;27:457-64.
49. Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572-80.
50. Davies CA, Mann DM, Sumpter PQ, Yates PO. A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. J Neurol Sci 1987;78:151-64.
51. Masliah E, Crews L, Hansen L. Synaptic remodeling during aging and in Alzheimer's disease. J Alzheimers Dis 2006;9: Suppl:91-9.
52. Lister JP, Barnes CA. Neurobiological changes in the hippocampus during normative aging. Arch Neurol 2009;66:829-33.
53. Larson J, Lynch G, Games D, Seubert P. Alterations in synaptic transmission and long-term potentiation in hippocampal slices from young and aged PDAPP mice. Brain Res 1999;840:23-35.
54. Chapman PF, White GL, Jones MW, et al. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. Nat Neurosci 1999;2: 271-6.
55. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci 2007;27:2866-75.
56. Snyder EM, Nong Y, Almeida CG, et al. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 2005;8: 1051-8.
57. Hsieh H, Boehm J, Sato C, et al. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron 2006;52:831-43.
58. Mucke L, Masliah E, Yu GQ, et al. High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J Neurosci 2000;20:4050-8.
59. Cooper JD, Salehi A, Delcroix JD, et al. Failed retrograde transport of NGF in a mouse model of Down's syndrome: reversal of cholinergic neurodegenerative phenotypes following NGF infusion. Proc Natl Acad Sci U S A 2001;98:10439-44.
60. Tuszynski MH. Nerve growth factor gene therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2007;21:179-89.
61. Connor B, Young D, Yan Q, Faull RL, Synek B, Dragunow M. Brain-derived neurotrophic factor is reduced in Alzheimer's disease. Brain Res Mol Brain Res 1997;49: 71-81.
62. Garzon DJ, Fahnestock M. Oligomeric amyloid decreases basal levels of brain-derived neurotrophic factor (BDNF) mRNA via specific downregulation of BDNF transcripts IV and V in differentiated human neuroblastoma cells. J Neurosci 2007;27: 2628-35.

63. Ernfors P, Bramham CR. The coupling of a trkB tyrosine residue to LTP. Trends Neurosci 2003;26:171-3.
64. Nagahara AH, Merrill DA, Coppola G, et al. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nat Med 2009;15:331-7.
65. Ikonomovic MD, Wecker L, Abrahamson EE, et al. Cortical alpha7 nicotinic acetylcholine receptor and beta-amyloid levels in early Alzheimer disease. Arch Neurol 2009;66:646-51.
66. Maelicke A, Samochocki M, Jostock R, et al. Allosteric sensitization of nicotinic receptors by galantamine, a new treatment strategy for Alzheimer's disease. Biol Psychiatry 2001;49:279-88.
67. Wang HY, Lee DH, D'Andrea MR, Peterson PA, Shank RP, Reitz AB. beta-Amyloid(1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity: implications for Alzheimer's disease pathology. J Biol Chem 2000;275:5626-32.
68. Nitsch RM. From acetylcholine to amyloid: neurotransmitters and the pathology of Alzheimer's disease. Neurodegeneration 1996;5:477-82.
69. Caccamo A, Oddo S, Billings LM, et al. M1 receptors play a central role in modulating AD-like pathology in transgenic mice. Neuron 2006;49:671-82.
70. Bitner RS, Nikkel AL, Markosyan S, Otte S, Puttfarcken P, Gopalakrishnan M. Selective alpha7 nicotinic acetylcholine receptor activation regulates glycogen synthase kinase3beta and decreases tau phosphorylation in vivo. Brain Res 2009;1265:65-74.
71. Bodick NC, Offen WW, Levey AI, et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. Arch Neurol 1997;54:465-73.
72. Nitsch RM, Deng M, Tennis M, Schoenfeld D, Growdon JH. The selective muscarinic M1 agonist AF102B decreases levels of total Abeta in cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 2000;48:913-8.
73. Mungarro-Menchaca X, Ferrera P, Moran J, Arias C. beta-Amyloid peptide induces ultrastructural changes in synaptosomes and potentiates mitochondrial dysfunction in the presence of ryanodine. J Neurosci Res 2002;68:89-96.
74. Hauptmann S, Keil U, Scherping I, Bonert A, Eckert A, Muller WE. Mitochondrial dysfunction in sporadic and genetic Alzheimer's disease. Exp Gerontol 2006;41:668-73.
75. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med 2008;14:45-53.
