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Review Article

Neuropathology and therapeutic management of Alzheimer's disease – an update

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which is the principal cause of dementia throughout the world and the fourth cause of death in developed countries. The pathological hallmarks of this disease are regionalized neuronal dysfunction/death, accumulation of senile plaques extracellularly and neurofibrillary tangles (NFTs) intraneuronally. Several hypotheses have been put forth to explain the pathophysiology of this disease, including aberrant β-amyloid (Aβ) metabolism, hyperphosphorylation of cytoskeletal proteins, genetic predisposition (mutations in genes coding for presenilin-1 and -2 (PS-1 and PS-2) and amyloid precursor protein (APP), apolipoprotein E genotype, oxidative stress, excitotoxicity, inflammation and abnormal cell cycle re-entry. However, none of these hypotheses alone is sufficient to explain the diversity of biochemical and pathological abnormalities in AD. Currently, medications approved by the United States FDA for AD include acetylcholinesterase (AChE) inhibitors and memantine. However, these drugs provide only symptomatic relief and do not stop disease progression. The major focus of research now is to find novel therapeutic drug candidates targeting the underlying pathophysiological mechanisms. These therapeutic strategies include drugs targeting amyloid and tau pathology, immunotherapy, neurotransmitter replacement therapy, nutraceuticals and disease-modifying therapies. The main focus of this review is to provide new insight on the various mechanisms involved in the neuropathology of AD and shed light on current and future treatment strategies aimed at improving both cognitive deficits and halting the deadly neurodegenerative progression of the disease.

Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder (1). It is characterized by progressive memory loss, impairments in language and visuospatial skills, episodes of psychosis, aggressiveness and agitation, ultimately leading to death (2, 3). Histologically, it is characterized by two main structural changes in the brain: intracellular protein deposits termed neurofibrillary tangles (NFTs) and extracellular amyloid protein deposits surrounded by dystrophic neuritis that contribute to senile plaques (4) (Fig. 1).

In 1907, 100 years ago, Alois Alzheimer described two pathological alterations in the brain of a female patient suffering from dementia (5). Alzheimer had described a 'peculiar substance' occurring as extracellular deposits in specific brain regions, which are now referred to as amyloid plaques. In the mid-1980s it was discovered that the plaques consisted of aggregates of small peptides characterized as amyloid plaques (6, 7). The second lesion described by Alzheimer were the NFTs, which were later found to be composed of abnormally hyperphosphorylated tau protein (8, 9). Although

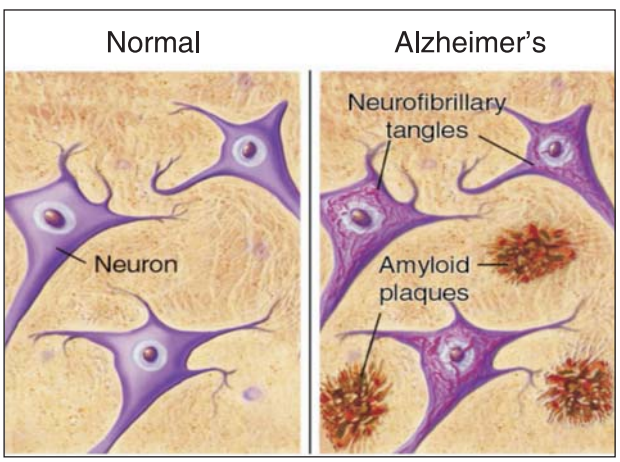


Fig. 1. A comparison of the normal and AD brain neurons where the AD brain shows the presence of the hallmark features, *i.e.*, amyloid plaques and neurofibrillary tangles.

plaques and NFTs are the main significant pathological changes occurring in the AD brain, other structural and functional alterations also ensue, including inflammatory responses and oxidative stress (10, 11).

Epidemiological studies reveal that AD affects nearly 25 million patients worldwide, with over 4 million in the U.S. alone. As the average life expectancy increases throughout the world, it is expected that the number of people at risk of developing AD will increase significantly. In fact, it is estimated that by 2050, 14 million Americans will have AD if preventive treatment does not become available (12). This debilitating disorder poses a great financial burden not only on society but also on caregivers. The minimal cost of treatment is estimated to be upwards of USD 100 billion per year, a figure that will rise as the prevalence increases (13).

Despite these daunting statistics and the progress made in understanding the molecular and cellular basis of this disorder, there is still a need to develop an effective therapy for the management of AD. Current medications that have received FDA approval for the treatment of AD include acetylcholinesterase (AChE) inhibitors for mild to moderate cases, and memantine, an NMDA receptor antagonist for the treatment of moderate to severe Alzheimer's dementia. However, these drugs only provide symptomatic relief in some patients but do not halt disease progression (14, 15). Thus, there is an enormous medical need to develop novel therapeutic strategies that target the underlying neuropathological mechanisms involved in the progression of AD.

The aim of this review is to provide an overview of the neuropathology of AD and present and future therapeutic strategies for AD which could be employed for effective management of this progressive neurodegenerative disorder.

Etiopathogenesis of AD

The etiology and pathophysiology of AD are multifactorial and several independent hypotheses have been proposed to link the pathological lesions and the neuronal cytopathology. However, none of these theories alone is sufficient to explain the diversity of biochemical and pathological abnormalities of AD (16). It is reasonable to speculate that AD occurs as a result of a series of insults to the brain. Various factors that are involved in the etiopathogenesis of AD have been suggested.

β-Amyloid

The amyloid cascade hypothesis is the most popular hypothesis which explains the mechanisms leading to AD. It states that Aβ, a fragment of the amyloid precursor protein (APP) plays a central role in the pathogenesis of AD (17). It is believed that accumulation of Aβ (in particular the $A\beta_{42}$ peptide) in the brain initiates a cascade of events that ultimately leads to neuronal dysfunction, neurodegeneration and dementia (18). More recent findings suggest that rather than highly aggregated Aβ species, soluble prefibrillar forms of Aβ (so-called Aβ-derived diffusible ligands, or ADDLs) may represent the neurotoxic entity in synaptic dysfunction (19, 20).

Aβ is generated by proteolytic cleavage of APP, an integral membrane protein, by two proteases termed β- and γ-secretase (21). APP cleavage by α-secretase, which was the first proteolytic cleavage to be identified, precludes Aβ generation since the α-secretase cleavage site is located within the Aβ sequence (22, 23). A brief outline of APP processing by the amyloidogenic and non-amyloidogenic pathways is represented in Figure 2. The accumulation of Aβ is thought to play a pivotal role in neuronal loss or dysfunction through a cascade of events that include oxidative stress, mitochondrial oxidative damage and inflammatory processes (24, 25). In summary, Aβ remains a putative pathogenic species involved in the progression of AD (26, 27).

Hyperphosphorylated tau

Abnormally phosphorylated tau is the major constituent of NFTs. Hyperphosphorylation causes disengagement of tau from microtubules and aggregation of the filamentous protein (9). The microtubule cytoskeleton and its numerous microtubule-associated proteins (MAPs) are involved in transporting the signaling molecules at a synapse to the nucleus to induce the appropriate responses (28). MAP tau also plays an important role in the developmental maturity of neurons. Thus, disturbances and disruption of these proteins lead to synaptic and neuritic atrophy. AD is characterized by abnormal orientation and depletion of dendritic microtubules (29, 30) and abnormal hyperphosphorylated MAP tau (9).

Hyperphosphorylated tau (paired helical filaments, or PHF-tau) is unable to bind the assembled microtubules (31) and indirectly disrupts cytoskeletal integrity, leading to neuronal dysfunction and NFT formation (32, 33) (Fig. 3). However, the molecular details of tau-related neurodegeneration are still not well understood.

Oxidative stress and cell cycle dysregulation

Oxidative stress can be defined as the breaching of the oxidant defenses with consequent detrimental cellular effects (34). Free radicals that are produced during oxidative stress are speculated to be pathologically important in AD (35, 36). Modifications driven by oxidative stress have been observed in virtually all classes of biomacromolecules in association with susceptible neurons of AD. These include DNA and RNA oxidation, which is marked by increased levels of 8-hydroxyguanosine (37, 38), protein oxidation involving the oxidative modification of various enzymes involved in ATP synthesis (34, 39), lipid peroxidation (40) and modification of sugars marked by increased glycation and glycoxidation (36, 41) (Fig. 4).

There is also increasing evidence that dysregulation of the cell cycle coupled with oxidative stress in hippocampal neurons initiates the pathophysiological cascade in AD (42). This is supported by the ectopic expres-