76. Caspersen C, Wang N, Yao J, et al. Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. FASEB J 2005;19:2040-1.
77. Hirai K, Aliev G, Nunomura A, et al. Mitochondrial abnormalities in Alzheimer's disease. J Neurosci 2001;21:3017-23.
78. Gouras GK, Almeida CG, Takahashi RH. Intraneuronal Abeta accumulation and origin of plaques in Alzheimer's disease. Neurobiol Aging 2005;26:1235-44.
79. Lustbader JW, Cirilli M, Lin C, et al. ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 2004;304:448-52.
80. Cardoso SM, Santana I, Swerdlow RH, Oliveira CR. Mitochondria dysfunction of Alzheimer's disease cybrids enhances Abeta toxicity. J Neurochem 2004;89:1417-26.
81. Wallace DC. Mitochondrial diseases in man and mouse. Science 1999;283:1482-8.
82. Cho DH, Nakamura T, Fang J, et al. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 2009;324:102-5.
83. Doody RS, Gavrilova SI, Sano M, et al. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet 2008;372:207-15.
84. Good PF, Werner P, Hsu A, Olanow CW, Perl DP. Evidence of neuronal oxidative damage in Alzheimer's disease. Am J Pathol 1996;149:21-8.
85. Smith MA, Perry G, Richey PL, et al. Oxidative damage in Alzheimer's. Nature 1996;382:120-1.
86. Nunomura A, Perry G, Aliev G, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol 2001;60:759-67.
87. Hensley K, Carney JM, Mattson MP, et al. A model for beta-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer disease. Proc Natl Acad Sci U S A 1994;91:3270-4.
88. Combs CK, Karlo JC, Kao SC, Landreth GE. beta-Amyloid stimulation of microglia and monocytes results in TNFalpha-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. J Neurosci 2001;21:1179-88.
89. Yan SD, Chen X, Fu J, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature 1996;382:685-91.
90. Keller JN, Mark RJ, Bruce AJ, et al. 4-Hydroxynonenal, an aldehydic product of membrane lipid peroxidation, impairs glutamate transport and mitochondrial function in synaptosomes. Neuroscience 1997;80:685-96.
91. Humphries KM, Szweda LI. Selective inactivation of alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase: reaction of lipoic acid with 4-hydroxy-2-nonenal. Biochemistry 1998;37:15835-41.
92. Smith MA, Richey Harris PL, Sayre LM, Beckman JS, Perry G. Widespread peroxynitrite-mediated damage in Alzheimer's disease. J Neurosci 1997;17:2653-7.
93. Mark RJ, Pang Z, Geddes JW, Uchida K, Mattson MP. Amyloid beta-peptide impairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. J Neurosci 1997;17:1046-54.
94. Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR. Copper, iron and zinc in Alzheimer's disease senile plaques. J Neurol Sci 1998;158:47-52.
95. Yamamoto A, Shin RW, Hasegawa K, et al. Iron (III) induces aggregation of hyperphosphorylated tau and its reduction to iron (II) reverses the aggregation: implications in the formation of neurofibrillary tangles of Alzheimer's disease. J Neurochem 2002;82:1137-47.
96. Arispe N, Pollard HB, Rojas E. Zn2+ interaction with Alzheimer amyloid beta protein calcium channels. Proc Natl Acad Sci U S A 1996;93:1710-5.
97. Cuajungco MP, Fagét KY. Zinc takes the center stage: its paradoxical role in Alzheimer's disease. Brain Res Brain Res Rev 2003;41:44-56.
98. Praticò D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. Trends Pharmacol Sci 2008;29:609-15.
99. Ritchie CW, Bush AI, Mackinnon A, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2008;7:779-86.
100. Craft S, Peskind E, Schwartz MW, Schellenberg GD, Raskind M, Porte D Jr. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology 1998;50:164-8.
101. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol 2004;61:661-6.
102. Messier C, Teutenberg K. The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. Neural Plast 2005;12:311-28.
103. de la Monte SM, Tong M, Lester-Coll N, Plater M Jr, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. J Alzheimers Dis 2006;10:89-109.
104. Cohen E, Bieschke J, Perciavalle RM, Kelly JW, Dillin A. Opposing activities protect against age-onset proteotoxicity. Science 2006;313:1604-10.
105. Wu W, Brickman AM, Luchsinger J, et al. The brain in the age of old: the hippocampal formation is targeted differentially by diseases of late life. Ann Neurol 2008;64:698-706.