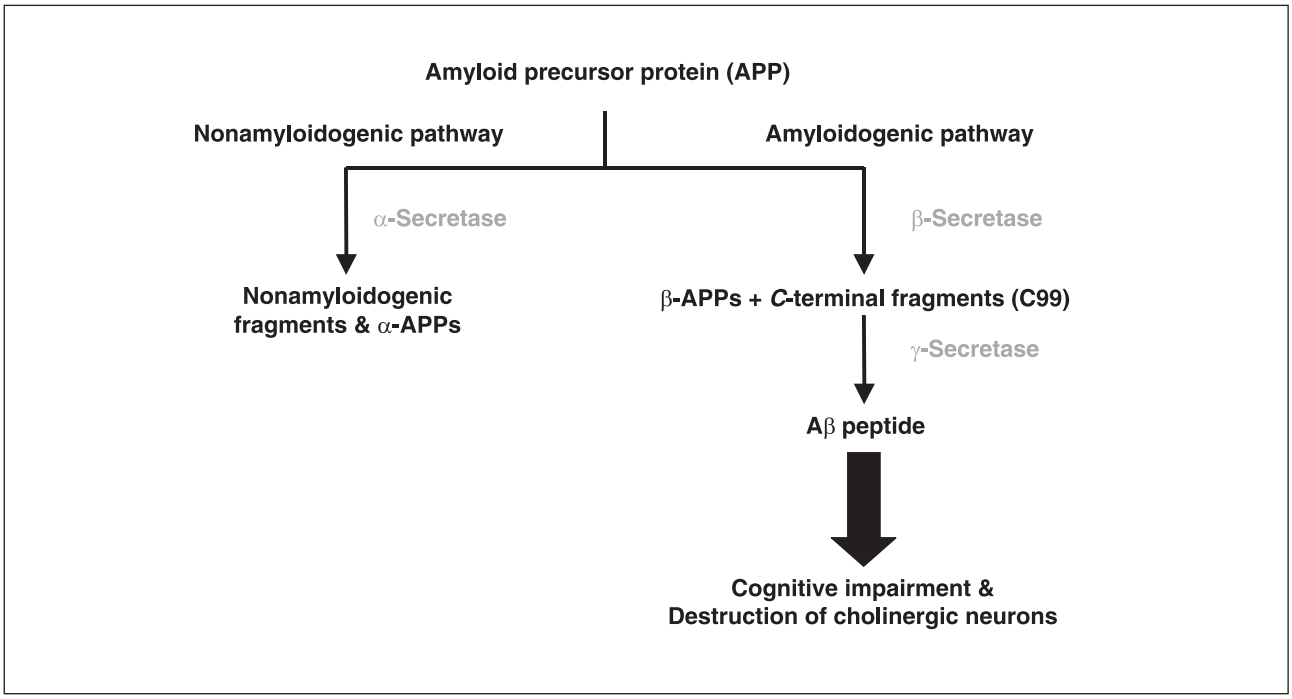


Fig. 2. Processing of amyloid precursor protein by α-, β- and γ-secretase to release β-amyloid (Aβ) peptide, the main culprit in AD pathophysiology.

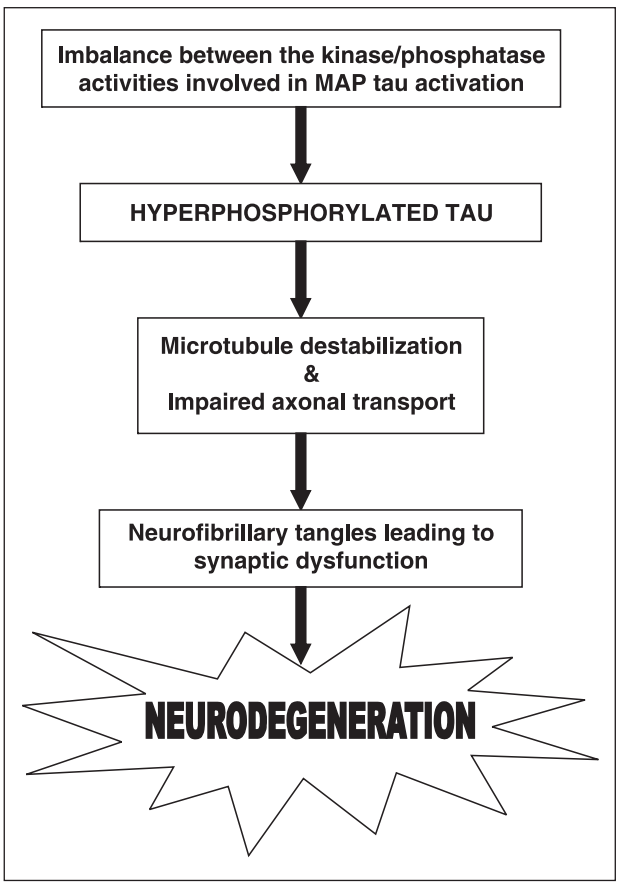


Fig. 3. Sequence of events leading to neurofibrillary tangle formation and neurodegeneration in AD.

sion of cell cycle markers (43), organelle kinesis (44) and cytoskeletal alterations. Cell cycle alterations lead to tau phosphorylation, a fact supported by the increased expression of proteins like cyclin D and cyclin-dependent kinase 4 (CDK4) involved in the G0/G1 transition during mitosis (45, 46). This cell cycle dysregulation plays an important role in the apoptotic death of postmitotic neurons (47), which finally leads to neurodegeneration. Thus, cell cycle dysregulation and oxidative stress work in synergy in the development of AD (42).

Evidence also indicates that cerebral metabolism is reduced in AD (48). The key player in this scenario is mitochondrial dysfunction (44), which results in oxidative phosphorylation and the generation of reactive oxygen species (ROS). These ROS not only have cellular targets but also damage the mitochondrial components themselves, particularly mitochondrial DNA, which is highly susceptible to oxidative stress due to a lack of histones (34). These dysfunctional mitochondria promote the interaction between redox metals and oxidative response elements (49), causing further neuronal damage.

Genetic mutations

Certain causative genetic mutations have been identified that account for less than 5% of the cases of AD, known as familial AD. These include mutations in genes coding for APP, presenilin-1 (PS-1) and presenilin-2 (PS-2). APP is a transmembrane glycoprotein that is proteolytically cleaved to generate Aβ (50). PS-1 is the most critical component of the γ-secretase complex and mutations in this gene cause the production of highly amy-

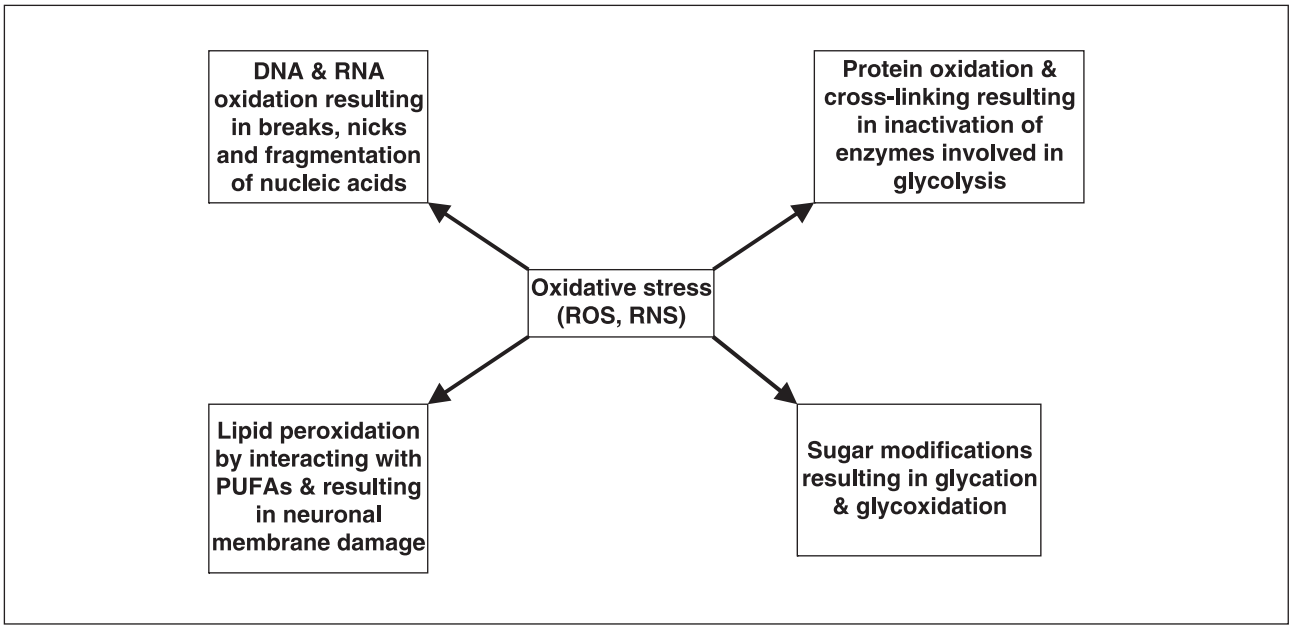


Fig. 4. Interplay between oxidative stress, nucleic acid oxidation, lipid peroxidation and protein oxidation and sugar modifications in AD.

loidogenic $A\beta_{42}$ (51-53). PS-2 is structurally similar to PS-1 but has distinct functions. It is important for the formation of a fully functional γ-secretase complex (50) and is involved in the proteolytic processing of APP. These mutations lead to increased production of Aβ, which aggregates in the brain to form the characteristic amyloid plaques (54, 55).

Neuroinflammation

In the AD brain, degenerating neurons, aggregated Aβ protein and NFTs are sites of neuroinflammation (56). Evidence highlights the strong association between AD and abnormal activity of proinflammatory cytokines such as interleukin-1β (IL-1β) (57), IL-6, transforming growth factor-β (TGF-β) (58), IL-18 and TGF-β1 (59). Aβ aggregates appear to be involved in triggering reactivity of glial cells, with the consequent release of nitric oxide (NO) (60), nerve growth factor (NGF) and signaling through the p75 cell death receptor (61). Abnormal release of IL-1 and IL-6 also affects the tau phosphorylation patterns and other intracellular events linked to neuronal degeneration (62). In addition to these findings, overexpression of IL-6 in the brain of transgenic mice that overproduce cytokines (63) is associated with gliosis and disruption of cholinergic neurotransmission in the hippocampus (64). Thus, Aβ itself stimulates the production of inflammatory cytokines by astrocytes and microglia, thereby triggering the early events of neurodegeneration associated with AD (65).

Aberrant lipid metabolism

Hypercholesterolemia and elevated levels of Aβ are linked to a risk for AD (66, 67). Cholesterol in the brain is involved in the formation of 'lipid rafts' which are implicated in cell transduction (68), and it also influences the activity of various enzymes, such as β-secretase (BACE1), which is involved in the metabolism of APP (67). The high concentration of cholesterol in these lipid rafts could facilitate the clustering of α- and β-secretases with their substrates in a configuration that leads to pathogenic cleavage of APP (67, 69). Additionally, a cluster of polymorphisms in cholesterol-related genes such as *APOE, SOAT1*, APOE5'-untranslated region, *OLR1, CYP46A1, LPL, LIPA* and *APOA4* has been shown to confer significant susceptibility to AD (70). Thus, a change in neuronal lipoprotein activity and cholesterol homeostasis poses an increased risk for the development of AD.

Excitotoxicity

Excitotoxicity describes the general phenomenon of neuronal cell death due to NMDA receptor-mediated calcium influx (71). It is theorized that excitotoxicity resulting from excessive activation of these receptors increases the vulnerability of CNS neurons, leading to neuronal degeneration (72) and causing synaptic failure (73). Recent studies have also shown that glutamine synthetase, an enzyme involved in the conversion of glutamate to glutamine, is oxidized in the brain of AD patients (74). Excessive glutamate in the synapse results in altered calcium homeostasis, excessive production of $A\beta_{42}$ and free radical generation, which ultimately leads to neuronal death.

Cholinergic deficit

AD is characterized by a deficit in cholinergic neurotransmission due to loss of cholinergic neurons of the

basal nucleus of Meynert (75). It has also been shown that the enzymes involved in the synthesis (choline acetyltransferase) and degradation (acetylcholinesterase) of acetylcholine have reduced activity and could be responsible for the deficit (76, 77). The basal forebrain cholinergic neurons are involved in the regulation of amyloidogenesis and hence APP processing pathways. Aβ peptide and NFTs cause neurotoxicity to the cholinergic innervations of the hippocampus and thus impair acetylcholine processing, leading to cognitive impairment.