106. Takashima A. GSK-3 is essential in the pathogenesis of Alzheimer's disease. J Alzheimers Dis 2006;9:Suppl:309-17.

107. Cook DG, Leverenz JB, McMillan PJ, et al. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. Am J Pathol 2003;162:313-9.
108. Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, Haynatzki GR. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. Exp Neurol 2006;199:265-73.
109. Risner ME, Saunders AM, Altman JF, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J 2006;6:246-54.
110. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurol 2003;2:89-98.
111. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke–Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220-41.
112. Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. Stroke 2004;35:Suppl 1:2616-9.
113. Roher AE, Esh C, Rahman A, Kokjohn TA, Beach TG. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke 2004;35:Suppl 1:2623-7.
114. Ruitenberg A, den Heijer T, Bakker SL, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol 2005;57:789-94.
115. Jagust WJ. Neuroimaging in dementia. Neurol Clin 2000;18:885-902.
116. Price JM, Chi X, Hellermann G, Sutton ET. Physiological levels of beta-amyloid induce cerebral vessel dysfunction and reduce endothelial nitric oxide production. Neurol Res 2001;23:506-12.
117. Paris D, Patel N, DelleDonne A, Quadros A, Smeed R, Mullan M. Impaired angiogenesis in a transgenic mouse model of cerebral amyloidosis. Neurosci Lett 2004;366:80-5.
118. Van Nostrand WE, Melchor JP, Ruffini L. Pathologic amyloid beta-protein cell surface fibril assembly on cultured human cerebrovascular smooth muscle cells. J Neurochem 1998;70:216-23.
119. Deane R, Zlokovic BV. Role of the blood-brain barrier in the pathogenesis of Alzheimer's disease. Curr Alzheimer Res 2007;4:191-7.
120. Sink KM, Leng X, Williamson J, et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. Arch Intern Med 2009;169:1195-202.
121. Hoffman LB, Schmeidler J, Lesser GT, et al. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. Neurology 2009;72:1720-6.
122. Luchsinger JA, Tang MX, Miller J, Green R, Mayeux R. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol 2007;64:86-92.
123. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 2008;300:1774-83.124.
124. Wilcock DM, Jantzen PT, Li Q, Morgan D, Gordon MN. Amyloid-beta vaccination, but not nitro-nonsteroidal anti-inflammatory drug treatment, increases vascular amyloid and microhemorrhage while both reduce parenchymal amyloid. Neuroscience 2007;144:950-60.
125. Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease — a double-edged sword. Neuron 2002;35:419-32.
126. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21:383-421.
127. Li Y, Liu L, Barger SW, Griffin WS. Interleukin-1 mediates pathological effects of microglia on tau phosphorylation and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. J Neurosci 2003;23:1605-11.
128. Simard AR, Soulet D, Gowing G, Julien JP, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron 2006;49:489-502.
129. McGeer EG, Yasojima K, Schwab C, McGeer PL. The pentraxins: possible role in Alzheimer's disease and other innate inflammatory diseases. Neurobiol Aging 2001;22:843-8.
130. Matsumoto Y, Yanase D, Noguchi-Shinohara M, Ono K, Yoshita M, Yamada M. Blood-brain barrier permeability correlates with medial temporal lobe atrophy but not with amyloid-beta protein transport across the blood-brain barrier in Alzheimer's disease. Dement Geriatr Cogn Disord 2007;23:241-5.
131. Clifford PM, Zarrabi S, Siu G, et al. Abeta peptides can enter the brain through a defective blood-brain barrier and bind selectively to neurons. Brain Res 2007;1142:223-36.
132. Fiala M, Lin J, Ringman J, et al. Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer's disease patients. J Alzheimers Dis 2005;7:221-32.
133. McGeer PL, McGeer EG. NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol Aging 2007;28:639-47.
134. Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. Neurology 2008;70:1672-7.
135. Lleó A, Berezovska O, Herl L, et al. Nonsteroidal anti-inflammatory drugs lower Abeta42 and change presenilin 1 conformation. Nat Med 2004;10:1065-6.
136. Weggen S, Eriksen JL, Sagi SA, et al. Evidence that nonsteroidal anti-inflammatory drugs decrease amyloid beta42 production by direct modulation of gamma-secretase activity. J Biol Chem 2003;278:31831-7.
137. Szekely CA, Breitner JC, Fitzpatrick AL, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. Neurology 2008;70:17-24.
138. Shen Y, Meri S. Yin and Yang: complement activation and regulation in Alzheimer's disease. Prog Neurobiol 2003;70:463-72.