Endocrine function

Menopause and andropause are characterized by a dramatic decline in sex steroids, resulting in an increase in the production of gonadotropins (78). It has been hypothesized that the marked reduction in sex hormone levels during the postmenopausal state results in a higher predisposition to develop AD (79, 80). Estrogen, which has been shown to have a neuroprotective effect by lowering brain Aβ levels (81) and improving synaptic plasticity (82), is depleted after menopause. This increases the risk for AD. Luteinizing hormone (LH), a powerful endogenous mitogen, is also increased during aging and AD. This leads to dysregulation of the cell cycle in hippocampal neurons and results in initiation of the pathophysiological cascade of AD (83). Thus, hormonal changes associated with age also play a role in the etiopathogenesis of AD.

Therapeutic interventions

The development of a comprehensive therapeutic treatment for AD is limited by our understanding of the underlying biochemical mechanisms that cause neuronal failure. Numerous dysfunctional mechanisms have been described, ranging from protein aggregation and oxidative stress to biometal dyshomeostasis and mitochondrial failure (84). Thus, developing an effective therapeutic strategy for AD poses a great challenge for the scientific community. Numerous strategies have been developed and are under clinical evaluation, targeting different pathophysiological cascades of AD. A brief summary of the major pathophysiological events and the therapeutic targets are as shown in Figure 5.

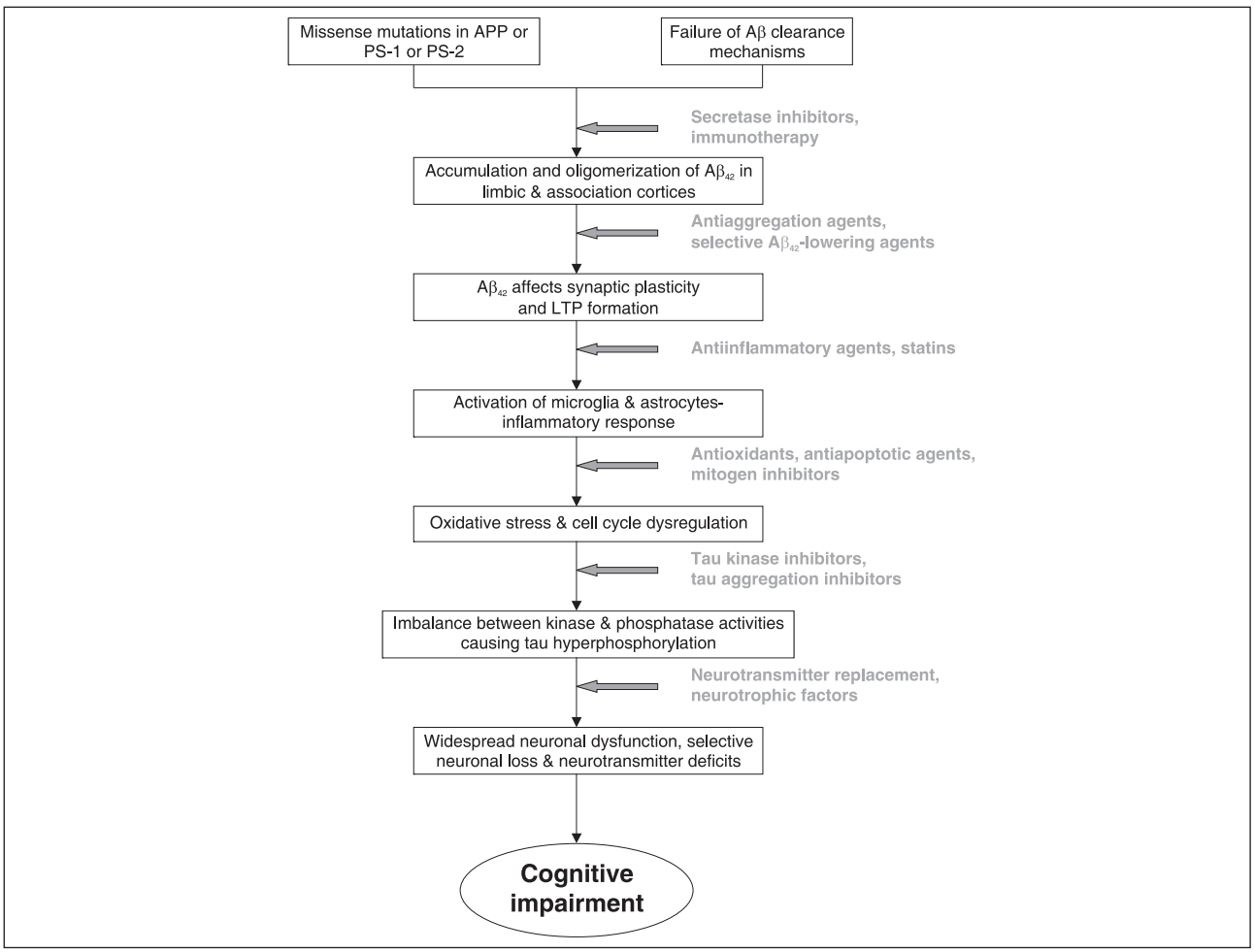


Fig. 5. A brief summary of the pathological events occurring in AD leading to cognitive impairment and selected strategies for therapeutic intervention.