139. Isaacs AM, Senn DB, Yuan M, Shine JP, Yankner BA. Acceleration of amyloid beta-peptide aggregation by physiological concentrations of calcium. J Biol Chem 2006;281:27916-23.
140. Pierrot N, Ghisdal P, Caumont AS, Octave JN. Intraneuronal amyloid-beta1-42 production triggered by sustained increase of cytosolic calcium concentration induces neuronal death. J Neurochem 2004;88:1140-50.
141. Leissring MA, Akbari Y, Fanger CM, Cahalan MD, Mattson MP, LaFerla FM. Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockin mice. J Cell Biol 2000;149:793-8.
142. Nelson O, Tu H, Lei T, Bentahir M, de Strooper B, Bezprozvanny I. Familial Alzheimer disease-linked mutations specifically disrupt Ca2+ leak function of presenilin 1. J Clin Invest 2007;117:1230-9.
143. LaFerla FM. Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. Nat Rev Neurosci 2002;3:862-72.
144. Rothman SM, Olney JW. Excitotoxicity and the NMDA re4ptor — still lethal after eight years. Trends Neurosci 1995;18:57-8.
145. Arispe N, Pollard HB, Rojas E. Giant multilevel cation channels formed by Alzheimer disease amyloid beta-protein [A beta P-(1-40)] in bilayer membranes. Proc Natl Acad Sci U S A 1993;90:10573-7.
146. Lin H, Bhatia R, Lal R. Amyloid beta protein forms ion channels: implications for Alzheimer's disease pathophysiology. FASEB J 2001;15:2433-44. [Erratum, FASEB J 2002;16:759.]
147. Koo EH, Sisodia SS, Archer DR, et al. Precursor of amyloid protein in Alzheimer disease undergoes fast anterograde axonal transport. Proc Natl Acad Sci U S A 1990;87:1561-5.
148. Lazarov O, Lee M, Peterson DA, Sisodia SS. Evidence that synaptically released beta-amyloid accumulates as extracellular deposits in the hippocampus of transgenic mice. J Neurosci 2002;22:9785-93.
149. Kamal A, Almenar-Queralt A, LeBlanc JF, Roberts EA, Goldstein LS. Kinesin-mediated axonal transport of a membrane compartment containing beta-secretase and presenilin-1 requires APP. Nature 2001;414:643-8.

150. Stokin GB, Lillo C, Falzone TL, et al. Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. Science 2005;307:1282-8.
151. Lazarov O, Morfini GA, Lee EB, et al. Axonal transport, amyloid precursor protein, kinesin-1, and the processing apparatus: revisited. J Neurosci 2005;25:2386-95.
152. Ring S, Weyer SW, Kilian SB, et al. The secreted beta-amyloid precursor protein ectodomain APPs alpha is sufficient to rescue the anatomical, behavioral, and electrophysiological abnormalities of APP-deficient mice. J Neurosci 2007;27:7817-26.
153. Dawson GR, Seabrook GR, Zheng H, et al. Age-related cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the beta-amyloid precursor protein. Neuroscience 1999;90:1-13.
154. Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. Neurology 1992;42:1681-8.
155. Roher AE, Weiss N, Kokjohn TA, et al. Increased A beta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease. Biochemistry 2002;41:11080-90.
156. Sisodia SS. Biomedicine: a cargo receptor mystery APParently solved? Science 2002;295:805-7.
157. Butler D, Bendiske J, Michaelis ML, Karanian DA, Bahr BA. Microtubule-stabilizing agent prevents protein accumulation-induced loss of synaptic markers. Eur J Pharmacol 2007;562:20-7.
158. Li G, Faibushevich A, Turunen BJ, et al. Stabilization of the cyclin-dependent kinase 5 activator, p35, by paclitaxel decreases beta-amyloid toxicity in cortical neurons. J Neurochem 2003;84:347-62.
159. Sigurdsson EM. Immunotherapy targeting pathological tau protein in Alzheimer's disease and related tauopathies. J Alzheimers Dis 2008;15:157-68.
160. Matsuoka Y, Jouroukhin Y, Gray AJ, et al. A neuronal microtubule-interacting agent, NAPVSIPQ, reduces tau pathology and enhances cognitive function in a mouse model of Alzheimer's disease. J Pharmacol Exp Ther 2008;325:146-53.
161. Busser J, Geldmacher DS, Herrup K. Ectopic cell cycle proteins predict the sites of neuronal cell death in Alzheimer's disease brain. J Neurosci 1998;18:2801-7.