Current FDA-approved drugs for AD and their limitations

AChE inhibitors (donepezil, rivastigmine and galantamine) and NMDA receptor antagonists (memantine) are the two classes of drugs approved for the management of AD. Both donepezil and galantamine are selective AChE inhibitors (85, 86), whereas rivastigmine is an inhibitor of both AChE and butyrylcholinesterase (BChE) (87). The cholinesterase inhibitors do exhibit improvements in patient memory and global function. However, their frequent use is limited by a short duration of action and an inadequate effect on disease progression (88). Memantine, developed on the basis of the excitotoxicity hypothesis, is another drug that has been approved for the symptomatic treatment of moderate to severe AD (89). It is only effective as a symptomatic agent, but does not halt disease progression. Thus, there is an urgent need to develop novel therapeutic strategies with strong disease-modifying properties.

Novel therapeutic strategies

1. Immunotherapy

Experiments proved that immunization with Aβ attenuates the AD-like pathology in a transgenic mouse model of AD (90). Active and passive immunization against Aβ can reduce learning deficits in APP transgenic mice (91, 92). The proposed mechanisms are that Aβ immunization triggers Fc receptor-mediated phagocytosis (90, 93) or can act as a chaperone and disrupt Aβ aggregates or prevent aggregation (94) and/or sequester Aβ, thereby shifting the equilibrium towards the periphery and reducing brain Aβ deposition (95). However, the main adverse effect of active immunization is aseptic meningioencephalitis (96-98). Therefore, alternative approaches need to be developed to avoid an unwanted T-cell response. Passive Aβ immunotherapy with monoclonal antibodies is also being evaluated, as well as DNA vaccines expressing Aβ and its fragments (17). Immunotherapy therefore holds great promise in future AD therapy.

2. Secretase inhibitors

The proteases, particularly γ-secretase and β-secretase, are attractive targets for developing drugs which could be used in the management of AD. Inhibitors of these secretases would block the formation of $A\beta_{42}$ and prevent the subsequent downstream pathology (99). However, safety and pharmacokinetic problems have hindered drug development (100). LY-450139 (**1**) is a γ-secretase inhibitor that is presently in phase II clinical trials. It has been shown to reduce the cerebrospinal fluid (CSF) concentrations of Aβ. It is well tolerated and only a few cases of diarrhea have been reported (101). β-Secretase inhibitors that have been identified to date are large molecules and do not penetrate the blood-brain barrier (100, 102), and none of these molecules have progressed to clinical trials so far (103).

3. Selective $A\beta_{42}$-lowering agents

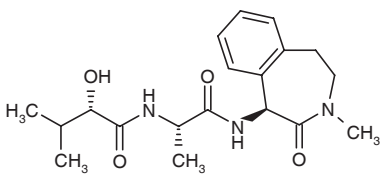
Tarenflurbil (**2**) is a pure (*R*)-enantiomer of flurbiprofen, the first in a novel class of disease-modifying drugs for mild AD (104, 105). This drug modulates γ-secretase, shifting the production away from $A\beta_{42}$ towards the less toxic, shorter fragments of Aβ ($A\beta_{38}$). It also does not interfere with the function of Notch or other γ-secretase substrates (105). Several FDA-approved nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, sulindac and indomethacin, have been shown to have selective $A\beta_{42}$-lowering properties. Although the exact mechanism is not clear, it is independent of cyclooxygenase inhibition (106). Thus, this therapeutic strategy is worthy of future investigation.

4. Statins

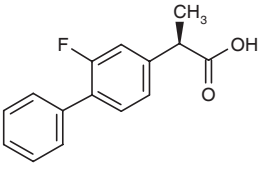
Epidemiological studies show that cholesterol-lowering drugs may have an impact on the progression of AD. The involvement of *APOE*, an established AD risk factor, in cholesterol metabolism provides support for this hypothesis (107). Statins act by preventing cholesterol-dependent cerebrovascular damage by inhibiting HMG-CoA reductase (108), and they upregulate α-secretase activity by inhibiting Rho-associated protein kinase 1 (ROCK1), an enzyme that modulates α-secretase activity. By enhancing the activity of α-secretase, the production of $A\beta_{42}$ is prevented (109). Atorvastatin (**3**) and simvastatin (**4**) are presently in clinical trials.

5. Peroxisome proliferator-activated receptor γ (PPARγ) agonists

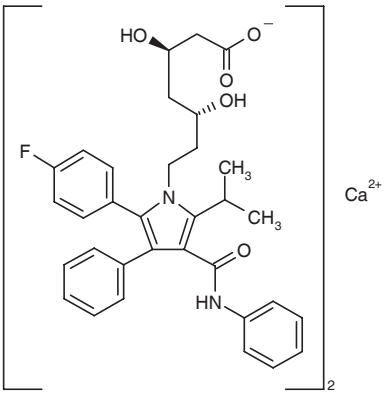
The PPARγ agonists rosiglitazone (**5**) and pioglitazone (**6**) are being assessed in phase II clinical trials as disease-modifying treatments for AD. These drugs act by reducing Aβ levels, plaque deposition and microglia-mediated inflammation (110). More recently, it has been demonstrated that PPARγ regulates BACE1 mRNA, protein and activities via a PPAR response element (PPRE) in the promoter region of the *BACE1* gene (111). It also modulates BACE1 activity at the molecular level, thereby influencing



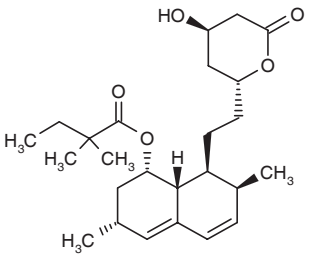
LY-450139 (**1**)



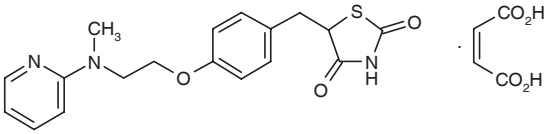
Tarenflurbil (**2**)



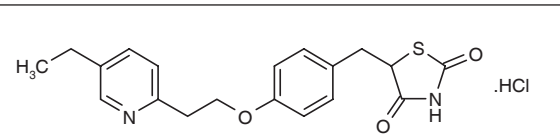
Atorvastatin (**3**)



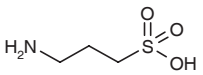
Simvastatin (**4**)



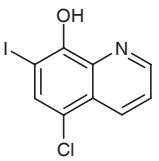
Rosiglitazone (**5**)



Pioglitazone (**6**)



Tramiprosate (**7**)



Clioquinol (**8**)

APP metabolism. Apart from the glitazones, NSAIDs such as ibuprofen, indomethacin and naproxen also activate PPARγ receptors and decrease the risk of AD (112, 113).

6. Antiaggregation agents

Preventing the formation of toxic oligomeric aggregates of Aβ using small molecules represents another approach for the development of novel therapeutics for treating AD. The glycosaminoglycan mimetic tramiprosate (**7**) is presently in phase III clinical trials (102). It reduces the plaque burden by competing with the sulfated glycosaminoglycans for the GAG binding sites and prevents fibril formation (114-116).

Another antiaggregant is O-CLN (Colostrinin™), a polypeptide complex derived from sheep colon that inhibits Aβ aggregation (117) and improves cognitive performance in animal models of AD (118). Following clinical trials in AD (119, 120), the company launched the product in 2007. Clioquinol (**8**), an antibiotic and Cu/Zn chelator, has also been shown to prevent aggregation of Aβ by chelating Zn and other divalent cations required for Aβ aggregation (121, 122). It is a reasonably well-tolerated drug in humans and is in phase II clinical trials for AD.

7. NSAIDs

Epidemiological evidence suggests that long-term use of NSAIDs protects against AD (123), but prospective studies of rofecoxib, naproxen and diclofenac failed to show their efficacy in delaying cognitive decline (124-126). Indomethacin has been shown to cross the blood-brain barrier and improve cognitive function. This effect may be mediated by its ability to activate PPARγ receptors, thereby inhibiting the activation of NF-κB, and prevent the expression of inducible nitric oxide synthase (iNOS) and other inflammatory cytokines, such as tumor necrosis factor α (TNF-α) and IL-1β (56). NSAIDs also have an allosteric effect on γ-secretase and thus reduce $A\beta_{42}$ levels. However, this Aβ-lowering activity is achieved at high concentrations. These agents have therapeutic potential in AD, but their gastrointestinal and cardiovascular toxicity limits their use (127).

8. Antioxidants

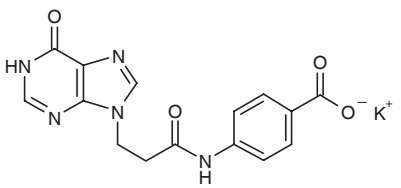
Oxidative damage appears to occur as one of the earliest pathophysiological events in AD and an increased intake of antioxidants lowers the risk of disease progression (128). Antioxidants such as acetyl-L-carnitine, aged garlic extract, α-lipoic acid, *Bacopa monniera*, ubiquinone, curcumin, ferulic acid, *Gingko biloba* extract, ginseng, green tea, huperzine A, melatonin, resveratrol, vitamin C and vitamin E have potential therapeutic value in AD (129). Their mechanism of action in AD management is shown in Table I.

9. Neurotrophic factors

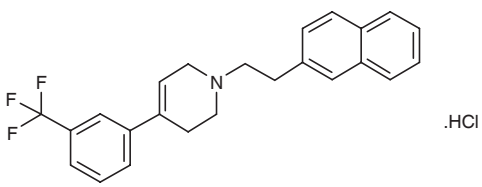
NGF has been shown to stimulate the growth of cholinergic neurons, but the design of an effective deliv-

Table I: Brief summary of some common antioxidants and their proposed mechanism of action.