162. Yang Y, Mufson EJ, Herrup K. Neuronal cell death is preceded by cell cycle events at all stages of Alzheimer's disease. J Neurosci 2003;23:2557-63.
163. Liu DX, Greene LA. Neuronal apoptosis at the G1/S cell cycle checkpoint. Cell Tissue Res 2001;305:217-28.
164. Mosch B, Morawski M, Mittag A, Lenz D, Tarnok A, Arendt T. Aneuploidy and DNA replication in the normal human brain and Alzheimer's disease. J Neurosci 2007;27:6859-67.
165. Ogawa O, Lee HG, Zhu X, et al. Increased p27, an essential component of cell cycle control, in Alzheimer's disease. Aging Cell 2003;2:105-10.
166. Klein JA, Ackerman SL. Oxidative stress, cell cycle, and neurodegeneration. J Clin Invest 2003;111:785-93.
167. Yang Y, Herrup K. Cell division in the CNS: protective response or lethal event in post-mitotic neurons? Biochim Biophys Acta 2007;1772:457-66.
168. Ehehalt R, Keller P, Haass C, Thiele C, Simons K. Amyloidogenic processing of the Alzheimer beta-amyloid precursor protein depends on lipid rafts. J Cell Biol 2003;160:113-23.
169. St George-Hyslop PH. Molecular genetics of Alzheimer's disease. Biol Psychiatry 2000;47:183-99.
170. Strittmatter WJ, Roses AD. Apolipoprotein E and Alzheimer's disease. Annu Rev Neurosci 1996;19:53-77.
171. Reiman EM, Chen K, Liu X, et al. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc Natl Acad Sci U S A 2009;106:6820-5.
172. Holtzman DM, Bales KR, Tenkova T, et al. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 2000;97:2892-7.
173. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322:1447-51.
174. Vega GL, Weiner MF, Lipton AM, et al. Reduction in levels of 24S-hydroxycholesterol by statin treatment in patients with Alzheimer disease. Arch Neurol 2003;60:510-5.
175. Cordle A, Landreth G. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors attenuate beta-amyloid-induced microglial inflammatory responses. J Neurosci 2005;25:299-307.
176. Pedrini S, Carter TL, Prendergast G, Petanceska S, Ehrlich ME, Gandy S. Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. PLoS Med 2005;2(1):e18.
177. Sparks DL, Sabbagh MN, Connor DJ, et al. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. Arch Neurol 2005;62:753-7.
178. Jones RW, Kivipelto M, Feldman H, et al. The Atorvastatin/Donepezil in Alzheimer's Disease Study (LEADe): design and baseline characteristics. Alzheimers Dement 2008;4:145-53.
179. Hutter-Paier B, Huttunen HJ, Puglielli L, et al. The ACAT inhibitor CP-113,818 markedly reduces amyloid pathology in a mouse model of Alzheimer's disease. Neuron 2004;44:227-38.
180. Quinn JF, Raman R, Thomas RG, et al. A clinical trial of docosahexanoic acid (DHA) for the treatment of Alzheimer's disease. Alzheimers and Dement 2009;5:Suppl:84. abstract.
181. Lu T, Pan Y, Kao SY, et al. Gene regulation and DNA damage in the ageing human brain. Nature 2004;429:883-91.
182. Bertram L, Lange C, Mullin K, et al. Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. Am J Hum Genet 2008;83:623-32.
183. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 2009;41:1094-9.
184. Sager KL, Wuu J, Leurgans SE, et al. Neuronal LR11/sorLA expression is reduced in mild cognitive impairment. Ann Neurol 2007;62:640-7.
185. Rogaeva E, Meng Y, Lee JH, et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet 2007;39:168-77.
186. Planel E, Bretteville A, Liu L, et al. Acceleration and persistence of neurofibrillary pathology in a mouse model of tauopathy following anesthesia. FASEB J 2009;23:2595-604.
187. Xie Z, Culley DJ, Dong Y, et al. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. Ann Neurol 2008;64:618-27.
188. Henderson VW. Estrogens, episodic memory, and Alzheimer's disease: a critical update. Semin Reprod Med 2009;27:283-93.
189. Csernansky JG, Dong H, Fagan AM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry 2006;163:2164-9.
190. Hall CB, Lipton RB, Sliwinski M, Katz MJ, Derby CA, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology 2009;73:356-61.
191. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
192. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. N Engl J Med 2009;360:2302-9.