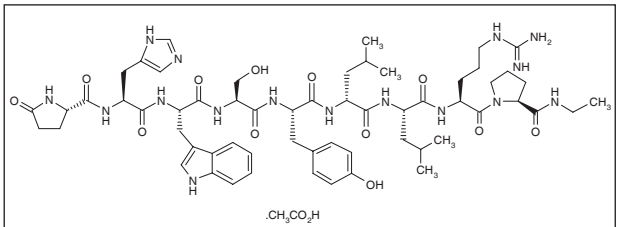
Antioxidant	Proposed mechanism of action in AD	Outcome in clinical trials
Acetyl-L-carnitine	Cholinomimetic, antioxidant	Promising
α-Lipoic acid	Mitochondrial antioxidant, neuroprotective	Promising
Bacopa monniera	Adaptogen, acetylcholinesterase inhibitor	Promising
Curcumin	Metal chelator, antioxidant, antiinflammatory, antiamyloidogenic	Promising
Gingko biloba extract	Antioxidant, antiapoptotic, neuroprotective against hippocampal cells, mitochondrial protector	Promising
Huperzine A	Antioxidant, reversible acetylcholinesterase inhibitor, memory enhancer	Promising
Melatonin	Antioxidant, antiamyloidogenic	Promising
Vitamin C & E (combination)	Antioxidants (chain terminators), neuroprotective	Promising



Leteprinim potassium (**9**)



Xaliproden (**10**)



Leuprolide acetate (**11**)

ery system is a challenge as NGF does not cross the blood-brain barrier (130). Leteprinim potassium (AIT-082; **9**) has been tested in a phase I study and was shown to increase the availability of NGF (131). Other related compounds, including xaliproden (SR-57746A; **10**; phase III), are also in clinical development.

10. Endocrine-based interventions

Dysregulation of reproductive hormones has been associated with the etiopathogenesis of AD. Gonadal hormones have been shown to be neuroprotective. 17β-Estradiol and progesterone have been shown to possess antioxidant, antiinflammatory and antiamyloidogenic activity (132). Leuprolide acetate (**11**), an antigonadotropin, has entered phase III clinical trials for mild to moderate AD. The rationale for studying leuprolide is that LH is implicated in the pathogenesis of AD (133) and it has been shown to decrease the levels of $A\beta_{42}$ in the brain tissue of mice (134). Given the diverse actions of reproductive hormones and their negative effects (increased risk of stroke, pulmonary embolism, etc.), further studies are needed.

11. Targeting tau hyperphosphorylation

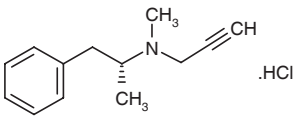
The phosphorylation of tau is controlled by different kinases and phosphatases. Protein phosphatase-2A (phosphoprotein phosphatase) increases the dephosphorylation of tau and also stimulates mitogen-activated protein kinases (MAPKs), which phosphorylate tau (135). Cyclin-dependent kinase 5 (CDK5) is another kinase which phosphorylates tau, and inhibitors of this enzyme may suppress tau phosphorylation and prevent tangle formation (136). Glycogen synthase kinase-3-β (GSK-3β) has also been suggested as a drug target to inhibit tangle formation (137). Lithium, a mood stabilizer, has been shown to block this kinase, but further studies are required to prove its protective effect.

12. Monoamine oxidase (MAO) inhibitors

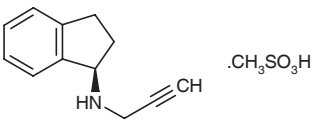
MAO inhibitors have neuroprotective effects. They have been shown to reduce the formation of toxic metabolites and ROS by blocking the enzymatic activity of MAO-A and MAO-B. Selegiline (**12**) has been shown to exert some symptomatic benefits in clinical trials in AD patients (138). Rasagiline (**13**; phase II) acts by influencing amyloid metabolism and induces antiapoptotic genes such as *BCL2* and *BCL-XL* (139, 140). They also interact with histone-modifying enzymes in the nucleus at the molecular level, thereby promoting gene expression (141).

13. Neurotransmitter replacement therapy

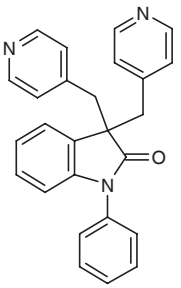
Acetylcholine has been thought of as the core neurotransmitter deficient in AD (142), but increasing evidence now suggests that noradrenergic (143), serotonergic (144, 145), γ-aminobutyric acid (GABA) (146) and



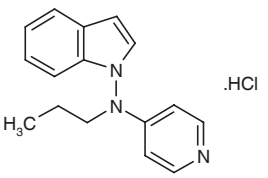
Selegiline (**12**)



Rasagiline (**13**)



Linopirdine (**14**)



Besipirdine (**15**)

dopaminergic system deficiencies may also be involved in the pathophysiological process of AD. Although numerous neurotransmitter replacement strategies have been attempted, none have been successful. One approach is now to administer agents that cause multisystem augmentation. Of particular interest are DuP-996 (linopirdine; **14**), an agent with positive effects on the cholinergic, serotonergic and dopaminergic systems, and HP-749 (besipirdine; **15**), which strengthens both cholinergic and noradrenergic systems. This approach seems promising and could have a role in the management of AD as adjuvant therapy (147).

Conclusions

Given the current momentum of clinical research and developments in the understanding of the neuropathology of AD, improvements in the treatment of AD appear to be within sight. The focus will now be to diagnose the disease at an early stage so that novel disease-modifying interventions can be used to achieve optimal benefit. Thus, as we enter the second century of AD, there is hope that improved treatment and diagnostic methods will soon be available.

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